CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

200-603/S010

Trade Name: Latuda®

Generic Name: Lurasidone hydrochloride

Sponsor: Sunovion Pharmaceuticals, Inc.

Approval Date: 6/28/2013

Indication: LATUDA is an atypical antipsychotic for the treatment of:

- Schizophrenia
- Depressive episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200603/S-010 and S-011

SUPPLEMENT APPROVALS

Sunovion Pharmaceuticals, Inc.
Attention: Bridget Walton, MS, RAC
Director, Regulatory Affairs
One Bridge Plaza North, Suite 510
Fort Lee, NJ 07024

Dear Ms. Walton:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received August 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Latuda (lurasidone hydrochloride) 20 mg, 40 mg, 80 mg, and 120 mg tablets.

We acknowledge receipt of your amendments dated October 12, 2012, November 21, 2012, February 28, 2013, March 19, 2013, March 20, 2013, March 25, 2013, May 7, 2013, and May 20, 2013.

These "Prior Approval" supplemental new drug applications propose the following additional indications: treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), 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.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for birth to 9 years because necessary studies are impossible or highly impracticable. This is because it is extremely difficult to make a diagnosis of bipolar disorder in children younger than 10 years. Therefore, studies in children younger than 10 years would be highly impractical.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because adult studies are completed and ready for approval.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act/FDCA. This required study is listed below.

2058-1 A controlled efficacy and safety study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder

Final Protocol Submission:	December 30, 2013
Study/Trial Completion:	December 30, 2015
Final Report Submission:	December 30, 2016

2058-2 A long-term, open-label safety study of study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder

Final Protocol Submission:	December 30, 2013

Study/Trial Completion:	December 30, 2016
Final Report Submission:	December 30, 2017

Submit the protocol(s) to your IND 103427, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2058-3 A placebo-controlled, randomized withdrawal maintenance study of lurasidone in patients with bipolar I disorder

The timetable you communicated on June 24, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 6, 2013 (We acknowledge that this milestone has been completed)
Study/Trial Completion:	September 30, 2015
Final Report Submission	March 30, 2016

Submit clinical protocols to your IND 103427 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
06/28/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information for LATUDA.

LATUDA (lurasidone hydrochloride) tablets, for oral use
Initial U.S. Approval: 2010

WARNINGS:
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.**
- **LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.2)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)**

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

Boxed Warnings, Suicidal Thoughts and Behaviors (5.2)	m/20xx
Indications and Usage, Bipolar Depression (1.2)	m/20xx
Dosage and Administration, Bipolar Depression (2.1)	m/20xx
Warnings and Precautions (5.2, 5.6, 5.7, 5.9, 5.10, 5.11, 5.13, 5.14)	m/20xx

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

LATUDA is an atypical antipsychotic for the treatment of:

- Schizophrenia (1.1, 14.1)
- Depressive Episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate (1.2, 14.2).

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

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA (2.3, 12.3).

Indication	Starting Dose	Recommended Dose
Schizophrenia (2.1)	40 mg per day	40 to 160 mg per day
Bipolar Depression (2.2)	20 mg per day	20 to 120 mg per day

- Moderate and Severe Renal Impairment: Recommended starting dose is 20 mg per day, and the maximum recommended dose is 80 mg per day (2.4, 8.6).
- Moderate and Severe Hepatic Impairment: Recommended starting dose is 20 mg per day. The maximum recommended dose is 80 mg per day in moderate hepatic impairment and 40 mg per day in severe hepatic impairment (2.4, 8.6).
- Concomitant Use of a Strong CYP3A4 Inhibitor (e.g., ketoconazole): LATUDA should not be co-administered with a strong CYP3A4 inhibitor (2.5, 4, 7.1).
- Concomitant Use of a Strong CYP3A4 Inducer (e.g., rifampin): LATUDA should not be co-administered with a strong CYP3A4 inducer (2.5, 4, 7.1).
- Concomitant Use of a Moderate CYP3A4 inhibitor (e.g., diltiazem): LATUDA dose should be reduced to half of the original dose level. Recommended starting dose is 20 mg per day. Maximum recommended dose is 80 mg per day (2.5, 7.1)
- Concomitant Use of a Moderate CYP3A4 Inducer: It may be necessary to increase the dose of LATUDA (2.5, 7.1)

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

Tablets: 20 mg, 40 mg, 80 mg and 120 mg (3)

----------**CONTRAINDICATIONS**----------

- Known hypersensitivity to LATUDA or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (4, 7.1).
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (4, 7.1).

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

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.2).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4).
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.5).
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.6).
  - *Hyperglycemia and Diabetes Mellitus* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
  - *Dyslipidemia* Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - *Weight Gain* Gain in body weight has been observed. Monitor weight.
- Hyperprolactinemia: Prolactin elevations may occur (5.7).
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing LATUDA if a clinically significant decline in WBC occurs in the absence of other causative factors (5.8).
- Orthostatic Hypotension and Syncope: Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. In patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients, consider a lower starting dose and slower titration (5.9).

----------**ADVERSE REACTIONS**----------

Commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) were (6.1):

- Schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Bipolar depression: akathisia, extrapyramidal symptoms, and somnolence

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Pregnancy: Use LATUDA during pregnancy only if the potential benefit justifies the potential risk (8.1).
- Nursing Mothers: Discontinue drug or nursing, considering risk of drug discontinuation to the mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: XX/2013

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INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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

FULL PRESCRIBING INFORMATION

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

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[see Warnings and Precautions (5.1)]*.**
- **LATUDA is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.**
- **In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

1.2 Depressive Episodes Associated with Bipolar I Disorder

Monotherapy: LATUDA is indicated as monotherapy for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week monotherapy study in adult patients with bipolar depression *[see Clinical Studies (14.2)]*.

Adjunctive Therapy with Lithium or Valproate: LATUDA is indicated as adjunctive therapy with either lithium or valproate for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week study in adult patients with bipolar depression who were treated adjunctively with lithium or valproate *[see Clinical Studies (14.2)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.2)]*.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 160 mg per day *[see Clinical Studies (14.1)]*. The maximum recommended dose is 160 mg per day.

2.2 Depressive Episodes Associated with Bipolar I Disorder

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg per day to 120 mg per day as monotherapy or as adjunctive therapy with lithium or valproate *[see Clinical Studies (14.2)]*. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy on average, compared to the lower dose range (20 to 60 mg per day) *[see Clinical Studies (14.2)*.

2.3 Administration Instructions

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the Cmax approximately 3-fold. In the clinical studies, LATUDA was administered with food *[see Clinical Pharmacology (12.3)]*.

2.4 Dose Modifications in Special Populations

Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg per day. The dose in moderate hepatic impairment patients should not exceed 80 mg per day and the dose in severe hepatic impairment patients should not exceed 40 mg/day *[see Use in Specific Populations (8.6)]*.

2.5 Dose Modifications Due to Drug Interactions

Concomitant Use with CYP3A4 Inhibitors

LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Contraindications (4)]*.

If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being

prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg per day, and the maximum recommended dose of LATUDA is 80 mg per day *[see Contraindications (4); Drug Interactions (7.1)]*.

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA [*see Drug Interactions (7.1)*].

Concomitant Use with CYP3A4 Inducers

LATUDA should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Contraindications (4); Drug Interactions (7.1)]*. If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

3 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing:

Table 1: LATUDA Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
20 mg	white to off-white round	L20
40 mg	white to off-white round	L40
80 mg	pale green oval	L80
120 mg	white to off-white oval	L120

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.1)]*.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Drug Interactions (7.1)]*.
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Drug Interactions (7.1)]*.

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 drug-treated patients of between 1.6- to 1.7-times the risk of death 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 the placebo group. 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2.

Table 2

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidal thoughts and behaviors, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LATUDA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, 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 developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the

syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While 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 or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 3.

Table 3: Change in Fasting Glucose in Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
	Mean Change from Baseline (mg/dL)					
	n=680	**n=71**	**n=478**	**n=508**	**n=283**	**n=113**
Serum Glucose	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
	Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/260)	5.6% (6/108)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 4.

Table 4: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
	Mean Change from Baseline (mg/dL)		
	n=148	**n=140**	**n=143**
Serum Glucose	+1.8	-0.8	+1.8
	Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	4.3% (6/141)	2.2% (3/138)	6.4% (9/141)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 5.

Table 5: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

	Placebo	LATUDA 20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=302	**n=319**
Serum Glucose	-0.9	+1.2
Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	1.0% (3/290)	1.3% (4/316)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 6.

Table 6: Change in Fasting Lipids in Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
Mean Change from Baseline (mg/dL)						
	n=660	**n=71**	**n=466**	**n=499**	**n=268**	**n=115**
Total Cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 7.

Table 7: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
	Mean Change from Baseline (mg/dL)		
	n=147	**n=140**	**n=144**
Total cholesterol	-3.2	+1.2	-4.6
Triglycerides	+6.0	+5.6	+0.4
	Proportion of Patients with Shifts		
Total cholesterol (≥ 240 mg/dL)	4.2% (5/118)	4.4% (5/113)	4.4% (5/114)
Triglycerides (≥ 200 mg/dL)	4.8% (6/126)	10.1% (12/119)	9.8% (12/122)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=130) and -1.0 (n=130) mg/dL at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in Table 8.

Table 8: Change in Fasting Lipids in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	**20 to 120 mg/day**
	Mean Change from Baseline (mg/dL)	
	n=303	**n=321**
Total cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6
	Proportion of Patients with Shifts	
Total cholesterol (≥ 240 mg/dL)	5.7% (15/263)	5.4% (15/276)

	Placebo	LATUDA 20 to 120 mg/day
	Mean Change from Baseline (mg/dL)	
Triglycerides (≥ 200 mg/dL)	8.6% (21/243)	10.8% (28/260)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and 5.3 (n=88) mg/dL at week 24, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 9. The mean weight gain was 0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 *[see Clinical Studies (14.1)]*, respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo (n=696)	**20 mg/day (n=71)**	**40 mg/day (n=484)**	**80 mg/day (n=526)**	**120 mg/day (n=291)**	**160 mg/day (n=114)**
All Patients	-0.02	-0.15	+0.22	+0.54	+0.68	+0.60

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 10. The mean weight gain was 0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo (n=151)	**20 to 60 mg/day (n=143)**	**80 to 120 mg/day (n=147)**
All Patients	0.0	+0.56	+0.02

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 11. The mean weight gain was 0.11 kg for LATUDA-treated patients compared to 0.16 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients versus 0.3% for placebo-treated patients.

Table 11: Mean Change in Weight (kg) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo (n=334)	**20 to 120 mg/day (n=327)**
All Patients	+0.16	+0.11

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association

between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Table 12: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	+3.3 (n=284)	+3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	+6.7 (n=70)	+7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	+3.1 (n=214)	+2.4 (n=79)

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Bipolar Depression

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
All Patients	+0.3 (n=147)	+1.7 (n=140)	+3.5 (n=144)
Females	0.0 (n=82)	+1.8 (n=78)	+5.3 (n=88)
Males	0.4 (n=65)	+1.2 (n=62)	+1.9 (n=56)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 14.

Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	**20 to 120 mg/day**
All Patients	0.0 (n=301)	+2.8 (n=321)
Females	+0.4 (n=156)	+3.2 (n=162)
Males	-0.1 (n=145)	+2.4 (n=159)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

5.8 Leukopenia, Neutropenia and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia

The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

5.10 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no patient experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

5.11 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Bipolar Depression

Monotherapy

In the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 80 to120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

5.12 Body Temperature Dysregulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

5.13 Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania

Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

6 ADVERSE REACTIONS

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) *[see Warnings and Precautions (5.6)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[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)]*
- Suicide *[see Warnings and Precautions (5.13)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds to with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia

The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:
Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 15.

Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction						
		LATUDA					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All LATUDA (N=1508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Akathisia	3	6	11	12	22	7	13
Extrapyramidal Disorder*	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Somnolence**	7	15	16	15	26	8	17
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5%, in either dose group, and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 16.

Table 16: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Monotherapy Bipolar Depression Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=168) (%)**	**LATUDA 20-60 mg/day (N=164) (%)**	**LATUDA 80-120 mg/day (N=167) (%)**	**All LATUDA (N=331) (%)**
Gastrointestinal Disorders				
Nausea	8	10	17	14
Dry Mouth	4	6	4	5
Vomiting	2	2	6	4
Diarrhea	2	5	3	4
Infections and infestations				
Nasopharyngitis	1	4	4	4
Influenza	1	<1	2	2
Urinary Tract Infection	<1	2	2	2
Musculoskeletal and Connective Tissue Disorders				
Back Pain	<1	3	<1	2
Nervous System Disorders				
Extrapyramidal Symptoms*	2	5	9	7
Somnolence**	7	7	14	11
Akathisia	2	8	11	9
Psychiatric Disorders				
Anxiety	1	4	5	4

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see Clinical Studies (14.2)] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

The following findings are based on two short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 17.

Table 17: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Adjunctive Therapy Bipolar Depression Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=334) (%)**	**LATUDA 20 to 120 mg/day (N=360) (%)**
Gastrointestinal Disorders		
Nausea	10	14
Vomiting	1	4
General Disorders		
Fatigue	2	3
Infections and Infestations		
Nasopharyngitis	2	4
Investigations		
Weight Increased	1	3
Metabolism and Nutrition Disorders		
Increased Appetite	2	3
Nervous System Disorders		
Extrapyramidal Symptoms*	9	14
Somnolence**	5	11
Akathisia	5	11
Psychiatric Disorders		
Restlessness	1	

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Extrapyramidal Symptoms

Schizophrenia

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in Schizophrenia Studies

		LATUDA				
Adverse Event Term	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Bipolar Depression

Monotherapy

In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 19.

Table 19: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

Adverse Event Term	Placebo (N=168) (%)	LATUDA 20 to 60 mg/day (N=164) (%)	LATUDA 80 to 120 mg/day (N=167) (%)
All EPS events	5	12	20
All EPS events, excluding Akathisia/Restlessness	2	5	9
Akathisia	2	8	11
Dystonia*	0	0	2
Parkinsonism**	2	5	8
Restlessness	<1	0	3

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 15.3% versus 9.8% for placebo. The incidence of akathisia for LATUDA-treated patients was 7.7% versus 4.3% for placebo-treated patients. Incidence of EPS is provided in Table 20.

Table 20: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies

Adverse Event Term	Placebo (N=334) (%)	LATUDA 20 to 120 mg/day (N=360) (%)
All EPS events	**13**	**24**
All EPS events, excluding Akathisia/Restlessness	**9**	**14**
Akathisia	5	11
Dystonia*	1	1
Parkinsonism**	8	13
Restlessness	1	4

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Dystonia

Class Effect: 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. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 15 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye Disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis*

General Disorders and Administrative Site Conditions: ***Rare:*** *sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolism and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *cerebrovascular accident, dysarthria*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Frequent:*** *hypertension*

Clinical Laboratory Changes

Schizophrenia

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 21).

Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies

Laboratory Parameter	Placebo (N=708)	LATUDA 20 mg/day (N=71)	LATUDA 40 mg/day (N=487)	LATUDA 80 mg/day (N=538)	LATUDA 120 mg/day (N=291)	LATUDA 160 mg/day (N=121)
Serum Creatinine Elevated	2%	1%	2%	2%	5%	7%

Bipolar Depression

Monotherapy

Serum Creatinine: In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 22).

Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

Laboratory Parameter	Placebo (N=168)	LATUDA 20 to 60 mg/day (N=164)	LATUDA 80 to 120 mg/day (N=167)
Serum Creatinine Elevated	<1%	2%	4%

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 23).

Table 23: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

Laboratory Parameter	Placebo (N=334)	LATUDA 20 to 120 mg/day (N=360)
Serum Creatinine Elevated	2%	4%

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

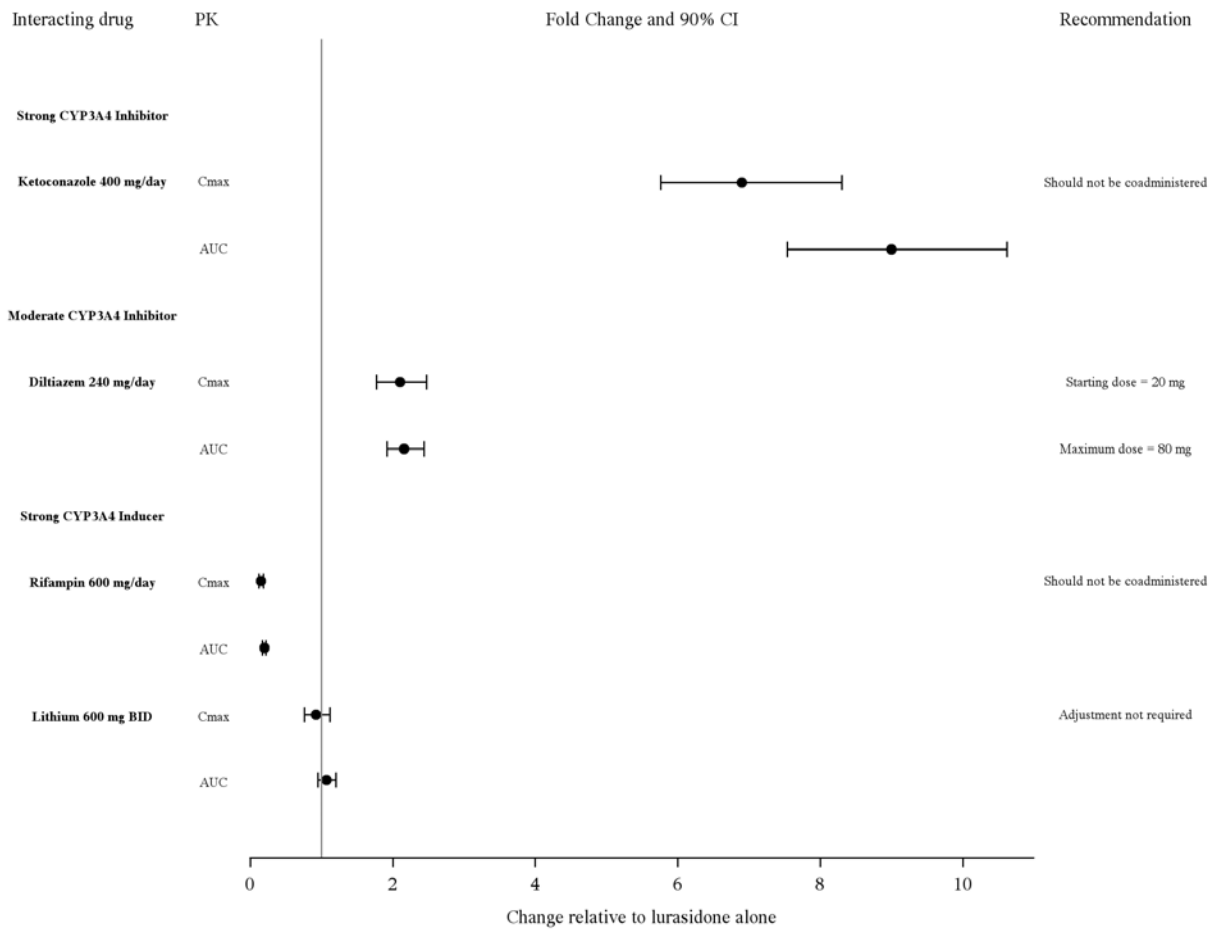
LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Contraindications (4)]*. The LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose *[see Dosage and Administration (2.5)]*.

Lithium: It is not necessary to adjust the LATUDA dose when used concomitantly with lithium (Figure 1).

Valproate: It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies valproate levels were not affected by lurasidone, and lurasidone concentrations were not affected by valproate.

Grapefruit: Grapefruit and grapefruit juice should be avoided in patients taking LATUDA [*see Dosage and Administration (2.5)*].

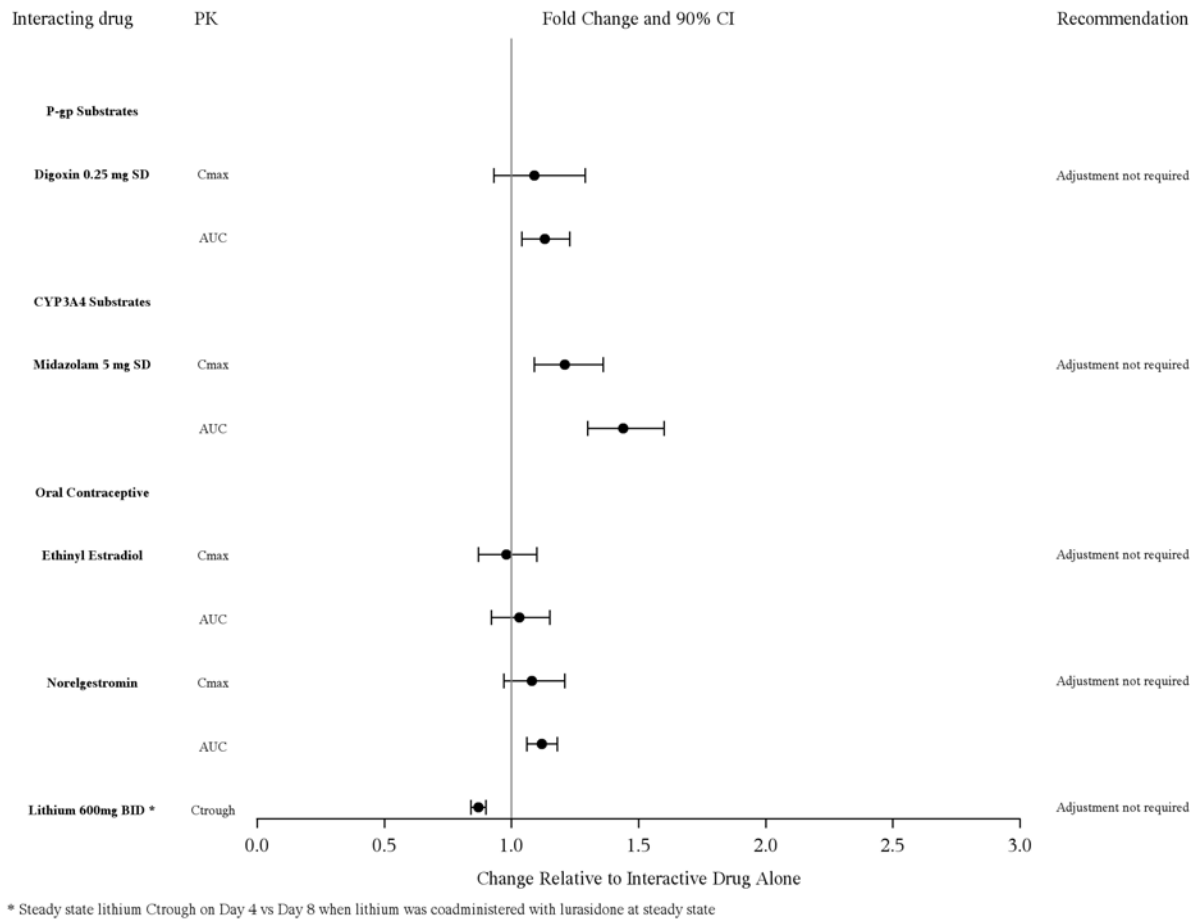
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed on the dose of lithium, valproate, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m^2 body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m^2 body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

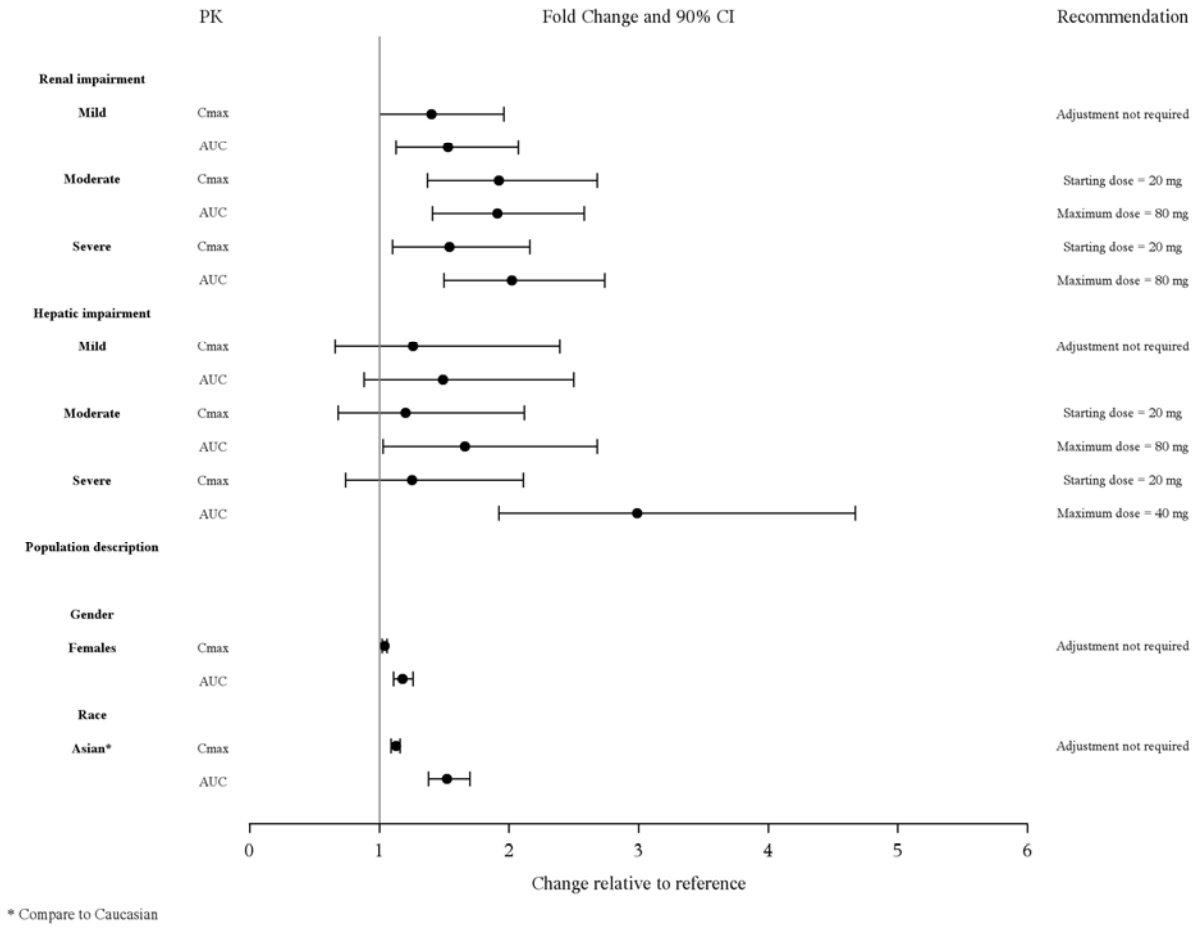
Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LATUDA is not a controlled substance.

9.2 Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

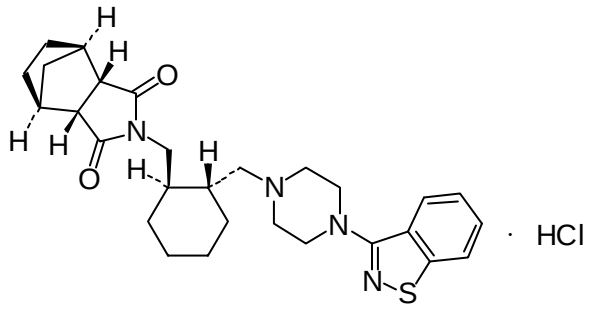
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11 DESCRIPTION

LATUDA is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S \cdot HCl$ and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, 80 mg, or 120 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of LATUDA in the treatment of schizophrenia and bipolar depression is unknown. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

LATUDA is an antagonist with high affinity binding at the dopamine D_2 receptors (Ki=1 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT_{2A} (Ki=0.5 nM) and 5-HT_7 (Ki=0.5 nM) receptors. It also binds with moderate affinity to the human α_{2C} adrenergic receptors (Ki=11 nM), is a partial agonist at serotonin 5-HT_{1A} (Ki=6.4 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki=41 nM). LATUDA exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} > 1,000 nM).

ECG Changes

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel-dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

In short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

12.3 Pharmacokinetics

The activity of LATUDA is primarily due to the parent drug. The pharmacokinetics of LATUDA is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of LATUDA are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: LATUDA is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. LATUDA is highly bound (~99%) to serum proteins.

In a food effect study, LATUDA mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. LATUDA exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content *[see Dosage and Administration (2.3)]*.

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food *[see Dosage and Administration (2.3)]*.

Metabolism and Elimination: LATUDA is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. LATUDA is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). Based on *in vitro* studies, LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because LATUDA is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of LATUDA.

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [^{14}C]-labeled LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: LATUDA increased incidences of malignant mammary gland tumors and pituitary gland adenomas in female mice orally dosed with 30, 100, 300, or 650 mg/kg/day. The lowest dose produced plasma levels (AUC) approximately equal to those in humans receiving the MRHD of 160 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14-times those in humans receiving the MRHD.

LATUDA increased the incidence of mammary gland carcinomas in females rats orally dosed at 12 and 36 mg/kg/day: the lowest dose; 3 mg/kg/day is the no-effect dose which produced plasma levels (AUC) 0.4-times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to the highest dose tested, which produced plasma levels (AUC) 6-times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents to humans is unknown *[see Warnings and Precautions (5.7)]*.

Mutagenesis: LATUDA did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo*. LATUDA was negative in the Ames gene mutation test, the Chinese Hamster Lung (CHL) cells, and in the *in vivo* mouse bone marrow micronucleus test up to 2000 mg/kg (61 times the MRHD of 160 mg/day based on mg/m^2 body surface area).

Impairment of Fertility: Estrus cycle irregularities were seen in rats orally administered LATUDA at 1.5, 15 and 150 mg/kg/day for 15 consecutive days prior to mating, during the

mating period, and through day 7 of gestation. The no-effect dose is 0.1 mg/kg which is approximately 0.006-times the MRHD of 160 mg/day based on body surface area. Fertility was reduced only at the highest dose, which was reversible after a 14-day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is approximately equal to the MRHD based on body surface area.

LATUDA had no effect on fertility in male rats treated orally with LATUDA for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (9-times the MRHD based on mg/m^2 body surface area).

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of LATUDA for the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active-control arm (olanzapine or quetiapine extended-release) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. The BPRSd consists of 18 items rated on a scale of 1 (not present) to 7 (severe). BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a clinician-rated scale that measures the subject's current illness state on a 1- to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. Study 1: In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. Study 2: In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. Study 3: In a 6-week, placebo- and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

4. Study 4: In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. Study 5: In a 6-week, placebo- and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 or 160 mg/day) and an active control (quetiapine extended-release), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80, 120 and 160 mg/day has been established (Table 24).

Table 24: Primary Efficacy Results for Studies in Schizophrenia (BPRSd or PANSS Scores)

Study	Treatment Group	Primary Efficacy Measure: BPRSd		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
1	LATUDA (40 mg/day)*	54.2 (8.8)	-9.4 (1.6)	-5.6 (-9.8, -1.4)
	LATUDA (120 mg/day)*	52.7 (7.6)	-11.0 (1.6)	-6.7 (-11.0, -2.5)
	Placebo	54.7 (8.1)	-3.8 (1.6)	--
2	LATUDA (80 mg/day)*	55.1 (6.0)	-8.9 (1.3)	-4.7 (-8.3, -1.1)
	Placebo	56.1 (6.8)	-4.2 (1.4)	--
		Primary Efficacy Measure: PANSS		
3	LATUDA (40 mg/day)*	96.6 (10.7)	-25.7 (2.0)	-9.7 (-15.3, -4.1)
	LATUDA (120 mg/day)*	97.9 (11.3)	-23.6 (2.1)	-7.5 (-13.4, -1.7)
	Olanzapine (15 mg/day)*[b]	96.3 (12.2)	-28.7 (1.9)	-12.6 (-18.2, -7.9)
	Placebo	95.8 (10.8)	-16.0 (2.1)	--
4	LATUDA (40 mg/day)	96.5 (11.5)	-19.2 (1.7)	-2.1 (-7.0, 2.8)
	LATUDA (80 mg/day)*	96.0 (10.8)	-23.4 (1.8)	-6.4 (-11.3, -1.5)
	LATUDA (120 mg/day)	96.0 (9.7)	-20.5 (1.8)	-3.5 (-8.4, 1.4)
	Placebo	96.8 (11.1)	-17.0 (1.8)	--
5	LATUDA (80 mg/day)*	97.7 (9.7)	-22.2 (1.8)	-11.9 (-16.9, -6.9)
	LATUDA (160 mg/day)*	97.5 (11.8)	-26.5 (1.8)	-16.2 (-21.2, -11.2)
	Quetiapine Extended-release (600 mg/day)*[b]	97.7 (10.2)	-27.8 (1.8)	-17.5 (-22.5, -12.4)
	Placebo	96.6 (10.2)	-10.3 (1.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Included for assay sensitivity.
* Doses statistically significantly superior to placebo.

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

14.2 Depressive Episodes Associated with Bipolar I Disorder

Monotherapy

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.5 years, range 18 to 74) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=485). Patients were randomized to one of two flexible-dose ranges of LATUDA (20 to 60 mg/day, or 80 to 120 mg/day) or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S), a clinician-rated scale that measures the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

For both dose groups, LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6. The primary efficacy results are provided in Table 25. The high dose range (80 to 120 mg per day) did not provide additional efficacy on average, compared to the low dose range (20 to 60 mg per day).

Adjunctive Therapy with Lithium or Valproate

The efficacy of LATUDA, as an adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.7 years, range 18 to 72) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=340). Patients who remained symptomatic after treatment with lithium or valproate were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the MADRS. The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the CGI-BP-S scale.

LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6, as an adjunctive therapy with lithium or valproate (Table 25).

Table 25: Primary Efficacy Results for Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

Study	Treatment Group	Primary Efficacy Measure MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Monotherapy study	LATUDA (20-60 mg/day)*	30.3 (5.0)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	LATUDA (80-120 mg/day)*	30.6 (4.9)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	Placebo	30.5 (5.0)	-10.7 (0.8)	--
Adjunctive Therapy study	LATUDA (20-120 mg/day)* + lithium or valproate	30.6 (5.3)	-17.1 (0.9)	-3.6 (-6.0, -1.1)
	Placebo + lithium or valproate	30.8 (4.8)	-13.5 (0.9)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg), pale green, oval (80 mg) or white to off-white, oval (120 mg) and identified with strength-specific one-sided debossing, "L20" (20 mg), "L40" (40 mg), "L80" (80 mg) or "L120" (120 mg). Tablets are supplied in the following strengths and package configurations (Table 26):

Table 26: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration	NDC Code
20 mg	Bottles of 30	63402-302-30
	Bottles of 90	63402-302-90
	Bottles of 500	63402-302-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-302-10 Carton 63402-302-01 Blister
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister
120 mg	Bottles of 30	63402-312-30
	Bottles of 90	63402-312-90
	Bottles of 500	63402-312-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-312-10 Carton 63402-312-01 Blister

Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) *[See USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Advise patients and caregivers that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning; Warnings and Precautions (5.1)]*.

17.2 Suicidal Thoughts and Behaviors; and Activation of Mania or Hypomania

Educate patients, families, and caregivers about the risk of suicidal thoughts and behaviors with antidepressant treatment, as well as the risk of mania and hypomania. Advise them about monitoring for the emergence of suicidal thoughts and behavior, manic/hypomanic symptoms, irritability, agitation, or unusual changes in behavior. Instruct patients, families, and caregivers to report such symptoms to the healthcare provider *[see Warnings and Precautions (5.2 and 5.14)]*.

17.3 Neuroleptic Malignant Syndrome

Advise patients and caregivers that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.4)]*.

17.4 Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)

Educate patients and caregivers about the risk of metabolic changes and the need for specific monitoring. The risks include hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, and cardiovascular reactions. Educate patients and caregivers about the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness). Monitor all patients for these symptoms. Patients who are diagnosed with diabetes or have risk factors for diabetes (obesity, family history of diabetes) should have their fasting blood glucose monitored before beginning treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia should have assessments of fasting glucose. Clinical monitoring of weight is recommended *[see Warnings and Precautions (5.6)]*.

17.5 Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.9)]*.

17.6 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 LATUDA *[see Warnings and Precautions (5.8)]*.

17.7 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 LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

17.8 Pregnancy and Nursing

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA *[see Use in Specific Populations (8.1)]*.

17.9 Concomitant Medication and Alcohol

Instruct patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, because there is a potential for drug interactions. Advise patients to avoid alcohol while taking LATUDA *[see Drug Interactions (7)]*.

17.10 Heat Exposure and Dehydration

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

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

Revised: Month Year

901456RXX

Medication Guide

LATUDA (luh-TOO-duh)

(lurasidone hydrochloride)

Tablets

Read this Medication Guide before you start taking LATUDA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

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

LATUDA may cause serious side effects, including:

1. **risk of death in the elderly with dementia:** Medicines like LATUDA can increase the risk of death in elderly people who have memory loss (dementia). LATUDA is not for treating psychosis in the elderly with dementia.
2. **risk of suicidal thoughts or actions (antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions).**
   - **Talk to your, or your family member's, healthcare provider about:**
     - all risks and benefits of treatment with antidepressant medicines
     - all treatment choices for depression or other serious mental illness
   - **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
   - **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or suicidal thoughts or 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 an antidepressant medicine is started or when the dose is changed.
     - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
     - Keep all follow-up visits with the healthcare provider as scheduled. Call the 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 has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to your healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

What is LATUDA?

LATUDA is a prescription medicine used to treat:

- schizophrenia
- depressive episodes associated with bipolar I disorder, alone or with lithium or valproate

Who should not take LATUDA?

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

What should I tell my healthcare provider before taking LATUDA?

Before you take LATUDA, tell your healthcare provider if you have or have had:

- diabetes or high blood sugar in you or your family. Your healthcare provider should check your blood sugar before you start LATUDA and also during therapy.
- high levels of total cholesterol, triglycerides or LDL-cholesterol or low levels of HDL-cholesterol
- low or high blood pressure
- low white blood cell count
- seizures
- abnormal thyroid tests
- high prolactin levels
- heart problems
- liver problems
- any other medical condition
- pregnancy or plans to become pregnant. It is not known if LATUDA will harm your unborn baby
- breast-feeding or plans to breast-feed. LATUDA can pass into your breast milk. You and your healthcare provider should decide if you will take LATUDA or breast-feed. You should not do both.

Tell the healthcare provider about all the medicines that you take or recently have taken including prescription medicines, over-the-counter medicines, herbal supplements and vitamins.

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

How should I take LATUDA?

- Take LATUDA exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take LATUDA by mouth, with food (at least 350 calories).
- LATUDA should be swallowed whole and not split, chewed or crushed.

- If you miss a dose of LATUDA, take it as soon as you remember. If you are close to your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time unless your healthcare provider tells you to. If you are not sure about your dosing, call your healthcare provider.
- If you take too much LATUDA, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What should I avoid while taking LATUDA?

- Do not drive, operate machinery, or do other dangerous activities until you know how LATUDA affects you. LATUDA may make you drowsy.
- Avoid getting overheated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.
- Do not drink alcohol while taking LATUDA. It may make some side effects of LATUDA worse.

What are possible side effects of LATUDA?

LATUDA can cause serious side effects, including:

- **See "What is the most important information I should know about LATUDA?"**
- **stroke that can lead to death can happen in elderly people with dementia who take medicines like LATUDA**
- **neuroleptic malignant syndrome (NMS).** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including LATUDA. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have some or all of these symptoms:
  - high fever
  - excessive sweating
  - rigid muscles
  - confusion
  - changes in your breathing, heartbeat, and blood pressure
- **high blood sugar (hyperglycemia).** High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:
  - build up of acid in your blood due to ketones (ketoacidosis)
  - coma
  - death

  Increases in blood sugar can happen in some people who take LATUDA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes) your healthcare

provider should check your blood sugar before you start LATUDA and during therapy.

Call your healthcare provider if you have any of these symptoms of high blood sugar (hyperglycemia) while taking LATUDA:

- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity

- **high fat levels in your blood (increased cholesterol and triglycerides).** High fat levels may happen in people treated with LATUDA. You may not have any symptoms, so your healthcare provider may decide to check your cholesterol and triglycerides during your treatment with LATUDA.
- **increase in weight (weight gain).** Weight gain has been reported in patients taking medicines like LATUDA. You and your healthcare provider should check your weight regularly. Talk to your healthcare provider about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.
- **movements you cannot control in your face, tongue, or other body parts (tardive dyskinesia).** These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking LATUDA. Tardive dyskinesia may also start after you stop taking LATUDA.
- **decreased blood pressure (orthostatic hypotension),** including lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
- **low white blood cell count**
- **seizures**
- **increases in prolactin levels:** Your healthcare provider may do blood tests to check your prolactin levels.
- **difficulty swallowing:** may lead to aspiration and choking

The most common side effects of LATUDA include:

- inner sense of restlessness/need to move (akathisia)
- difficulty moving, slow movements, muscle stiffness, or tremor
- sleepiness
- nausea
- vomiting
- diarrhea
- anxiety

These are not all the possible side effects of LATUDA. For more information, ask your healthcare provider or pharmacist.

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 LATUDA?

- Store LATUDA tablets at room temperature, between 59° to 86°F (15° to 30°C).
- Keep LATUDA and all medicines out of the reach of children.

General information about the safe and effective use of LATUDA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LATUDA for a condition for which it was not prescribed. Do not give LATUDA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about LATUDA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LATUDA that is written for health professionals.

For more information, go to www.LATUDA.com, or call 1-888-394-7377.

What are the ingredients in LATUDA?

Active ingredient: lurasidone hydrochloride

Inactive ingredients: mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 200603/S-010 and S-011

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Balimane, Praveen
Birkner, Thomas
Holmes, Loretta
Levin, Robert
Mathis, Mitchell
Mehta, Reema
Ritter, Mark
Tabacova, Sonia
Yang, Peiling
Zhu, Hao

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

OFFICE DIRECTOR MEMO

M E M O R A N D U M

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

DATE: 28 June 2013

FROM: Mitchell V. Mathis, M.D.
Acting Director
Division of Psychiatry Products, HFD-130

TO: File NDA 200603; S010, S011 [31 August 2012 submission]

SUBJECT: Approval recommendation for lurasidone (Latuda) for the treatment of bipolar depression, monotherapy and adjunctive therapy to lithium or valproic acid

Background and Summary

Lurasidone (Latuda) is an atypical antipsychotic approved for the treatment of schizophrenia. The sponsor submitted the current supplements to support safety and efficacy in bipolar depression. Two controlled safety and efficacy studies were initially submitted to support this indication: Study 236 for monotherapy and Study 235 for adjunctive use with lithium or valproate. A third study was requested during the review: Study 292 was an add-on to lithium or valproate study that was negative at its primary endpoint, but was very similar in design to Study 235 and so we requested the safety and efficacy data from this study as part of our review. A 24-week open-label extension study (Study 256) was also submitted to provide longer-term safety data.

Studies 235 and 236 are positive for efficacy overall and therefore support approval, but there was a fair amount of discussion among the team members about regional differences in efficacy. The clinical reviewer has recommended a Complete Response action secondary to a lack of differentiation from placebo in the US subgroup of patients in Study 235. The concern has been that without a signal of efficacy in the US population, the drug should not be approved in the US.

The statistical team noted the same lack of differentiation of drug from placebo in the US subgroup in Study 235, but their recommendation was for approval because the studies submitted were positive overall and good statistical practice would dictate that the studies should be analyzed for efficacy as they were planned, and that subgroup decisions are likely to be uninformative, unless a valid reason to explain the subgroup (in this case, population) differences, can be identified. No evidence of significant subpopulation differences has been identified by the clinical team, statistical team, or our inspections of the clinical study sites. There were no significant differences in the two populations (US and non-US) in terms of demographics, severity of illness, differential diagnosis patterns, or in any other factor that could reasonably explain the subgroup differences in efficacy.

In addition, the team evaluated Study 292 which was a multiregional trial with 44% of patients from North America (39 percent of ITT population from the US and 5 percent from Canada) and this study was designed very similarly to Study 235. Although this study was negative at its primary

endpoint (6 weeks), it was positive from weeks 2 through 5, and more importantly, the US study population contributed to efficacy during weeks 2 through 5.

Having considered all of the evidence, I agree with the statistical team and the Cross-Discipline Team Leader that efficacy has been demonstrated for treatment of bipolar depression, both as monotherapy and as adjunctive therapy to lithium or valproate. The data as analyzed by the SAP support approval with two positive trials, one monotherapy and one as add-on to lithium or valproic acid. Having reached this conclusion, it would be in my view, uninformative and potentially confusing to include regional differences information in labeling.

Chemistry Manufacturing and Controls
No new CMC information was included in this submission.

Nonclinical Pharmacology/Toxicology
There are no pharmacology/toxicology data provided as part of this application.

Office of Clinical Pharmacology (OCP)
No new data were required or submitted as part of this supplement.

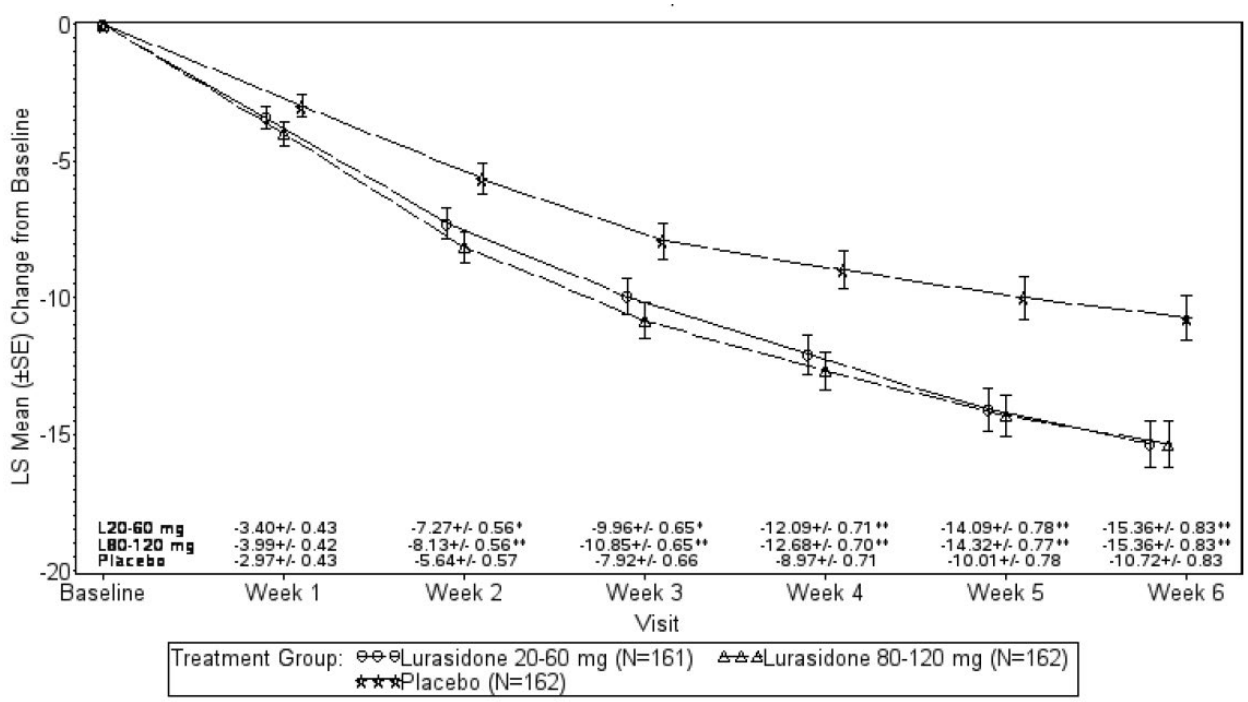
Clinical
Study 236—Monotherapy
This was a 6-week, outpatient, multicenter, randomized, double-blind, placebo-controlled monotherapy study of two fixed-flexible dose ranges of lurasidone in the treatment of major depressive episodes in adults (n=505) with bipolar I disorder. The baseline Montgomery Asberg Depression Rating Scale (MADRS) score was required to be at least 20 for a minimum of 4 weeks (patients were depressed but not included if psychotically depressed) and the Young Mania Rating Scale (YMRS) score was required to be less than 12 (patients were not manic) prior to randomization. The primary efficacy endpoint was change from baseline in MADRS total score at 6 weeks. The key secondary efficacy endpoint was change from baseline to week 6 on the Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S).

Results
Study 236 demonstrated efficacy of lurasidone in the treatment of bipolar depression (see below). The results were statistically significant in both dose range groups, although there was no increased benefit in the higher dose range group compared to the lower dose range group. Treatment effects were seen and were statistically significant from week 2 through week 6. The key secondary endpoint was also positive.

Primary Efficacy Results for Monotherapy Study 236 (MADRS Scores)

Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
LATUDA (20-60 mg/day)	30.3 (5.0)	-15.4 (0.83)	-4.6 (-6.9, -2.3) P < 0.001
LATUDA (80-120 mg/day)	30.6 (4.9)	-15.4 (0.83)	-4.6 (-6.9, -2.3) P < 0.001
Placebo	30.5 (5.0)	-10.7 (0.83)	--

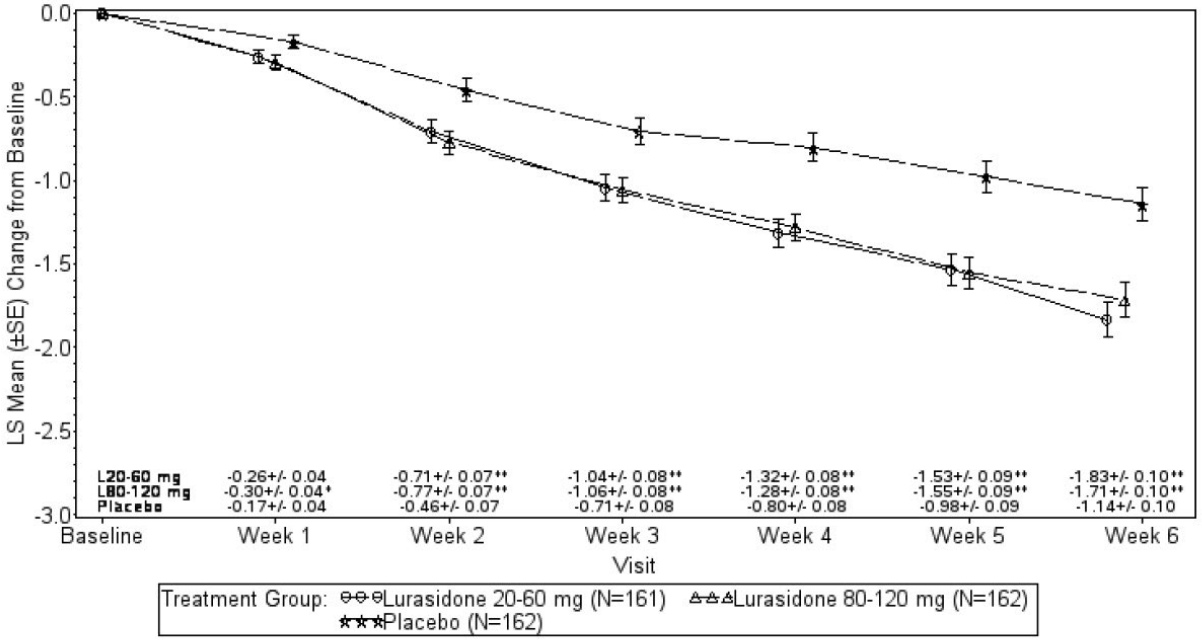
Study 236 (Monotherapy): Change from Baseline (LS Mean ± SE) in Montgomery-Asberg Depression Rating Scale Total Score in Subjects Treated with Lurasidone or Placebo – Repeated Measures (ITT Population)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: L = lurasidone; LS = least square; N = number of subjects summarized; SE = standard error.

A similar pattern can be seen in the key secondary endpoint: Clinical Global Impression Bipolar Version—Severity Scale (CGI_BP_S) and is presented graphically below.

Study 236 (Monotherapy): Change from Baseline (LS Mean ± SE) in Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S) in Subjects Treated with Lurasidone or Placebo (ITT Population)



Note: Display represents model estimate of change from Baseline ± SE.
Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: CGI-BP-S Clinical Global Impression Bipolar version – Severity Scale; L = lurasidone; LS = least square; N = number of subjects summarized; SE = standard error.

Regional Differences

Drs. Ritter and Levin from the clinical team agree that there was a positive efficacy trend in the US population (40% of the enrolled study population) for Study 236, and both agree this was a positive study. Results by US compared to the rest of the world are presented below. Larger treatment and placebo effects were seen in US patients compared to patients outside of the US.

Study 236 (Monotherapy): Efficacy Results by Region: US vs. Non-US

Treatment Group	North America N=195	Rest of the World* N=290
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-13.2 (1.53)	-8.9 (0.96)
Lurasidone 20-60 mg (SE)	-17.1 (1.46)	-14.0 (1.00)
Lurasidone 80-12 0mg (SE)	-15.3 (1.45)	-15.4 (0.99)
Placebo-subtracted Difference at Week 6		
Lurasidone 20-60 mg (SE)	-3.9 (2.11) p=0.068	-5.2 (1.38) p<0.001
Lurasidone 80-120 mg (SE)	-2.1 (2.11) p=0.330	-6.6 (1.37) p<0.001

*includes Europe (Czech Republic, France, Romania, Russia and Ukraine), India, and South Africa

Conclusions from Study 236

This is a positive study for monotherapy use of lurasidone to treat bipolar depression. It should be labeled that doses above 60 mg/day were not shown to confer additional benefit. Statistical differences can be seen as early as week 2. There was a trend toward efficacy in the US subgroup.

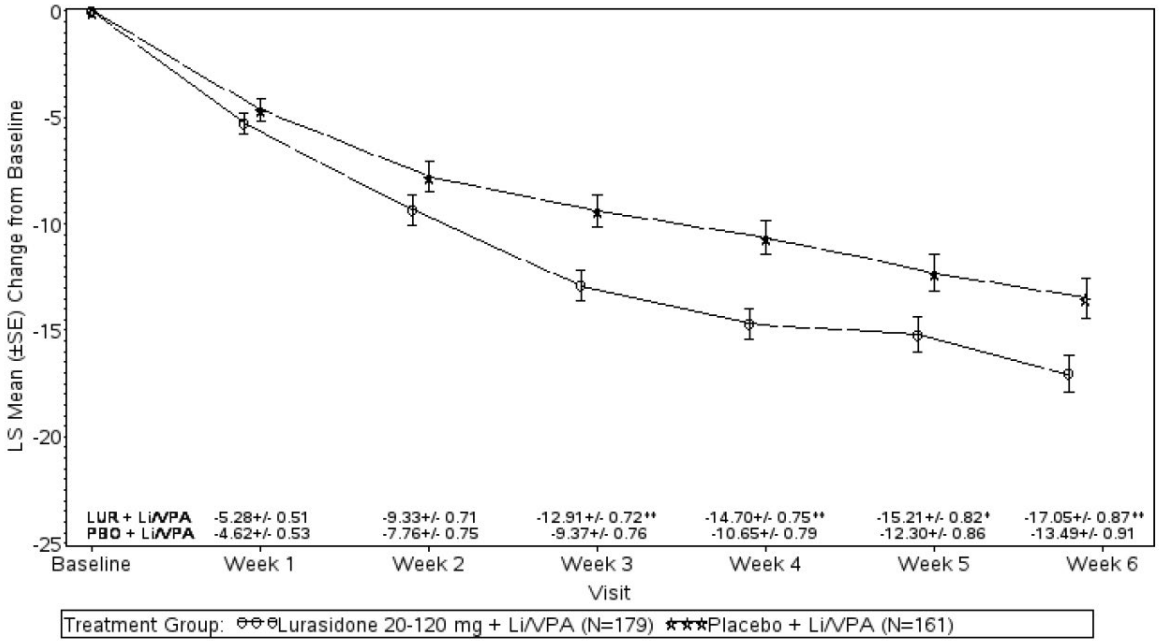
Study 235—Adjunctive use with lithium or valproate

This was an 6-week, randomized, double-blind, multicenter, placebo-controlled, flexible dose (20 mg to 120 mg) safety and efficacy study of lurasidone in the treatment of major depressive episodes in 348 adult patients with bipolar I disorder who were being treated concomitantly with lithium or valproic acid (mood stabilizers). Therapeutic lithium or valproic acid levels were required (patients treated with lithium or valproic acid for at least 28 days) prior to randomization. Thirty two percent of the patients were from US study sites. The primary efficacy endpoint was change from baseline in MADRS total score at six weeks. The key secondary efficacy endpoint was change from baseline to week six on the Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S).

Results

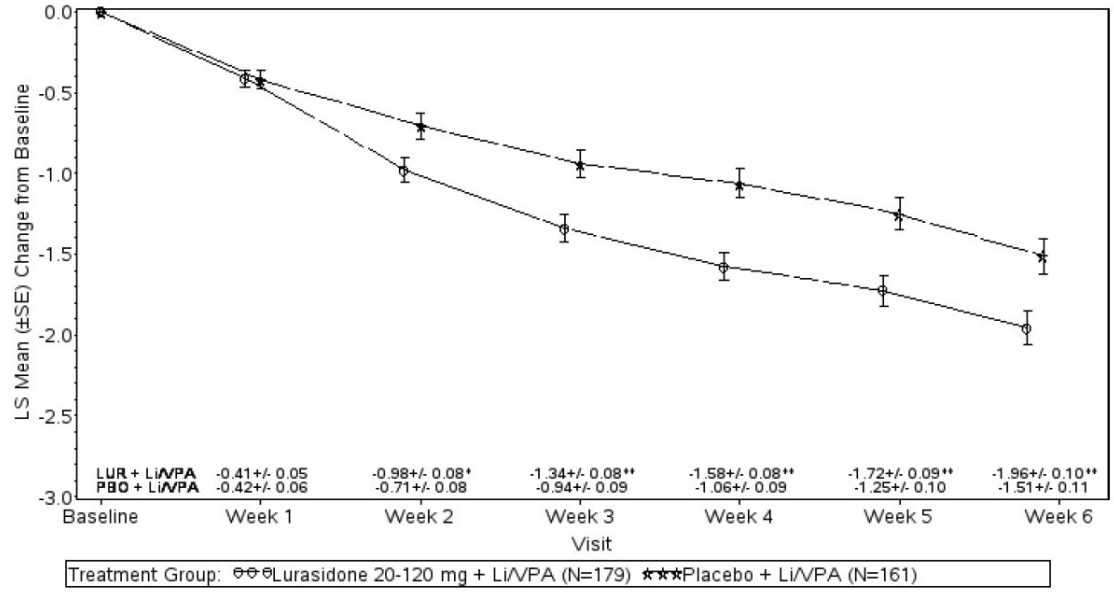
Study 235 demonstrated efficacy of lurasidone in the treatment of bipolar depression when given concomitantly with lithium or valproic acid (see below). The results were statistically significant for the primary and key secondary endpoints. Regional heterogeneity was observed with no treatment effect contributed from US patients. Treatment effect was present overall and was statistically significant from week 3 through week 6. The key secondary endpoint was similarly positive.

Study 235 (Adjunctive Therapy): Change from Baseline (LS Mean ± SE) in Montgomery-Asberg Depression Rating Scale Total Score in Subjects Treated with Lurasidone or Placebo – Repeated Measures (ITT Population)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: LUR = lurasidone; LI – Lithum; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.

Study 235 (Adjunctive Therapy): Change from Baseline (LS Mean ± SE) in Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S) in Subjects Treated with Lurasidone or Placebo (ITT Population)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: LUR = lurasidone; LI – Lithum; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.

Regional Differences

The point estimate of reduction in MADRS total score at endpoint in the US patients in this study was greater (better) for the placebo group compared to the treatment group (see below).

Study 235 (Adjunctive Therapy): MADRS Total Score Change from Baseline to Week 6 by Region (MMRM analysis)

Geographic Region	MADRS total score change from baseline (LS mean ± SE)		Treatment difference to Placebo (LS mean diff ± SE)
	Placebo + Li/VPA	Lur 20 - 120 mg + Li/VPA	
North America (USA)	-13.8 ± 1.70	-12.7 ± 1.66	1.1 ± 2.38
Rest of the World	-13.3 ± 1.03	-19.1 ± 0.98	-5.8 ± 1.41

Dr. Ritter, the primary clinical reviewer, was influenced in his decision to recommend a Complete Response (CR) action because the US subgroup in this study did not have an independent signal of efficacy, although he agreed that the study was positive overall on its preplanned endpoints. Dr. Levin, who has written two memos for this application, recommends in his second memo that the application be approved secondary to his agreement with Dr. Birkner's (Statistical Reviewer) view that unplanned subgroup analyses should not change our interpretation of efficacy results. I agree with Drs. Levin and Birkner and believe that regional subgroup differences are related to the study not (by design) being powered to show a regional difference, wide variance within the US population studied, and the study population not being stratified by region.

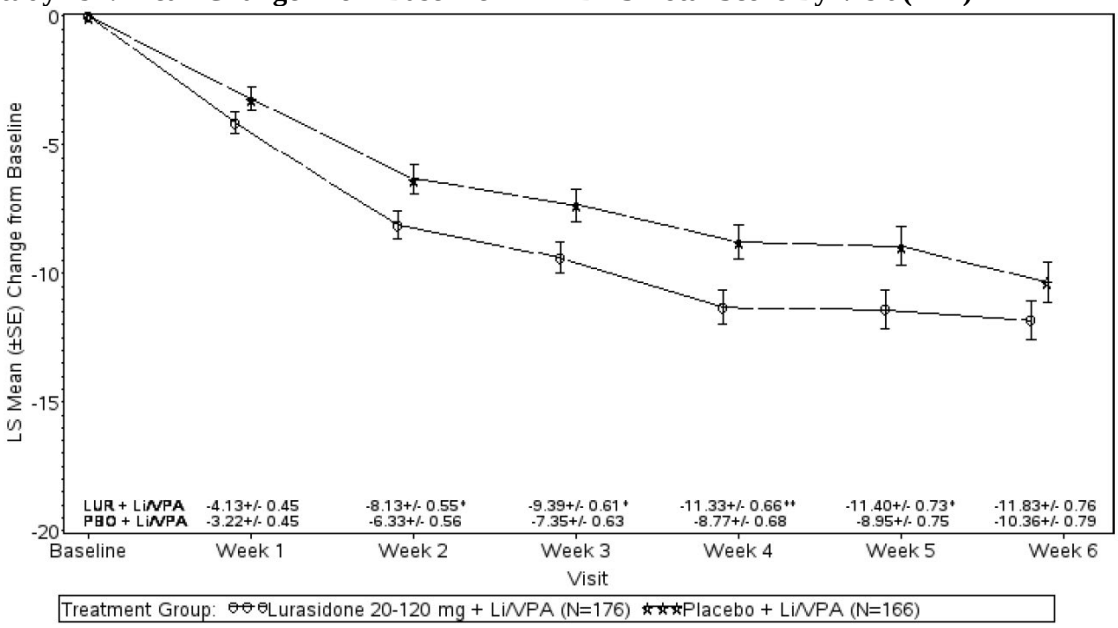
Conclusions from Study 235

This is a positive study. The point estimate in the US population should not be interpreted as evidence that the drug does not work for bipolar depression in the US, but rather should be interpreted in light of the large standard error for the treatment difference in the US patients. Looked at in this light, it is more accurate to interpret these results as the treatment effect is not distinguishable from placebo in the US subpopulation, but the study remains positive overall.

Study 292—Adjunct to lithium or valproate (supportive evidence of efficacy)

This study was designed similarly to study 235 and while it was negative overall at endpoint (week 6), there was a positive numerical trend toward efficacy in the North American subgroup and in the overall group at week 5. The US contributed 39% of the ITT population in this study. Our exploratory analysis confirmed the study to be positive overall from week 2 through week 5 (see below).

Study 292: Mean Change From Baseline in MADRS Total Score By Visit (ITT)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: LUR = lurasidone; LI = Lithium; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.

Regional Differences

Mean change differences were seen in this study as well, with North America having a slightly larger treatment effect compared to the rest of the world at endpoint (see below).

Study 292: Mean Change from Baseline MADRS Total Score at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America* N=151 (80L,71 P)	Rest of the World** N=191 (96L,95P)
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-8.7 (1.24)	-11.4(0.99)
Lurasidone 20-120mg (SE)	-10.4(1.19)	-12.9(0.97)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-120mg (SE)	-1.7(1.71) p=0.320	-1.5(1.35) p=0.282

*includes USA and Canada

Conclusions from Study 292

This is a negative study at 6 weeks. It is valuable in overall interpretation of efficacy results because there is a trend toward efficacy seen in North America (39% of ITT population were US patients), which was a concern of the review team when interpreting Study 236 that had a similar design and had no trend toward efficacy in the US.

Overall Conclusions for Efficacy

I believe it can be concluded that the sponsor has presented two positive trials to support efficacy in bipolar depression. There is regional heterogeneity seen between the US sites and the rest of the world, but these differences are not consistently seen across the studies and should be ascribed to

lack of power to detect regional differences and lack of randomization based upon region rather than lack of efficacy.

Safety
Safety was analyzed from the controlled trials and Study 256 which was a 24-week open-label extension study. Drs. Ritter and Levin agree that no new or unexpected safety findings were identified in this development program and that the labeling provides the proper information for safe use, and I agree with them. No deaths were reported and the safety profiles from the new studies were consistent with what is known and labeled for Latuda.

Inspections
Four domestic trial sites and two overseas sites were inspected and no data integrity issues or major violations were identified by OSI and their recommendation is to consider the data reliable.

Revised Labeling
Labeling (including a new Medication Guide) has been negotiated to current Division and OPDP standards and agreement has been reached with the sponsor. The new indication has been added and the safety sections for suicidal ideation and behavior and activation of mania with antidepressants (Boxed Warning and Warnings and Precautions and Medication Guide) have been included. New safety data from the submitted trials have been incorporated in labeling, we have negotiated these changes with the sponsor and we have final, agreed upon labeling and Medication Guide to include in the approval letter.

There was some discussion among team members about adding information to labeling to inform clinicians that Study 235 did not demonstrate a difference from placebo in the US subpopulation, yet all agreed that this should not be communicated in a way that could be interpreted by clinicians to mean there was a lack of efficacy in US patients. I believe that including this language in labeling, while perhaps informative, does not add useful information to labeling, but rather confuses the issue and could have negative practical implications for patients prescribed the drug in the US. As discussed above, I, the CDTL, and Statistics all agree that the lack of an efficacy finding in a subpopulation in one of three multiregional studies is more likely related to a lack of power to detect regional subgroup differences and lack of stratification by region than it is to lack of efficacy. While several options for including this information in labeling have been discussed with my team and with the sponsor, I think this is not the prudent course of action for the reasons described and have decided not to include this language in labeling.

Postmarketing Requirements/Commitments
We have requested, and the sponsor has agreed to conduct a controlled trial in the treatment of pediatric (10-17 years old) bipolar depression. We also requested long-term safety data in pediatric patients. In addition, the sponsor is currently conducting our usual maintenance study for adults with bipolar depression. The endpoint of interest in this study will be relapse to any mood episode (mania or depression).

Conclusions and Recommendations
The sponsor has submitted two adequate and controlled clinical trials that demonstrate efficacy of lurasidone in the treatment of bipolar depression. Efficacy is seen both as monotherapy and as adjunctive therapy to lithium or valproate.

The labeling and Medication Guide has been negotiated to current Division standards.

The sponsor has agreed to labeling and the postmarketing requirements/commitments and this application should be approved by the PDUFA date.

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/s/

MITCHELL V Mathis
06/28/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

CROSS DISCIPLINE TEAM LEADER REVIEW

200603 CDTL Addendum - OSI Inspection Findings and Conclusions

John Lee, M.D. from the Office of Scientific Investigations has filed a second review. In this review, he discusses the findings from two of the European sites that participated in monotherapy study 236 and adjunctive therapy study 235. He also summarized his previous findings from the four US sites that were inspected. There were no significant findings from the 4 US sites: Rosario Hidalgo, M.D., Raymond Manning, M.D., Howard Hassman, M.D., and David Walling, M.D. All four investigators participated in monotherapy 236 and adjunctive therapy study 235. Dr. Lee concluded that the data from all 4 sites were reliable, and they supported the applications.

The Division requested additional inspections of non-US sites for several reasons. In studies 235 and 236, there were significant regional differences in the mean treatment effects (point estimates of the mean change in MADRS score). The treatment effects were largest in Europe. It appeared that the positive overall results of the studies were largely driven by the efficacy results from Europe. We requested inspections of 2 particular European sites (191 in Russia and 618 in the Czech Republic), because they had relatively large, outlier treatment effects; and they were relatively high-enrolling sites participating in both studies. In addition, at Site 191 in Study 236, there appeared to be an atypical pattern of treatment responses; the lurasidone and placebo group each had a homogeneous pattern of changes in MADRS scores among subjects within the site. This atypical pattern did not occur at Site 191 in adjunctive therapy Study 235.

Findings at Site 191:

Vladimir Tochilov, M.D. was the principal investigator at Site 191 in Russia. There were 22 subjects enrolled in Study 236, and there were 13 subjects enrolled in Study 235. The OSI inspection focused on the potential for unblinded study conduct and biased data collection. The items inspected included: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, adverse event monitoring and reporting, and adherence to the study protocol and applicable GCP regulations. The inspector verified the following types of data: primary and secondary endpoints, adverse events, subject randomization, protocol deviations, and subject discontinuations. The inspector conducted a detailed review of records for all subjects enrolled at the site.

OSI concluded that there were no significant deficiencies at the site. There was no evidence of unblinded study conduct or biased assessments of endpoints. All assessments were performed by apparently adequately trained and qualified study personnel. The inspector verified all data. The inspector did not observe underreporting of adverse events. Drug accountability was well documented, and there was adequate study monitoring and IRB oversight. OSI concluded that the data from the Site 191 are reliable and support the application.

Findings at Site 618:

Michaela Klabusayova, M.D. was the principal investigator at Site 618 in the Czech Republic. There were 17 subjects enrolled in Study 236, and there were 17 subjects enrolled in Study 235. There were also 4 subjects enrolled in adjunctive therapy study 292. The OSI inspection assessed the identical types of data and factors as those assessed at Site 191. There were no significant inspection findings. There was no evidence of unblinded study conduct or biased assessment of efficacy or safety data. All assessments were performed by apparently adequately trained and qualified study personnel. The inspector verified all data. The inspector did not observe underreporting of adverse events. Drug accountability was well documented, and there was adequate study monitoring and IRB oversight. The OSI reviewer concluded that the data from Site 618 are reliable and support the application.

In summary, Dr. Lee has concluded that there were no significant findings from the inspections at any of the inspected sites (4 in the US and 2 in Europe). There was no evidence of unblinded study conduct, biased assessment or biased data collection, or significant GCP deficiencies at any of the sites in all studies. The data from all sites appear to be reliable.

I agree with Dr. Lee's conclusions. The data from the two European sites are reliable, and they support the application.

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/s/

ROBERT L LEVIN
06/27/2013

200603 Addendum to Cross-Discipline Team Leader Review Memo

NDA:	200603 Supplements 10 and 11
Sponsor:	Sunovion
Drug:	Lurasidone (Latuda)
Formulation:	Oral Tablet (20 mg, 40 mg, 80 mg, 120 mg)
Indications:	Depressive Episodes associated with Bipolar I Disorder (1) Monotherapy and 2) Concomitant Therapy with Lithium or Valproate)
Date of submission:	August 31, 2012
Date of review:	June, 20 2013
Recommendation:	Approval

1. Introduction

I recommend approval of these supplemental NDAs for lurasidone in the treatment of depressive episodes associated with bipolar I disorder. This is the second cross-discipline team leader review memo that I have filed regarding NDA 200603 Supplements 10 and 11. The first review was filed on June 8, 2013. In the first review, I had recommended a complete response action, based on differential regional efficacy findings (US vs. Non-US). Monotherapy Study 236 and concomitant therapy (with lithium or valproate) Study 235 were positive studies. However, the mean lurasidone treatment effects were smaller in the US subgroups, compared to the Non-US subgroups. In Study 235, the point estimates of the mean change in MADRS scores suggested that in the US subgroup, the lurasidone treatment effect was smaller than in the treatment effect in the placebo group.

In this review, I will discuss in more detail the statistical and clinical considerations regarding the regional efficacy trends. This will include a discussion of Thomas Birkner's (statistical reviewer) findings from his review of the concomitant therapy studies 235 and 292 (filed on May 30, 2013). I have reconsidered the issues, and I recommend approval of the application.

2. Reasons for Recommending Approval

I recommend approval of the application for several reasons.

1. There are Two Positive Lurasidone Studies in Bipolar Depression

The sponsor demonstrated the efficacy of lurasidone in bipolar depression in two adequate and well controlled studies. These included monotherapy study 236 and concomitant therapy study 235. Both studies demonstrated that the lurasidone treatment effect was statistically significant as assessed by the primary endpoint: the mean change from baseline to Week 6 on the MADRS in the overall study population (US and non-US subgroups combined). The Agency has not required the sponsor to formally demonstrate that the efficacy results are statistically significant in the US subgroup. The Agency has not required the sponsor to collect the majority of efficacy data from the US.

Dr. Birkner notes that the primary efficacy analysis in Study 235 assessed the change from baseline in MADRS total score at the end of Week 6, using an MMRM model with restricted maximum likelihood estimation under the assumption of an unstructured covariance matrix for within-subject correlation. The analysis evaluated the mean change in MADRS scores as well as the difference in patterns of change between treatment groups. The model included factors for treatment, pooled center, visit (as a categorical variable), stratification variable (lithium or divalproex), baseline MADRS score, and treatment-by-visit interaction. An exploratory analysis was also conducted by geographic region (the US versus the Non-US populations). All treatment groups were included in the MMRM models.

In the primary analysis for the overall study population, the decrease in the MADRS total score from baseline to Week 6 was -17.1 (SE = 0.87) for the lurasidone group and -13.5 (SE = 0.91) for the placebo group, resulting in a statistically significant difference of -3.6 (SE = 1.25) with $p = 0.005$. The treatment difference between the lurasidone and placebo groups was statistically significant at nominal alpha = 0.05 beginning at week 3 through the end of the study.

2. One Cannot Make Formal Statistical Conclusions about the US Subgroup

One cannot conclude that studies 235 and 236 were not positive in the US subgroups. The point estimates of the treatment effects (mean changes in MADRS scores) suggest that the effects were lower in the US than Non-US regions; and they suggest that the lurasidone treatment effect in Study 235 was lower than the placebo effect. However, there are several statistical issues that prevent one from making the formal statistical conclusion that lurasidone was not effective in the US subgroup; there is not enough information from the US subgroups to draw formal statistical conclusions. The studies were not powered to detect a statistically significant difference in the US subgroups. In Study 236, the US subgroup accounted for only 40% of the total sample size. In Study 235, the US subgroup accounted for only 32% of the sample size. In addition, one

cannot be certain that all of the observed and unobserved covariates are balanced between the lurasidone and placebo groups in any of the geographical subgroups, because randomization was not stratified by country or region. Also, no multiplicity adjustment was used in the numerous subgroup analyses. In summary, the geographic subgroup analyses were exploratory. It is possible that the results of these analyses would not be confirmed in a trial that was designed to include only patients from countries or regions in which there were favorable subgroup efficacy results in a previous trial.

Dr. Birkner discussed the regional subgroup efficacy analysis. Study 235 was conducted in 10 countries: US, Czech Republic, France, Germany, India, Poland, Romania, Russia, South Africa, and Ukraine. Approximately 32% of the study population was from the US. Table 1 below presents the geographic subgroup analysis (US and Non-US).

MADRS Total Score Change from Baseline to Week 6 by Region (MMRM analysis)

Geographic Region	**(LS mean ± SE)**		**Treatment difference from Placebo (LS mean diff ± SE)**
	Placebo + Li/VPA	**LUR 20 to 120 mg + Li/VPA**	
North America (USA)	-13.8 ± 1.70	-12.7 ± 1.66	1.1 ± 2.38
Rest of the World	-13.3 ± 1.03	-19.1 ± 0.98	-5.8 ± 1.41

(Source: Study report p. 99)

Dr. Birkner notes that the point estimate of the reduction in MADRS total score at week 6 in the US is greater for the placebo group compared to the lurasidone group (-13.8 vs. -12.7). However, he notes that there is a large standard error for the treatment difference in the US, implying that the treatments are indistinguishable in a statistical sense. For the Rest of the World there appears to be a clear treatment benefit when considering the MADRS score (Placebo -13.3; Drug -19.1).

3. Supportive Results from Concomitant Therapy Study 292

Although concomitant therapy study 292 did not demonstrate efficacy for the primary analysis at Week 6, the results demonstrate that there was a positive numerical trend toward efficacy in the US subgroup as well as in the overall study population (US plus non-US). In addition, an exploratory analysis suggests that the overall results were positive from weeks 2 through 5. There was not a significant difference in regional efficacy results between the US and non-US

subgroups. Furthermore, in Study 292, the US subgroup accounted for a larger proportion (45%) of the total sample size, compared to Study 235 (35%).

4. There Were No Clearly Significant Differences Between US and Non-US Subjects

The Division requested that the sponsor conduct additional analyses to explore potential reasons for the differential regional efficacy findings. The sponsor conducted analyses on the following factors: sample size, age, gender, body weight, ethnicity, baseline severity of illness, placebo response, discontinuation patterns, dose, and lurasidone exposure.

The sponsor noted that the US subgroup accounted for only 32% of the study population in Study 235. The Division and the sponsor agree that there was probably insufficient power within the US database to detect a statistically significant treatment effect. The Division and the sponsor also agree that within the US dataset, there was a wide confidence interval, making it difficult to interpret the data and draw formal statistical conclusions. The sponsor also noted that in the similarly designed concomitant therapy study 292, the US subgroup accounted for a greater proportion (45%) of the total sample size than Study 235 (32%); and in Study 292, there was a trend towards efficacy in the US subgroup that was similar to the trend in the non-US subgroup.

There were some regional differences in age; the mean age was 44.5 years in the US and 40.4 in the non-US subgroup. There were some regional differences in duration of bipolar disease and presence of rapid cycling bipolar disorder. The average duration of bipolar disorder was longer in the US (17.1 years) compared to non-US (11.1 years). The average duration of the index depressive episode was longer in the US (14.7 weeks) compared to 11.1 weeks in non-US. In the US subgroup, a greater proportion had rapid cycling bipolar disorder (8%) than in non-US subjects (1%). The mean daily dose in the US (70 mg) was slightly higher than in the non-US regions (64.6 mg). The mean baseline body weight was 85.9 kg for the US subgroup and 73.3 kg for the non-US subgroup.

Dr. Ritter, Dr. Birkner, and I agree with the sponsor that none of the investigated factors seems to have an obvious role in explaining the regional differences in efficacy between the US and non-US subgroups. There is no clear explanation of the regional findings, based on these factors. At this point, the Division and the sponsor have not identified differences between US and non-US patients that would clearly explain the differences in regional findings.

Dr. Ritter has discussed the possibility that the differences between the US and non-US study populations in baseline disease characteristics, demographic features, and history of psychiatric disease including bipolar disorder and co-morbid psychiatric disorders could explain the differential regional effects. In my opinion, the differences in these parameters between the US and non-US regions were modest and unlikely to explain the differential regional findings completely.

5. Applicability of Overall Efficacy Results to US Patients

Dr. Ritter has discussed the possibility that cultural and socioeconomic differences, as well as unexplored or unknown intrinsic and extrinsic factors, could have contributed to the differential regional efficacy results. Dr. Ritter stated that in his opinion, factors such as socio-cultural and geographical variations in psychopathology, epidemiology, diagnosis, clinical psychiatric presentations, and the presence of concomitant illnesses can be significantly different between US and non-US psychiatric patients. Theoretically, such factors could contribute to differences in regional efficacy findings; however, with the available data, it is difficult to directly assess these possibilities.

Dr. Ritter concluded that the non-US efficacy findings from Study 235 are not entirely applicable to the US population of patients with bipolar depression. He stated that the positive efficacy findings in the non-US subgroup are not adequate for supporting the indication for patients in the US. Dr. Ritter concluded that the sponsor has not demonstrated the efficacy of lurasidone "for the conditions of use." He interprets the "conditions of use" as "the use of the drug in the United States," i.e., for the treatment of US patients with bipolar depression.

In my opinion, there is not adequate evidence to conclude that lurasidone was not effective in US patients. One cannot make such a formal conclusion based on the exploratory subgroup analyses. There is not clear evidence that the positive overall efficacy results would not be applicable or generalizable to patients in the US. In my opinion, the analyses of factors to explain the regional differences did not demonstrate significant differences between regions that could explain the differential regional efficacy results. As Dr. Ritter and the sponsor note, it is theoretically possible that there are unexplored, unknown, or unidentified intrinsic or extrinsic differences between the US and non-US populations that could explain the regional findings. However, it is difficult to test these hypotheses.

3. Conclusions and Recommendations

I recommend approval of the supplemental NDAs 200603-S-010 and 2006030-S-011 for lurasidone in the treatment of bipolar depression as monotherapy and as concomitant therapy with lithium or valproate, respectively. The sponsor has demonstrated the efficacy of lurasidone in one monotherapy study (236) and one concomitant therapy study (235).

I recommend that the Division require that the sponsor conduct the following postmarketing studies as postmarketing commitments:

1. Pediatric Studies under PREA

   The sponsor will be required to conduct a short-term, randomized, double-blind, placebo-controlled, efficacy and safety study of lurasidone in pediatric patients (ages 10 to 17) with

bipolar I disorder, current depressive episode. In addition, the sponsor will be required to conduct a long-term, open-label, safety study of lurasidone in pediatric patients (10 to 17 years) with bipolar depression. The Division agrees with the sponsor's proposed pediatric plan, and we conveyed this to PeRC. PeRC agreed with the pediatric plan.

The sponsor is currently conducting a pediatric pharmacokinetic, safety, and tolerability study in response to a Written Request (issued on April 20, 2012) for studies in pediatric patients with schizophrenia and in pediatric patients with autism. Study D1050300 is an ongoing phase 1, open-label, single- and multiple- ascending dose study of lurasidone in pediatric patients (6 to 12 years) with schizophrenia, bipolar disorder, or autism spectrum disorders. The dose range of lurasidone is 20 mg/day to 160 mg/day in this study. The sponsor is conducting appropriate safety and pharmacokinetic assessments.

The Agency has granted a waiver for conducting studies in bipolar depression in pediatric patients younger than 10 years old. It is extremely difficult to make a diagnosis of bipolar disorder in children younger than 10 years. The symptoms and behavioral features of bipolar disorder have significant overlap with other diagnoses including schizophrenia, unipolar depression, anxiety disorders, ADHD, and other psychiatric disorders. Thus, studies in children younger than 10 years would be highly impractical.

2. Thorough QT Study

I recommend that the Division consider requiring the sponsor to conduct an adequately designed thorough QT study. Lurasidone has a signal for QT interval prolongation. For the original NDA, the sponsor conducted a non-thorough QT study that the Cardiorenal QT Interdisciplinary Review Team (QT IRT) determined was inadequately designed and did not adequately characterize the potential for lurasidone to prolong the QT interval. The study did not include a placebo group, and it did not include moxifloxacin as an active comparator; although, it did include ziprasidone as an active comparator. The QT IRT concluded that there were additional important problems with the design that limited the ability to adequately assess the risk and interpret the data.

The QT IRT determined that the QT study results were inconclusive for a number of reasons. The primary endpoint was inadequately defined. The QT study used time-matched mean changes from baseline in QTcI (i.e., ΔQTcI) as the primary endpoint. This primary variable is inappropriate because it does not account for between-day shifting for ECG signals, which can be pronounced with an 11-day difference between the observation day and baseline day. A time-matched, baseline-corrected, and placebo-adjusted QTc (ΔΔQTc) should be used as the primary variable in a parallel thorough QT study. However, this variable cannot be derived from the current trial because of the absence of the placebo arm. In addition, assay sensitivity was not established in the QT study. The QT study used ziprasidone as active control. There are

limitations in using ziprasidone as the control. The results were described by using ΔQTc rather than ΔΔQTc. At the tested dose level, the QTc interval change appears to be larger than the small changes defined by ICH E14 guidance.

Despite the inadequacies of the QT study design, the study demonstrated that there was a signal for QT prolongation. In fact, the sponsor has included cautionary language in labeling about using lurasidone concomitantly with other drugs that prolong the QT interval. However, the lurasidone label does not currently include a warning for QT interval prolongation. It would be important to have adequate data from an acceptably designed thorough QT data, in order to adequately assess and quantify the risk of QT prolongation with lurasidone. If there is a significant QT effect, it would be important to include a QT warning in labeling to inform clinicians about the risk and mitigation strategies.

3. Maintenance Study

I recommend that the Division consider requiring that the sponsor conduct a placebo-controlled, randomized withdrawal, maintenance study in patients with bipolar disorder. There would be two possible types of studies: 1) a maintenance study in stabilized patients with a recent depressive episode, specifically designed to assess time to relapse of depressive episodes only; or 2) a study in stabilized bipolar patients to assess the time to relapse of any affective episode (depression or mania). I would recommend a maintenance study assessing relapse of any episode (depressive or manic episode), because (1) antidepressant treatment can increase the risk of developing manic episodes and (2) ideally a maintenance treatment for bipolar disorder would prevent the risk of relapse of all types of affective episodes.

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/s/

ROBERT L LEVIN
06/20/2013

200603 Cross-Discipline Team Leader Review Memo

NDA:	200603 Supplements 10 and 11
Sponsor:	Sunovion
Drug:	Lurasidone (Latuda)
Formulation:	Oral Tablet (20 mg, 40 mg, 80 mg, 120 mg)
Indications:	Depressive Episodes associated with Bipolar I Disorder (Monotherapy and Adjunctive Therapy with Lithium or Valproate)
Date of submission:	August 31, 2012
Date of review:	June 8, 2013
Recommendation:	Complete Response

1. Introduction and Background

Lurasidone (Latuda) is an atypical antipsychotic indicated for the treatment of schizophrenia. Lurasidone was approved for the treatment of schizophrenia on October 28, 2010. Lurasidone has high affinities for dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7 receptors, moderate affinity for serotonin 5-HT_{1A} and noradrenaline α_{2C} and α_{2A} receptors, and little or no affinity for histamine H_1 and muscarinic M_1 receptors. This receptor binding profile and data from animal models of depression provided support for the evaluation of lurasidone for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

Regulatory History:

Sunovion performed a post-hoc analysis of data from a lurasidone schizophrenia study (D1050196). The analysis demonstrated a significant decrease in depressive symptoms as measured by the Montgomery Asberg Depression Rating Scale. As a result, the sponsor decided to conduct a clinical program in patients with bipolar depression. Sunovion requested a pre-IND meeting with the Division on June 19, 2008 to discuss the proposed development plan for bipolar depression. The meeting request was denied; however the Division provided written feedback about the planned IND on October 14, 2008. The Division considered the proposed clinical program and study designs acceptable. Sunovion submitted IND 103,427 (on 17 December 2008) for the investigational use of lurasidone in the treatment of subjects with bipolar depression. Following completion of two adequate and well-controlled studies, Sunovion

requested a Pre-sNDA meeting (on April 12, 2012) to obtain FDA guidance and concurrence regarding the submission of a supplemental NDA for lurasidone as monotherapy and as adjunctive therapy with lithium or valproate in patients with bipolar depression. The Division provided written comments on May 24, 2012, and the meeting was canceled by Sunovion. The sponsor submitted two supplemental sNDAs under NDA 200603 (S-10 and S-11) to support a new indication for lurasidone in the treatment of depressive episodes associated with bipolar I disorder (as both monotherapy and as adjunctive therapy to lithium or valproate). Studies D1050235 and D1050236 were randomized, double-blind, placebo-controlled, 6-week studies performed in patients with bipolar depression. In Study D1050236 lurasidone was administered as monotherapy; in D1050235 lurasidone was administered adjunctively with lithium or valproate.

Conclusions and Recommendations:
Disciplines: Clinical, Statistics, Office of Scientific Investigation. I agree with their findings and conclusions. There were no new chemistry/manufacturing/control data, pharmacology/toxicology data, or clinical pharmacology data to review for the submission. I recommend a complete response action, because each of the three studies did not demonstrate efficacy in the U.S.

2. Clinical Review

Mark Ritter, M.D. performed the clinical review. Dr. Ritter recommends that the Division take a Complete Response action, primarily because none of three studies demonstrated efficacy in the US. The overall findings of monotherapy study 236 were positive; however, the results were not statistically significant in the US (although there was a trend towards efficacy in the US. In Study 236, the results were also negative in Asia (India) and Africa (South Africa). The results of Study 236 were positive only in Europe. Adjunctive study 235 was positive overall. However, in the US, not only were the results negative, the lurasidone treatment effect was worse than placebo. In Study 235, the results were positively only in Europe. Finally, adjunctive study 292 was negative overall and in each region. I agree with Dr. Ritter's conclusions and recommendation for the Division to take a Complete Response action.

The sponsor conducted 3 placebo-controlled studies in patients with bipolar depression: 1) monotherapy study D1050236, 2) adjunctive therapy study (with lithium or valproate) D1050235, and 3) adjunctive therapy study (with lithium or valproate) D1050292. In the initial sNDA submissions, the sponsor only submitted the data for studies 235 and 236. During the review cycle, the sponsor informed the Division that they had completed a second adjunctive treatment study (292). This study did not demonstrate the efficacy of lurasidone in bipolar depression. The Division requested that the sponsor submit all of the efficacy and safety data for Study 292.

2.1 Designs of the Studies

Study 236 was a phase 3, six-week, outpatient, multicenter, randomized, double-blind, placebo-controlled, monotherapy study of two fixed-flexible-dose ranges of lurasidone in the treatment of major depressive episodes in 505 adult subjects (ages 18 to 75 years) with bipolar I disorder (per DSM-IV-TR criteria), with or without rapid cycling and without psychotic symptoms. The duration of the depressive episode must have been at least 4 weeks but less than one year. The baseline Montgomery Asberg Depression Rating Scale (MADRS) score must have been $\geq$ 20. The baseline Young Mania Rating Scale (YMRS) score must have been less than 12. The dose ranges of lurasidone were 1) 20 mg to 60 mg per day, and 2) 80 mg to 120 mg per day. The primary efficacy measure was the MADRS. The primary statistical analysis was the change in MADRS score at the end of Week 6, employing an MMRM model. Primary Analysis: The key secondary endpoint was the change from baseline on the Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP) score.

Study 236 was conducted in the US (40%), Europe (33%), India (15%), and South Africa (11%). The Czech Republic accounted for 11% of subjects, followed by Ukraine (10%), Russia (6%), Romania (3%), and France 3%). There were 24 sites in the US, 4 sites in the Czech Republic, one site in France, 9 sites in India, 4 sites in Romania, 4 sites in Russia, 4 sites in South Africa, and 5 sites in the Ukraine. The study began on 29 April 2009 and ended on 01 February 2012.

Study 235 was a phase 3, six-week, outpatient, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study of lurasidone (20 mg to 120 mg) in the treatment of major depressive episodes in 348 adult subjects (ages 18 to 75) with bipolar I disorder (with or without rapid cycling) who were treated concomitantly with lithium or valproate. Subjects must have been treated with stable doses of lithium or valproate for at least 28 days before the baseline visit of the study. In addition, subjects must have had therapeutic serum levels of lithium (0.6 to 1.2 mEq/L) or valproic acid (50-125 mcg/mL). The duration of the depressive episode must have been at least 4 weeks but less than one year. The baseline MADRS score must have been $\geq$ 20. The baseline YMRS score must have been less than 12.

Study 235 was conducted in the US (32%), Europe (39%), India (15%), and South Africa (5%) in a total of 10 countries. The European countries included the Czech Republic (14%), Ukraine (7%), Russia (6%), France (5%), Poland (4%), Germany (2%), and Romania (1%). The study began on 11 May 2009 and ended on 09 January 2012.

Study 292 essentially had the same design as study 235. There were two differences. If subjects had not been treated with lithium or valproate upon screening, they could have been started on lithium or valproate after the screening period. As in Study 235, they must have been on stable doses and with therapeutic levels for at least 28 days before the baseline visit. Study 292 included subjects from South America instead of South Africa.

Study 292 was conducted in the North America (45%) [US and Canada], Europe (30%), India (15%), South America (10%) [Colombia and Peru], and Japan in a total of 10 countries. The European countries included: Czech Republic, Lithuania, Slovakia, and Ukraine. The study began on 13 December 2010 and ended on 07 August 2012.

Study 256 was a 24-week, multicenter, open-label extension study of lurasidone in 504 subjects with bipolar depression. All subjects had completed study 235 or 236. Patients in the placebo group in the controlled studies were treated with lurasidone in Study 256.

2.2 Sponsor's Efficacy Findings

2.2.1 Monotherapy Study 236

Study 236 demonstrated the efficacy of lurasidone in the treatment of bipolar depression. The results were statistically significant for both dose groups: 20 mg to 60 mg per day and 80 mg to 120 mg per day. There was no increased benefit in the high dose group compared to the low dose group; the placebo-subtracted treatment effect was identical in the two groups (-4.6 points on the MADRS). The treatment effects were statistically significant from the end of Week 2 through the end of Week 6.

Table 1 Primary Efficacy Results for Monotherapy Study 236 (MADR Scores)

Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
LATUDA (20-60 mg/day)*	30.3 (5.0)	-15.4 (0.83)	-4.6 (-6.9, -2.3) P < 0.001
LATUDA (80-120 mg/day)*	30.6 (4.9)	-15.4 (0.83)	-4.6 (-6.9, -2.3) P < 0.001
Placebo	30.5 (5.0)	-10.7 (0.83)	--

Regional Efficacy Effects in Study 236:

In the US, the treatment effects in both groups were not statistically significant. [Is this correct?]. In the US, the raw treatment effect in the low-dose group (-17.1) was larger than the effect in the non-US regions (-14). For the high-dose group, the effects were nearly identical (-15.3 and -15.4, respectively). The most striking differences between the US and non-US regions was that the placebo effect was larger in the US (-13.2, compared to -8.9 in the non-US regions. Although the overall study results were positive and there was a trend for an effect in the US, the treatment effects in the US for both dose groups were not statistically significant (p=0.068 and p=0.33).

Table 2 Efficacy Results by Region: US vs. Non-US

Treatment Group	North America N=195	Rest of the World* N=290
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-13.2 (1.53)	-8.9 (0.96)
Lurasidone 20-60 mg (SE)	-17.1 (1.46)	-14.0 (1.00)
Lurasidone 80-12 0mg (SE)	-15.3 (1.45)	-15.4 (0.99)
Placebo-subtracted Difference at Week 6		
Lurasidone 20-60 mg (SE)	-3.9 (2.11) p=0.068	-5.2 (1.38) p<0.001
Lurasidone 80-120 mg (SE)	-2.1 (2.11) p=0.330	-6.6 (1.37) p<0.001

*includes Europe (Czech Republic, France, Romania, Russia and Ukraine), India, and South Africa

Results of a regional efficacy analysis excluding the US indicate that the positive results of Study 236 are driven by the statistically significant treatment effect in Europe. The results were not statistically significant in India or South Africa. Refer to the table below.

Table 3 Efficacy Results by Non-US Regions in Study 236

Treatment Group	Africa N=54	Asia N=73	Europe* N=163
Mean Change from Baseline MADRS at Week 6			
Placebo (SE)	-12.9 (1.60)	-12.6 (2.47)	-6.3 (1.25)
Lurasidone 20-60mg (SE)	-12.6 (1.60)	-16.2 (2.49)	-14.1 (1.33)
Lurasidone 80-120mg (SE)	-13.7 (1.70)	-15.4 (2.32)	-16.4 (1.32)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-60mg (SE)	0.4 (2.26) p=0.862	-3.6 (3.49) p=0.311	-7.8 (1.82) P<0.001
Lurasidone 80-120mg (SE)	-0.8 (2.33) p=0.749	-2.8 (3.40) p=0.418	-10.1 (1.82) P<0.001

*includes Czech Republic, France, Romania, Russia, and Ukraine

Sponsor's Discussion of the Regional Differences in Efficacy Results (Study 236):

The Division requested that the sponsor explore potential reasons for the differential regional effects. As Dr. Ritter noted, the sponsor conducted various analyses but concluded that there was no clear explanation for the findings. The sponsor explored various factors such as demographics (age, gender, body weight, ethnicity, baseline severity of illness and psychiatric history, discontinuation patterns, and doses. The sponsor concluded that differential discontinuation patterns between US and non-US subjects and in the two dose groups in the US could possible explain the findings that within the US, there was a larger treatment effect for the lower dose compared to the higher dose. However, the Division and the sponsor agree that there is no clear explanation for the differential findings.

2.2.2 Adjunctive Therapy Study 235

Overall Primary Efficacy Results: Study 235 demonstrated that for the overall study population, lurasidone demonstrated efficacy in the treatment of bipolar depression in patients treated concomitantly with lithium or valproate. The mean placebo-subtracted difference in treatment effects was -3.6. The result was statistically significant (p= 0.005).

Table 4 Primary Efficacy Results in Adjunctive Study 235 (Change in MADRS Scores)

Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
LATUDA (20-120 mg/day)* + lithium or valproate	30.6 (5.3)	-17.1 (0.9)	-3.6 (-6.0, -1.1) p= 0.005
Placebo + lithium or valproate	30.8 (4.8)	-13.5 (0.9)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

Efficacy Results by Region in Study 235:

In the US, the study did not demonstrate efficacy for lurasidone in the treatment of bipolar depression. In fact, the treatment effect for lurasidone was worse than placebo. In the placebo group, the mean change in MADRS was -13.8; in the US the mean change was -12.7. Thus the placebo-subtracted lurasidone treatment effect was +1.1. In the non-US regions, the placebo-subtracted difference (-5.8) was statistically significant (p, 0.001).

Table 5 MADRS Efficacy Results by Region: US vs. Non-US

Treatment Group	US (N=110)	Non-US (N=230)
MADRS Mean Change From Baseline at Week 6		
Placebo (SE)	-13.8 (1.70)	-13.3(1.03)
Lurasidone 20-120mg (SE)	-12.7(1.66)	-19.1(0.98)
Placebo-Subtracted Mean Difference at Week 6		
Lurasidone 20-120mg (SE)	+1.1 (2.38) p=0.642	-5.8 (1.41) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Germany, Poland, Romania, Russia and Ukraine)

Table 6 illustrates the results of the regional efficacy analysis excluding data from the US. As in the US, the results were negative in Africa and India. The results were statistically significant only in Europe: Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine. Thus, the positive results for the study overall were driven by the treatment effects in Europe. These regional results are similar to those in monotherapy study 236.

Table 6 MADRS Efficacy Results in Non-US Regions

Treatment Group	South Africa (N=18)	India (N=80)	Europe* (N=132)
MADRS Mean Change From Baseline at Week 6			
Placebo (SE)	-7.5 (3.07)	-17.6 (2.12)	-11.3 (1.21)
Lurasidone 20-120mg (SE)	-12.2 (2.82)	-21.2 (1.94)	-18.3 (1.18)
Placebo-Subtracted Mean Difference at Week 6			
Lurasidone 20-120mg (SE)	-4.7(4.16) p=0.280	-3.7 (2.84); p=0.203	-7.0(1.68); p<0.001

*includes Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine

The Division requested that the sponsor explore factors that could potentially explain the regional differences in efficacy results. The sponsor noted that the US accounted for only 32% of the study population; it is possible that there wasn't sufficient power with the US data to detect a treatment effect. For the US data, there was a wide confidence interval, making it difficult to interpret the data. The sponsor also noted that in Study 292 (with a similar design), 45% of the study population was from the US; and there was a trend towards efficacy in the US in Study

292. The sponsor conducted analyses exploring the potential factors that could have been related to the differential regional efficacy effects: baseline demographics (age, gender, weight, and ethnicity), baseline severity of illness and parameters of psychiatric history, concomitant medications. There did not appear to be any significant differences in these parameters among regions. There were some differences in age, duration of bipolar disease, and presence of rapid cycling bipolar disorder; however, the analyses did not identify a clear explanation for the regional differences.

The magnitude of the placebo effects in the US and non-US regions were similar. There were no pharmacokinetic factors that could explain the differences. There were differences in the discontinuation patterns between the US and non-US; in the US a greater proportion of subjects in the lurasidone group discontinued compared to non-US subjects, and a slightly greater of subjects in the US discontinued in the last 2 weeks of the study.

Overall, the Division and the sponsor agreed that there was no clear explanation for the regional differences in efficacy results in Study 235. The differences could be attributable to unknown or unexplored factors.

2.2.3 Adjunctive Therapy Study 292

Adjunctive study 292 did not demonstrate the efficacy of lurasidone in the treatment of bipolar depression. The treatment effects overall, and in each region, were not statistically significant. However, there was a trend toward efficacy overall and for the US. The primary and key secondary efficacy results were negative. At the end of Week 6, the placebo-subtracted treatment effect for lurasidone was -1.4 (p= .0176). The lurasidone treatment effect was -1.7 (p=0.320) in North America (US and Canada) and -1.5 (p=0.282) in the rest of the World. There were no marked regional differences in efficacy; the treatment effects were similarly low in all regions.

Compared to studies 235 and 236, in Study 292 there was a larger proportion of subjects was from North America (45%). There were no subjects from Africa or Russia, added subjects from South America. The mean age was slightly higher, higher proportion of female subjects, higher proportion of subjects with rapid cycling bipolar disorder. The mean and modal doses were similar to those in Study 235.

2.3 Dr. Ritter's Efficacy Conclusions

Dr. Ritter concluded that monotherapy study 236 demonstrated the efficacy of lurasidone in the treatment of bipolar depression in the overall study population. However, he notes that the results were not statistically significant in the US (although there was a trend toward efficacy). The results were also negative in all other regions (Asia and Africa) except Europe. The overall positive results of the study were driven by the statistically significant effect in Europe.

Furthermore, Dr. Ritter notes that there is no clear explanation for the difference in regional efficacy findings. After conducting several analyses to try to explain the regional differences in efficacy, the Division and the sponsor agreed that there is no clear explanation of the findings. Another concern about study 236 is that, in the US, there was a larger treatment effect in the low-dose group than in the high-dose group.

For adjunctive therapy study 235, Dr. Ritter concluded that the study was positive overall for all regions combined. However, there were important regional differences in efficacy findings. The study was negative for the analysis of subjects in the US. In fact, in the US, the lurasidone treatment effect was worse than the placebo treatment effect. The study was also negative in Asia and Africa. As in Study 236, the positive overall results were driven by the statistically significant findings in Europe. Furthermore, neither the sponsor nor the Division could identify factors that could explain the differential regional efficacy results.

For adjunctive study 292, Dr. Ritter agrees with the sponsor that this was a negative study overall. The treatment effects were small and not statistically significant in each region (North America, Europe, Asia, and South America). There were no marked regional differences in treatment effects in Study 292. However, in South America there was a trend towards worse treatment effects in the lurasidone group compared to the placebo group.

Dr. Ritter reasons that because there is only one positive study and each of the 3 studies was negative in the US, the sponsor has not demonstrated the efficacy of lurasidone "for the conditions of use." Dr. Ritter interprets the "conditions of use" as "the use of the drug in the United States," i.e., the treatment of US patients with bipolar depression. Dr. Ritter concluded that the overall positive efficacy results in studies 235 and 236 are not adequately applicable or generalizable to the US population of patients with bipolar depression.

Dr. Ritter refers to regulation 21 U.S.C. §355(d)(5), regarding the need to demonstrate efficacy for the conditions of use. He states that the regulation does not allow for approval of an application if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

In his review, Dr. Ritter discusses the possibility that the differential regional efficacy findings could be explained by the presence of different intrinsic and extrinsic factors among regions. For example, there were differences between the US and other regions in psychiatric history and baseline characteristics. The average duration of bipolar disorder was longer in the US compared to non-US regions, and the average duration of the index depressive episode was longer in the US. In addition, in US subjects there was a greater proportion of subjects with rapid cycling bipolar disorder and concomitant psychiatric conditions, compared to non-US regions. Dr. Ritter stated that in his opinion, particular extrinsic factors such as socio-cultural and geographical

variations in psychopathology, epidemiology, diagnosis, clinical psychiatric presentations, and the presence of concomitant illnesses can be significantly different between US and non-US psychiatric patients. Thus, Dr. Ritter concludes that positive foreign data would not be entirely applicable for supporting a psychiatric indication in the US.

In summary, Dr. Ritter concluded that the data from the lurasidone bipolar depression program are not adequate to support approval of the NDA or the use of lurasidone in the US to treat patients with bipolar disorder. He recommends that the Division take a Complete Response action. He recommends that the sponsor conduct an additional study of lurasidone in bipolar depression to confirm that the drug has efficacy in the US to support the application. In general, I agree with Dr. Ritter's conclusions and recommendations.

2.3 Safety Findings

Dr. Ritter reviewed the safety data from placebo-controlled studies 235, 236, and 292, as well as non-controlled data from the long-term, open-label safety study of lurasidone in bipolar depression (Study 256). Dr. Ritter concluded that lurasidone was reasonably safe and well tolerated in patients with bipolar depression (as monotherapy and as concomitant treatment with lithium or valproate). Dr. Ritter concluded that the safety database and safety assessments were adequate for assessing the safety profile of lurasidone in patients with bipolar depression. I agree with his conclusions.

In summary, there were no new or unexpected safety findings in the bipolar depression program, compared to the known safety profile of lurasidone. In the controlled studies, a total of 514 subjects were exposed to lurasidone doses ranging from 20 mg to 120 mg.

There were no deaths in the program attributable to treatment with lurasidone. Several serious adverse reactions and discontinuations because of adverse events were probably or possibly related to lurasidone: akathisia, weight gain, hypersalivation, nausea, abdominal pain, anaphylaxis, angioedema, somnolence, dizziness, CPK elevation. All of these adverse reactions have been known and labeled for lurasidone. The most common adverse reactions in the monotherapy and concomitant therapy studies were akathisia, extrapyramidal symptoms, sedation, and nausea. Generally, there was a trend for dose-relatedness for these adverse reactions.

As in the schizophrenia program, there were small increases in mean serum creatinine; and in the lurasidone group, there was a significantly higher proportion of subjects with abnormally high serum creatinine compared to the placebo group. In the monotherapy study, 2.8% of subjects in the lurasidone group had elevated creatine concentrations, and 0.5% of the placebo group had abnormal values. In the adjunctive therapy studies, 4.5% of the lurasidone group and 1.9% of the placebo group had elevated serum creatinine. As in the schizophrenia studies, there was a mean

increase in serum prolactin concentration as well as a higher proportion of subjects with abnormally high prolactin concentrations in the lurasidone group compared to the placebo group.

3. Statistics Review

Thomas Birkner, Ph.D. performed the statistical reviews, one for the monotherapy study and one for the adjunctive therapy studies (filed on May 30, 2013). Dr. Birkner replicated the sponsor's efficacy findings for studies 235, 236, and 292. In addition, Dr. Birkner conducted a number of analyses on the regional differences in efficacy results. In summary, he agrees with the sponsor's findings regarding the regional differences, and he generally agrees with Dr. Ritter's conclusions about the importance of the differential regional efficacy results between the US and non-US regions. Dr. Birkner conducted excellent, thorough, and extensive analyses of these regional factors, and he worked extremely closely with the clinical team. He had a substantial impact on the clinical team's ability to understand and explore the efficacy findings in the lurasidone bipolar depression program.

3.1 Study 236 Primary Statistical Analysis and Conclusions

The primary efficacy analysis assessed the change from Baseline in MADRS total score at Week 6, employing an MMRM model with restricted maximum likelihood estimation under the assumption of an unstructured covariance matrix for within-subject correlation. The analysis evaluated the mean change from Baseline in MADRS total score over 6 weeks and how changes differed among the treatment groups. The model included factors for treatment, pooled center, visit (as a categorical variable), Baseline MADRS total score, and treatment-by-visit interaction. The Kenward-Rogers method was used to estimate the denominator degrees of freedom. The treatment and treatment by visit interaction terms allowed for comparisons of the treatment groups at each of the following time points: Weeks 1, 2, 3, 4, 5, and 6.

Dr. Birkner performed additional analyses for the primary efficacy parameter to assess the consistency of the treatment effect across sites. A repeated measures model examined the change from Baseline in MADRS total score, with fixed effects for treatment, pooled center, visit, Baseline score, treatment by visit interaction, and treatment by pooled center interaction, assuming an unstructured covariance matrix. If there appeared to be a significant treatment by pooled center interaction effect (defined by sponsor as p-value < 0.10), estimates by pooled center were to be examined to determine the nature of the interaction.

The primary analysis was based on the ITT population. The analysis was also conducted for the per protocol population. The analysis was conducted by geographic region and North America versus Rest of World for the ITT population.

Dr. Birkner's Primary Efficacy Analysis:

The model results show a decrease in MADRS total score for both the lurasidone and the placebo group, indicating an improvement in depressive symptoms. The mean decrease (LS mean ± SE) in the MADRS total score from Baseline to Week 6 is -15.4 ± 0.83 for both the lurasidone 20-60 mg and for the lurasidone 80-120 mg group, the mean decrease for the placebo group is -10.7 ± 0.83. The treatment difference at week 6 (lurasidone minus placebo) of -4.6 (95% CI: -6.9, -2.3) is statistically significant after adjustment for multiplicity for both lurasidone treatment groups (adjusted $p < 0.001$). The treatment differences are statistically significant starting at week 2 in both lurasidone groups. Table 6 provides the detailed MMRM model results.

Table 7: Change from Baseline in Montgomery-Asberg Depression Rating Scale Total Score – Repeated Measures (ITT Population)

Parameter	Estimate	SE	95% CI	p-value
Number of Subjects	485	--	--	--
Lurasidone 20-60 mg	161	--	--	--
Lurasidone 80-120 mg	162	--	--	--

Placebo	162	--	--	--
Repeated Measures Model:				
Pooled Center	--	--	--	<0.001
Visit	--	--	--	<0.001
Baseline Score	--	--	--	<0.001
Treatment	--	--	--	<0.001
Treatment*Visit	--	--	--	0.041
Model Estimates:	--	--	--	--
Change from Baseline:	--	--	--	--
Lurasidone 20-60 mg	--	--	--	--
Week 1	-3.4	0.43	(-4.2, -2.6)	--
Week 2	-7.3	0.56	(-8.4, -6.2)	--
Week 3	-10.0	0.65	(-11.2, -8.7)	--
Week 4	-12.1	0.71	(-13.5,-10.7)	--
Week 5	-14.1	0.78	(-15.6,-12.6)	--
Week 6	-15.4	0.83	(-17.0,-13.7)	--
Change from Baseline:				
Lurasidone 80-120 mg				
Week 1	-4.0	0.42	(-4.8, -3.2)	--
Week 2	-8.1	0.56	(-9.2, -7.0)	--
Week 3	-10.8	0.65	(-12.1, -9.6)	--
Week 4	-12.7	0.70	(-14.1,-11.3)	--
Week 5	-14.3	0.77	(-15.8,-12.8)	--
Week 6	-15.4	0.83	(-17.0,-13.7)	--
Change from Baseline:				
Placebo				
Week 1	-3.0	0.43	(-3.8, -2.1)	--
Week 2	-5.6	0.57	(-6.7, -4.5)	--
Week 3	-7.9	0.66	(-9.2, -6.6)	--
Week 4	-9.0	0.71	(-10.4, -7.6)	--
Week 5	-10.0	0.78	(-11.5, -8.5)	--
Week 6	-10.7	0.83	(-12.4, -9.1)	--
Contrast: Lurasidone 20-60 mg versus Placebo				

Parameter	Estimate	SE	95% CI	p-value
Change from Baseline:				
Week 1	-0.4	0.59	(-1.6, 0.7)	0.463
Week 2	-1.6	0.79	(-3.2, -0.1)	0.040
Week 3	-2.0	0.92	(-3.8, -0.2)	0.027
Week 4	-3.1	1.00	(-5.1, -1.2)	0.002
Week 5	-4.1	1.09	(-6.2, -1.9)	<0.001
Week 6	-4.6	1.17	(-6.9, -2.3)	<0.001, <0.001[a]
Contrast: Lurasidone 80-120 mg versus Placebo				
Change from Baseline:				
Week 1	-1.0	0.59	(-2.2, 0.1)	0.085
Week 2	-2.5	0.79	(-4.1, -0.9)	0.002
Week 3	-2.9	0.92	(-4.7, -1.1)	0.001
Week 4	-3.7	1.00	(-5.7, -1.7)	<0.001
Week 5	-4.3	1.09	(-6.5, -2.2)	<0.001
Week 6	-4.6	1.17	(-6.9, -2.3)	<0.001, <0.001[a]
Tests of Dose-Response at Week 6:				
Linear Trend Test of 0, 20-60, 80-120 mg	--	--	--	<0.001
Lurasidone 80-120 mg versus 20-60 mg	-0.0	1.17	(-2.3, 2.3)	0.998
Treatment*Pooled Center Interaction	--	--	--	0.649

Note: Estimates, SE, CI, and p-values were based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. Adjusted p-values[a] were obtained with Hommel-based tree-gatekeeping procedures.
Note: Treatment*Pooled Center Interaction p-value was based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.
Note: Higher observed MADRS total scores indicate greater severity of depression.
Abbreviations: CI = confidence interval; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error.

(Source: Study report p. 93-95; the results were confirmed by this reviewer)

Subgroup Efficacy Analyses

Dr. Birkner performed a number of subgroup analyses on the change from Baseline results for MADRS total score to examine the effects of geographic region, gender, race (e.g., White, Black, Asian, and Other), ethnicity (Hispanic and Non-Hispanic), age (categorized as "<55" and "≥55"), and bipolar I diagnosis subtype (rapid cycling and non-rapid cycling). Geographic

regions included North America (USA), Europe (Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine), Africa (S. Africa), and Asia (India). Separate ANCOVA models including independent terms for treatment, pooled center, Baseline score, subgroup, and treatment-by-subgroup interaction were performed for each set of subgroups. For the by-geographic region analyses, pooled center was nested within region. All subgroup analyses were based on the ITT population.

Dr. Birkner performed a subgroup analysis by geographic region (US vs. Non-US) using the primary MMRM model. He concluded that there were two important findings from the subgroup analyses: 1) the estimated treatment difference is smaller in the US compared to the Non-US; and 2) the lower dose range shows a greater numeric decrease in the MADRS total score compared to the higher dose range for US patients. Dr. Ritter noted the identical findings.

MADRS Total Score Change from Baseline at Week 6 by Region (MMRM analysis)

Geographic Region	MADRS total score change from baseline (LS mean ± SE)			Treatment difference to Placebo (LS mean diff ± SE)	
	Placebo	L20-60 mg	L80-120 mg	L20-60 mg	L80-120 mg
North America	-13.2 ± 1.53	-17.1 ± 1.46	-15.3 ± 1.45	-3.9 ± 2.11	-2.1 ± 2.11
Rest of the World	-8.9 ± 0.96	-14.0 ± 1.00	-15.4 ± 0.99	-5.2 ± 1.38	-6.6 ± 1.37

Dr. Birkner's Efficacy Conclusions for Study 236

Dr. Birkner concluded that the statistical results provide adequate evidence to support the claim that lurasidone in monotherapy is more efficacious than placebo in treating patients with depressive episodes associated with bipolar I disorder. Dr. Birkner stated that although there is a trend in favor of lurasidone in US patients, the effect for both dose ranges is smaller compared to the Rest of the World. Also, US patients randomized to the lower dose range of 20-60 mg/day experienced a numerically greater effect compared to US patients on the higher dose of 80-120 mg/day. Complete explanations for those findings remain elusive.

3.2 Study 235 Primary Statistical Analysis and Conclusions

Dr. Birkner agrees that Study 235 is positive overall on the primary statistical analysis including all geographic regions. Essentially, Dr. Birkner replicated the sponsor's efficacy findings and agrees with the findings and conclusions of Dr. Ritter and the sponsor regarding the differential regional efficacy findings. Dr. Birkner agrees that the study did not demonstrate efficacy in the US. In fact, lurasidone was worse than placebo in the US.

3.2 Study 292 Primary Statistical Analysis and Conclusions

In summary, Dr. Birkner replicated the sponsor's efficacy analysis, and he agrees with the findings and conclusions of Dr. Ritter and the sponsor. Dr. Birkner agrees that Study 292 was negative overall on the primary statistical analysis. In addition, he agrees that the results were negative in all geographical regions, including the US.

4. Office of Scientific Investigation Review

John Lee, M.D. performed the OSI review (filed on February 11, 2013). Dr. Lee concluded that there were no major violations, and the data from these sites appear to be reliable to support the sNDAs. I agree with Dr. Lee's conclusions. OSI conducted inspections at 4 US clinical study sites participating in studies 235 and 236. These sites were selected randomly among those with: 1) subjects in both studies, 2) high enrollment in either study, 3) participation in a large number of INDs, and 4) having no history of prior FDA inspection or a remote history of FDA inspection. Dr. Lee concluded that the site-specific data for efficacy, safety, and protocol violations did not appear to be significantly different among the studies, and none of the investigators had significant conflicts of interest.

The Division requested inspections of several European sites in Russia (Site 191) and the Czech Republic (Site 618), based on concerns that these sites had large treatment effects that appeared to be outliers, compared to many of the other sites. Removal of Study 235 efficacy data from these two sites had a significant impact on the results of Study 235; it was a negative study upon removal of these 2 sites. The inspections of the Russian and Czech sites have not been completed. The table below presents information for the US sites that were inspected. The Division not request inspections for the second adjunctive therapy study (292).

Site	**Monotherapy Study 236 (Number of Subjects)**	**Adjunctive Study 235 (Number of Subjects)**
Rosario Hidalgo, M.D., Site 100 University of South Florida 3515 Fletcher Avenue Tampa, Florida 33613-4706	4	12
Raymond Manning, M.D., Site 94 CNRI – Los Angeles, LLC 8309 Telegraph Road Pico Rivera, CA 90660	14	20
David Walling, M.D., Site 105 Collaborative Neuroscience Network 12772 Valley View Street, Suite 3 Garden Grove, CA 92845	9	18

Howard Hassman, M.D., Site 120 CRI Worldwide, LLC 111 North 49th Street Philadelphia, PA 19139	8	13

Hidalgo Site Findings: OSI issued a Form FDA 483 for the following observations: One subject was screened for the study one day before obtaining informed consent. One subject was treated with 3 doses of erythromycin, a prohibited concomitant medication, to treat an upper respiratory infection. Erythromycin was prohibited because it inhibits CYP3A4 and prolongs the QT interval. Lurasidone is primarily metabolized by CYP3A4, and lurasidone can prolong the QT interval. Dr. Lee concluded that this error was not significant, and the data from this site are reliable.

Manning Site Findings: There were no significant findings, a Form FDA 483 was not issued, and data from the site were reliable.

Walling Site Findings: There were no significant findings, a Form FDA 483 was not issued, and the data from the site were reliable.

Hassman Site Findings: There were no significant findings, a Form FDA 483 was not issued, and data from the site were reliable.

5. Pediatric Issues – PREA Requirements, Pediatric Plan, and PeRC Meeting

The sponsor requested a waiver for conducting studies in bipolar depression in pediatric patients younger than 10 years old, and they requested a deferral for conducting studies in bipolar depression in patients ages 10 to 17 years. The Division agreed with the sponsor's requests; it is extremely difficult to make a diagnosis of bipolar disorder in children younger than 10 years. The symptoms and behavioral features of bipolar disorder have significant overlap with other diagnoses including schizophrenia, unipolar depression, anxiety disorders, ADHD, and other psychiatric disorders. It is especially difficult to diagnose this condition without having significant longitudinal information about the patient. Therefore, studies in children younger than 10 years would be highly impractical. If the NDA were approved, the Division recommended to PeRC that the Agency defer the requirement to conduct relevant studies in patients ages 10 to 17 years.

The Division presented the sponsor's requests and our recommendations to PeRC. We also presented to PeRC the sponsor's proposed pediatric plan for conducting pediatric studies. The sponsor is currently conducting a pediatric pharmacokinetic, safety, and tolerability study in response to a Written Request (issued on April 20, 2012) for studies in pediatric patients with Schizophrenia and Autism. Study D1050300 is an ongoing phase 1, open-label, single- and multiple- ascending dose study of lurasidone in pediatric patients (6 to 12 years) with

schizophrenia, bipolar disorder, or autism spectrum disorders. The dose range of lurasidone is 20 mg/day to 160 mg/day in this study. The sponsor is conducting appropriate safety and pharmacokinetic assessments. The Division agrees with this plan. If the sNDAs were approved, the sponsor agrees to conduct a short-term, randomized, double-blind, placebo-controlled, fixed- or flexible-dose efficacy and safety study of lurasidone in pediatric patients (ages 10 to 17) with Bipolar Disorder, Current Major Depressive Episode. The primary efficacy measure will be the Childhood Depression Rating Scale (CDRS). The study must also assess symptoms of mania/hypomania using an accepted scale for measuring mania in pediatric patients. In addition, the sponsor would be required to conduct a long-term, open-label, safety study of lurasidone in pediatric patients (10 to 17 years) with Bipolar Disorder, recent major depressive episode. The Division agrees with the sponsor's proposed plan, and we conveyed this to PeRC.

PeRC agreed to waive bipolar depression studies in patients younger than 10 years, agreed to defer bipolar depression studies in patients ages 10 to 17 years, and PeRC accepted the sponsor's proposed pediatric plan.

6. Labeling Review

The Division performed a complete labeling review, and we revised numerous sections of the label. The following review disciplines conducted the labeling review and provided suggested revisions: Chemistry Manufacturing and Controls, Pharmacology/Toxicology, Office of Clinical Pharmacology, Clinical, Statistics, and the Division of Medication Error Prevention and Analysis. We did not negotiate labeling with the sponsor during the review cycle, because we plan to take a complete response action.

We have made the following changes in labeling that do not pertain specifically to the bipolar depression indication:

1. We revised the Dosage and Administration section to provide an explanation for the need to administer lurasidone with food. Lurasidone has a significantly large food effect. Compared to administration under fasting conditions, administration with food substantially increases the absorption lurasidone: the AUC is increased 2-fold, and the Cmax is increased 3-fold. Patients must take lurasidone with food in order to achiever adequate serum concentrations of lurasidone.

2. We revised Dosage and Administration to include information and recommendations on dosing when using lurasidone concomitantly with CYP3A4 inhibitors and CYP3A4 inducers. Lurasidone is primarily metabolized in the liver via CYP3A4. Concomitant use with strong CYP3A4 inhibitors on strong CYP3A4 inducers in contraindicated. It is necessary to adjust the lurasidone dose when used concomitantly with a moderate CYP3A4 inhibitor. It might be necessary to adjust the dose of lurasidone if used concomitantly with a moderate CYP3A4 inducer.

3. We added information to the warning for orthostatic hypotension and syncope.
4. We added a specific warning about the increased risk of neurological adverse reactions in patients with Parkinson's disease or Dementia with Lewy Bodies.
5. We added information to the Adverse Reactions section about increases in serum creatinine.
6. We revised the drug interaction section regarding interactions with CYP3A4 inhibitors and inducers.
7. We revised Section 8.4 Use in Pregnancy to incorporate a risk summary statement.
8. We revised the management of overdosage section to include language about considering the possibility of multiple-drug overdose.
9. We revised Section 12.1 Mechanism of Action and 12.2 Pharmacodynamics.
10. We revised Section 13. Nonclinical Toxicology
11. We revised the efficacy data tables in Section 14 for the schizophrenia studies.

7. Discussion with Dr. Temple and Dr. Unger regarding the Regional Differences in Efficacy Results (June 4, 2013)

The clinical, statistical, and clinical pharmacology teams met with Dr. Temple and Dr. Unger to discuss the significant regional differences in efficacy between the US and non-US regions. Generally, there was a consensus that the findings were extremely important. All participants were concerned that in each of the 3 studies, the sponsor did not demonstrate the efficacy of lurasidone in the US for the treatment of bipolar depression. Dr. Ritter discussed his findings and conclusions, and he presented slides focusing on the significant regional efficacy differences. Dr. Temple and Dr. Unger were extremely concerned that the studies had not demonstrated efficacy in the US, and they agreed that the Division had a strong rationale for taking a complete response action based on these findings.

8. Conclusions and Recommendations

I agree with the conclusions of Dr. Ritter, Dr. Birkner, Dr. Temple, and Dr. Unger, and I recommend that the Division take a complete response action, because the sponsor has not demonstrated the efficacy of lurasidone in the US in each of the 3 studies in bipolar depression. I agree that the sponsor demonstrated the overall efficacy of lurasidone in monotherapy study 236 and in adjunctive study 292, and I agree that adjunctive study 292 was negative. Although

Study 236 was positive overall in the primary analysis including all geographic regions, the treatment effect was not significant in the US. The positive results of the study were driven by the statistically significant results in Europe. The results were negative in all other regions (US, Asia, and Africa). In adjunctive study 235, the results in the US were negative. In fact, the lurasidone treatment effect was worse than placebo. Adjunctive study 292 was negative overall, and it was negative in each region (North America, Europe, Asia, and South America).

As Dr. Ritter and the sponsor note, after conducting a number of analyses to determine the possible explanations of the regional findings, there is no clear explanation of the findings. Dr. Ritter has discussed the possibility that the differences between the US and non-US study populations in baseline disease characteristics, demographic features, and history of psychiatric disease including bipolar disorder and co-morbid psychiatric disorders could possibly explain the differential regional effects. In addition, is possible that cultural and socioeconomic differences, as well as unexplored or unknown factors could have contributed to the results.

Dr. Ritter has made the important point that the sponsor has not demonstrated the efficacy of lurasidone "for the conditions of use." Dr. Ritter interprets the "conditions of use" as "the use of the drug in the United States," i.e., for the treatment of US patients with bipolar depression. Dr. Ritter concluded that the overall positive efficacy results in studies 235 and 236 are not entirely applicable or generalizable to the US population of patients with bipolar depression.

The Division will recommend that the sponsor conduct an additional study to confirm the efficacy of lurasidone in the US in the treatment of bipolar depression. This could be a monotherapy or concomitant treatment study (with lithium or valproate).

Additional Considerations

1. Lurasidone has a signal for prolonging the QT interval. For the original NDA the sponsor conducted a non-thorough QT study that the Cardiorenal QT Interdisciplinary Review Team determined was inadequately designed and did not adequately characterize the potential for lurasidone to prolong the QT interval. The study did not include an active comparator such as moxifloxacin, and it did not include a placebo group. However, the study included ziprasidone as an active comparator, which demonstrated some degree of assay sensitivity. Most importantly, there was a QT signal with lurasidone. In fact, the sponsor has included in labeling cautionary language about using lurasidone concomitantly with other drugs that prolong the QT interval. However, the sponsor has not proposed a QT warning. I recommend that we consider requiring the sponsor to conduct an adequately designed thorough QT study, in consultation with the QT IRT.

2. There are several safety labeling revisions that are clinically important and would be useful for clinicians prescribing lurasidone. I recommend that we consider that the sponsor incorporate these changes in labeling.

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/s/

ROBERT L LEVIN
06/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplements
Application Number	200-603 S-010; S-011
Priority or Standard	Standard
Submission Date	31 August 2012
Received Date	31 August 2012
PDUFA Goal Date	30 June 2013
Division/Office	Division of Psychiatry Products/Office of Drug Evaluation 1
Reviewer Name	Mark Ritter, M.D. RPh.
Review Completion Date	30 May 2013
Established Name	Latuda®
Trade Name	Lurasidone Hydrochloride
Therapeutic Class	Antipsychotic
Applicant	Sunovion Pharmaceuticals
Formulation	Tablet
Dosing Regimen	Oral
Indication	Monotherapy and adjunctive therapy for bipolar depression
Intended Population	Adults

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, it is recommended that the Agency take a Complete Response (CR) action with regards to the monotherapy supplement S-010 and adjunctive therapy supplement S-011 at this time. Efficacy was demonstrated on the primary endpoint for the monotherapy study and adjunctive study respectively. However the unexplainable trend of worsening treatment scores with adjunctive lurasidone treatment within the U.S. subgroup with the sponsor's conclusion that additional factors are likely responsible for the worse trend within the U.S. subgroup makes the overall primary endpoint efficacy results for the adjunctive treatment study not entirely applicable to the U.S. subgroup. Consequently the adjunctive therapy *prima facie* positive study must be considered a negative study with regards to "conditions for use" within the United States in accordance with 21 U.S.C. §355(d)(5).

In addition, the sponsor completed and submitted (at Agency request) a second adjunctive study during the review of this new drug application (NDA). This study failed to demonstrate efficacy of lurasidone treatment over placebo on the study's overall primary endpoint, despite showing a favorable trend towards efficacy in the U.S. subgroup. In view of one adjunctive study failing to demonstrate efficacy and another study demonstrating an unexplainable trend of worsening depressive symptoms within the U.S. subgroup, these two negative studies provides less than substantial evidence that lurasidone is effective for the adjunctive treatment of bipolar depression within the United States.

It has been the view of the Agency that two (2) positive studies are required in order to approve a new indication. Since the monotherapy study was the only study to demonstrate both a trend towards efficacy in the U.S. subgroup and efficacy on the primary study endpoint, this reviewer is of the opinion that the monotherapy study should not be used as the sole support for the indication of depressive disorders associated with bipolar disorder. Hence a CR action is recommended to be taken on both supplements at this time.

The additional lack of explanation to delineate factors responsible for a very strong treatment effect between the European v. non-European subgroups in the adjunctive study and availability of other treatments for the treatment of bipolar depression within the United States are additional considerations that leads this reviewer to conclude that the Agency take a CR action on both supplements at this time.

Recommendations

1. Adopting the standards as described in the International Conference on Harmonization (ICH)-E5, substantial evidence of efficacy for the proposed-labeled indications for either supplemental NDA may be achieved, in this reviewer's opinion, if another adequate and well-controlled ICH-E5-defined "bridging study" for adjunctive therapy demonstrates efficacy on the primary endpoint and favorable efficacy trend within the U.S. subgroup, preferably ensuring that a majority of the patients are recruited from U.S. clinical sites.
2. Due to information posted on the sponsor's website[1] that an NDA for "Bipolar Disorder" was submitted to the Agency, this reviewer recommends that the Agency inform the

[1] http://www.sunovion.com/aboutSunovion/our-products html extracted from the internet 23 May 2013.

sponsor that additional studies are strongly recommended for the treatment of bipolar disorder, particularly due to lurasidone's category B pregnancy designation and potential treatment of bipolar disorder in pregnant and lactating patients. If the sponsor intends to seek approval for the bipolar depression supplements without conducting studies for bipolar disorder, failure to conduct bipolar disorder studies would lead to bipolar depression language reflecting that efficacy of lurasidone for the treatment of bipolar disorder has not been established, as well as a post-marketing requirement to conduct such studies.

3. In view of a small, but consistent shift of creatinine levels from normal/low to high in lurasidone-treated subjects compared to placebo treatment, the sponsor should be encouraged to conduct an in vitro study to examine the effects of lurasidone on creatinine secretion.
4. Due to an inadequate thorough QT-study that was conducted under the original lurasidone NDA application for schizophrenia, the sponsor should conduct another through QT-study that is acceptable to the Agency.

It should be noted that an action to refuse to approve based on lack of substantial efficacy due to geographical variation in efficacy results has been taken by the Agency for another psychiatric product previously. (b) (4)

1.2 Risk Benefit Assessment

Benefit Assessment
Currently, there are two (2) products already approved for the treatment of bipolar depression. However lurasidone may have a better metabolic and safety profile when comparing the metabolic and weight safety profile of lurasidone to the existing products.

In addition, lurasidone is a category B drug that could potentially be used to treat schizophrenia and bipolar depression in pregnant and nursing females.

Risk Assessment
After a review of the data from this submission, there are three issues to analyze with regards to risk of the use with lurasidone:

1. Whether or not there is substantial evidence from the submitted data to conclude that lurasidone is effective for the treatment of bipolar depression within the United States
2. Whether or not there is an explanation for the subgroup efficacy results and treatment effect that was demonstrated between the European and non-European subgroups.
3. Whether there is an unmet need for treatments in bipolar depression that would favor approval of this application despite an unexplained geographical variation in both U.S. v. non-U.S. and Europe v. non-European efficacy data.

Issue #1
The first issue to explore is whether or not the efficacy data submitted originally with the NDA and a further phase 3 double blind trial provides "substantial evidence" that lurasidone is effective

for the treatment of bipolar depression as monotherapy (S-010) or adjunctive therapy to lithium or valproic acid (S-011) under the conditions of use as suggested in the proposed labeling.

Legal Basis for Issue
The relevant rule of law for this issue is found in accordance with 21 U.S.C. §355(d)(5), which states that the Agency must issue an order refusing to approve an application if:

> "…(5) evaluated on the basis of the information submitted to [the Secretary of HHS] as part of the application and any other information before him with respect to such drug, there is lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof…"

The term "substantial evidence" is further defined in the statute later in the same subsection as to the following:

- "…the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the [HHS] Secretary determines, based on relevant science, that data from one controlled adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence."

Furthermore, the Agency has interpreted 21 U.S.C. §355(d)(5) under 21 C.F.R. §314.125(a)(4) that the Agency will refuse to approve an application if:

- "…There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its product labeling."

The Agency further states in 21 C.F.R. §314.126(a) that "…Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support claims of effectiveness for new drug." The characteristics required of an adequate and well controlled trial are then precisely delineated under 21 C.F.R. §314.126(b).

Analysis
Monotherapy Supplement S-010

The monotherapy supplement is supported by evidence from one (1) phase 3, double-blind clinical trial (study 236) which demonstrated efficacy [as measured by mean change from baseline scores on the Montgomery-Asperg Depression Rating Scale (MADRS) at week 6] when analyzed from the entire pooled data set and the European subgroup. There was a trend towards efficacy in all subgroups for study 236, to include the United States.

In this reviewer's opinion, study 236 was an adequate and well controlled study as defined under 21 C.F.R. §314.126(b). Since efficacy was established on the primary endpoint and a trend

towards efficacy was seen in all subgroups (including the United States subgroup), this reviewer concludes that this study is sufficient evidence to support the use of lurasidone in the treatment of bipolar depression as monotherapy, contingent on labeling reflecting that the efficacy of lurasidone for the treatment of bipolar disorder has not been established.

Adjunctive Supplement S-011

The adjunctive therapy supplement was originally supported from data from one (1) clinical trial, study 235, which again showed efficacy on the study's overall primary endpoint. However, lurasidone treatment was associated with an unexplainable trend towards a worse outcome on MADRS scores compared to placebo within the U.S. subgroup. During the course of this NDA review, a very similar adjunctive clinical trial was completed (study 292) which demonstrated a trend towards efficacy with lurasidone treatment within the U.S. subgroup. However the study failed to demonstrate efficacy on the study's primary endpoint. Notably there was another trend towards worse treatment scores in lurasidone-treated patients in South America in study 292.

In this reviewer's opinion, studies 235 and 292 were adequate and well controlled studies as defined under 21 C.F.R. §314.126(b). However, only study 235 was positive for efficacy with adjunctive lurasidone treatment on the study primary endpoint, yet U.S. patients treated with lurasidone had unexplainably worse depressive scores v. placebo compared to the rest of the world. The lack of efficacy seen in study 292, combined with an unexplainable worsening trend in depressive scores with lurasidone treatment in the U.S. subgroup for study 235 do not satisfy the remaining language noted under both 21 C.F.R. §314.125(a)(4) and 21 U.S.C. §355(d)(5) for "substantial evidence" that lurasidone is effective for the adjunctive treatment of bipolar depression, notably:

*"…the effect it purports or is represented to have under the **conditions of use** prescribed, recommended, or suggested in its product labeling".*

This language from the statute and from the regulations implies that the words "conditions of use" are defined as use of the product for its labeled indication **within the United States.** The Agency has been granted authority under statute to approve and regulate products solely for use for the stated condition within the United States. The unexplainable trend of a worse outcome with lurasidone treatment seen within the United States subgroup, as well as lack of efficacy noted in study 292 demonstrates insufficient evidence that lurasidone will be effective for the adjunctive treatment of bipolar depression within in the United States based upon data from studies 235 and 292.

Counterarguments with Rebuttals

1. One can initially argue that the finding of worse scores on the MADRS in adjunctive study 235 within the U.S subpopulation is a spurious finding since monotherapy treatment was associated with a trend towards efficacy in all subgroups. This argument assumes that monotherapy and adjunctive therapy populations have very similar psychiatric characteristics. However adjunctive therapy implies treatment with an additional medication in those patients who continue to have bipolar depression despite treatment. Current treatment guidelines from the American Psychiatric Association (2002) and a 2005 Guideline Watch indicate that lithium, olanzapine-fluoxetine, quetiapine, or lamotrigine are the first-line pharmacological treatments to be considered

for the treatment of acute depressive episodes associated with bipolar disorder[2,3]. Even though lithium or valproic acid (VPA) treatment does not have an Agency-indication for the treatment of depressive episodes of bipolar depression, patients in the adjunctive trials may be clinically considered as "partially non-responsive bipolar-depressed" patients since the studies were designed to randomized only those patients whose bipolar depression failed to remit after treatment with a mood stabilizer.

Evidence from this NDA submission indicating a lithium/VPA treatment effect for bipolar depression can be found in the fact that adjunctive lurasidone treatment was associated with a smaller treatment effect when compared with monotherapy [-3.6 (SE 1.25) adjunctive study 235 v. -4.6 (SE 1.17) monotherapy study]. Additional data from study 292 also shows that patients who received a run-in of lithium or valproate for 28 days prior to randomization to lurasidone had essentially no improvement in depressive symptoms compared to those patients already stabilized on lithium or VPA [run-in patients: -0.2 (95% CI -3.0,2.5) v. no run in: -3.0 (95% CI -6.4,0.5)]. As stated previously, adjunctive patients can be considered as "partially treatment resistant" for bipolar depression. With evidence of a lithium/VPA treatment effect, adjunctive patients are qualitatively different than monotherapy patients. Thus efficacy findings from the monotherapy study are not entirely applicable to adjunctive therapy patients and deserve separate consideration.

2. The trend towards worse symptoms in the U.S. subgroup seen in study 235 could also be argued as a chance finding, since study 292 demonstrated a trend towards efficacy in the U.S. subgroup. Although this argument has some merit, study 292 was a negative study. In addition, it must also be pointed out that geographical variation of efficacy was seen in South America in study 292 with the South American subgroup demonstrating a trend towards worse scores on MADRS compared to placebo treatment (MADRS score change from placebo 1.5 $\pm$3.09 South America v. -1.7 $\pm$1.71 in U.S.). Therefore there is reason to believe, beyond a chance finding, that lurasidone treatment may not be effective for the adjunctive treatment of bipolar depression.

3. Another argument could be made that results from a subgroup efficacy analysis are an insufficient reason to refuse to approve an application. As analyzed above, 21 C.F.R. §314.125(a)(4) provides the regulation that governs when not to approve an application based on lack of 'substantial evidence" of efficacy. Any lack of substantial evidence of efficacy for use within the United States (i.e. "conditions of use") *compels* the Agency to refuse to approve an application. Since there is evidence that placebo treatment was superior to lurasidone treatment within the U.S. subgroup, the U.S. subgroup efficacy findings are relevant with regards to regulatory action on this NDA.

4. One could argue that under 21 C.F.R §314.106 foreign data alone can be used as the basis for marketing approval for an NDA, thus implying that efficacy for any drug product

[2] Hirschfeld RMA, Bowden CL et al: " Practice Guideline for the treatment of patients with bipolar disorder second edition". DOI: 10.1176/appi.books.9780890423363.50051 obtained from http://psychiatryonline.org on 6 May 2013.
[3] Hirschfeld RMA "Guideline Watch: Practice Guideline for the treatment of patients with bipolar disorder second edition" DOI: 10.1176/appi.books.9780890423363.148430 obtained from http://psychiatryonline.org on 6 May 2013.

submitted to the Agency does not need to be shown within the United States. On first glance this argument seems to have merit. The sponsor could have chosen to conduct all the studies using all foreign data. However the sponsor randomized 40% of the total study subjects in study 292 from within the United States and 33% from the U.S. in study 235. Thus a comparative analysis of the geographical variation in the efficacy data becomes a factor in the approvability decision tree for this supplemental NDA.

5. In addition, a further reading of 21 C.F.R §314.106(b) states that approval of an NDA that has foreign data as a sole basis to support approval may be approved if "…*The foreign data are applicable to the U.S. population and U.S. medical practice.*" This clause assumes that that the medical condition (in this case bipolar-depression) and other extrinsic and intrinsic factors in patients from these foreign patients are sufficiently similar to the medical condition and intrinsic/extrinsic factors from patients within the United States. According to the International Conference on Harmonization(ICH) E5 guidelines "Ethnic Factors in the Acceptability of Foreign Clinical Data", extrinsic factors are factors associated with environment and culture where the person resides as compared to intrinsic factors which are factors that help define and identify a subpopulation, such as a genetic polymorphism. Thus one can make the argument that bipolar-depressed patients from U.S. are sufficiently and qualitatively similar to bipolar-depressed patients from outside the United States, i.e. no substantial variation in intrinsic/extrinsic factors exists between the two subgroups.

   Under the ICH-E5 guidelines, medical practice, disease definition/diagnostic therapeutic approaches are a few factors classified as extrinsic ethnic factors. For many indications, objectively-derived data based on objective measures are consistent between foreign and U.S. subgroups since the illnesses in question generally have a known pathophysiology, and have an international consensus on diagnostic criteria for the illness in question. In the case of psychiatric disorders, diagnosis is based on a set of *subjective* criteria that are then measured with objective, validated measures that have international validity. Unfortunately there is no world-wide agreement on psychiatric diagnostic criteria. In the United States, a psychiatric diagnosis is made through a psychiatric examination based on criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders (DSM), of which the current version is DSM-IV-TR and soon to be DSM-V. However psychiatric diagnostic criteria used by psychiatrists outside of the United States use a combination of DSM-IV-TR criteria and criteria from the International Statistical Classification of Diseases and Related Health Problems Dictionary-10th edition (ICD-10). Discordance between diagnostic criteria required to make a diagnosis of bipolar depression and many other psychiatric illnesses between ICD-10 and DSM-IV criteria has been consistently noted[4]. Thus there are clear differences in psychiatric diagnosis and presentations in psychiatric patients between U.S and non-U.S. psychiatric practice.

   In order to correct for this potential extrinsic ethnic variation in psychiatric diagnosis for this NDA application, the sponsor ensured (through rater control quality control programs and rater validation programs) that all investigators were qualified to make a DSM-IV diagnosis of bipolar depression using a validated scale with ICD-10 and DSM-IV validity. Nevertheless there were noteworthy differences in psychiatric diagnoses and

[4] First MB "Harmonization of ICD-11 and DSM-V: opportunities and challenges" *BJ Psych* (2009) 195:382-390

baseline characteristics between U.S. and non-U.S. patients study 235. Specifically, U.S. patients had a longer duration of bipolar illness than non-U.S and longer duration of current depressive episode for both studies. In addition, geographical differences in psychiatric diagnoses was present, with virtually all the patients with a diagnosis of rapid cycling or those patients with a concomitant psychiatric illness for both studies were from the U.S. compared to non-U.S patients.

The sponsor conducted an Agency-requested analysis to examine factors (intrinsic and extrinsic) that could be responsible for the variation in U.S. efficacy results compared to the non-U.S. subgroups in both study 235. The sponsor descriptively noted there were baseline differences in psychiatric baseline characteristics for both studies and performed an analysis to correct for the differences in psychiatric severity between U.S. and non-U.S. patients for only the adjunctive study 235 which rendered efficacy results unchanged after correcting for the variation in baseline psychiatric characteristics. An additional sponsor-conducted analysis to correct for the variation in concomitant psychiatric illnesses for study 235 also rendered efficacy results between U.S and non-U.S. sites unchanged. Nevertheless the sponsor concluded that the geographical variation in response in study 235 between U.S. v non U.S. subgroups may be attributed to known, unknown or a combination of known/unknown factors.

A recent article by Ni Khin, M.D. of the Agency discussed the applicability of foreign data in U.S. drug approvals, recommending that the interpretation of substantial regional differences must be interpreted cautiously, but could be related to chance, or due to regional differences in intrinsic and extrinsic factors[5]. The discussion of the geographic variation seen as being related to a chance finding was previously discussed in point 2 above. As far as an analysis of intrinsic and extrinsic factors related to U.S v. non-U.S. data, the sponsor concluded that the heterogeneity of the data from study 235 may be attributable to known/unknown intrinsic/extrinsic factors. Of note, the aforementioned article by Dr. Khin comments that evidence of a much smaller effect in the US population is "…troublesome when considering a drug for approval for the US population." (Khin NA p.6) In the case for this submission, there was a finding of a WORSE treatment effect with lurasidone treatment for the U.S subgroup.

Although the sponsor has examined the effects that some obvious intrinsic and extrinsic factors related to geographical efficacy response, one must conclude (as did the sponsor) that there are other factors present that have led to a geographical variation in response. Thus efficacy data derived from the U.S. was qualitatively different than non-U.S. obtained efficacy data.

Based on a review of the data and considering the Agency's perspective on applicability of foreign-derived data, this reviewer is of the opinion that the non-U.S.-derived efficacy data obtained from study 235 is not entirely applicable to U.S. psychiatric patients with bipolar depression or consistent with U.S. psychiatric practice unless a "bridging study" was conducted for both indications to determine if lurasidone treatment was effective for

[5] Khin NA, Yang P et al "Regulatory and scientific issues regarding use of foreign data in support of New Drug Applications in the United States: an FDA perspective" *Clin Pharm & Therapeutics* 1 May 2013 pp 1-13

the treatment of bipolar depression and a favorable U.S efficacy trend in a study that was preferably conducted with a majority of patients from the United States.

It is the general opinion of this reviewer that particular extrinsic factors such as socio-cultural variations in psychopathology and geographical variations in epidemiology, diagnosis and clinical psychiatric presentations/concomitant illnesses in non-U.S psychiatric patients are often qualitatively different from U.S. psychiatric patients. Hence the sole reliance on all foreign psychiatric data to support psychiatric NDA applications would not be entirely applicable to U.S. psychiatric patients or psychiatric practice, violating 21 C.F.R §314.106(b). It behooves the Agency to require some recruitment of United States patients for all pivotal, phase 3 psychiatric trials in order to comply with 21 C.F.R §314.106(b) and to ensure applicability of non-U.S.-derived psychiatric data.

6. One could also make an argument, based on the divergent baseline psychiatric characteristics noted above between U.S. and non-U.S. patients, that patients in the non-U.S. subgroup were diagnosed with a pure-form of bipolar depression and thus likely to demonstrate efficacy, citing the lack of additional psychiatric illness reported in non-U.S. patients. This argument would have some merit if it were not for the fact that a.) The treatment effect from the European subgroup in study 235 was so strong as to be strongly statistically significant by itself; b.) Geographical variation of efficacy was also seen in South America in study 292; c.) An internal analysis of the treatment effect from the non-European subgroup was clinically insignificant compared to Europe [MADRS score change compared to placebo -1.4 (SE 1.74) v. -7.0 (SE 1.68) respectively]; d.) the absence of the Russian subgroup from the European data set in study 292 led to a dramatic reduction in treatment effect in the European dataset when compared to study 292 [MADRS score change compared to placebo -2.9 $\pm$ 1.85 v. -7.0 (SE 1.68) respectively]. Therefore it is reasonable to believe that the European subgroup (particularly the Russian subgroup) is an outlier and not consistent with the results from the rest of the study. This will be further discussed under issue #2 below.

7. Another argument could state that an increase in placebo response rates in North American clinical trials has led to a reduced treatment effect in data obtained from North America for study 236. The recent trend in an increase in placebo-response rates from clinical trials over the past 20 years has recently been noted by the Agency[6,7]. One theory to explain these findings relies on the potential association that recruitment of paid study participants (an often-used recruitment mechanism in the United States) can confound study results by leading to an increase in placebo-response rates in U.S. study subjects compared to non-U.S. sites, since these compensated subjects often become "professional patients" and are biased to respond to any treatment. However for study 235 (the adjunctive study described below), the sponsor conducted Agency-requested analyses to examine for potential explanations for lack of efficacy findings in U.S. vs. non-U.S derived data. The findings from the sponsor's placebo-response analysis failed to correct

[6] Khin NA, Chen YF et al "Exploratory analyses of efficacy data from schizophrenia trials in support of new drug applications submitted to the US Food and Drug Administration" *J Clin Psychiatry* 2012 Jun; 73(6):856-64
[7] Khin NA, Chen YF et al "Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications" J Clin Psychiatry 2011 Apr; 72(4):464-72

for the variance seen in U.S. vs. non-U.S. efficacy results for study 235. There is little evidence to support the argument that increases in placebo-response from U.S. patients led to lack of efficacy in the U.S. subgroup.

8. Finally, one can argue that serum exposures to lurasidone, particularly with three-fold increase in serum concentrations with administration with food, may have been responsible for the geographical variation in efficacy. However there were no significant geographical variation in serum lurasidone concentrations noted in study 235 after review of the sponsor's-response to an April 2013 Agency request to examine geographical variation in lurasidone concentrations.

Conclusion
After review and analysis of the data and pertinent statutes and regulations, this reviewer concludes that the efficacy results from the adequate and well-controlled adjunctive therapy studies fail to provide "substantial evidence" that lurasidone is effective for adjunctive treatment of bipolar depression within the United States. Therefore IAW 21 U.S.C. §355(d)(5), the Agency must refuse to approve the adjunctive therapy supplement S-011.

Issue #2
A second issue that must be considered by the data is whether or not there is an explanation for the subgroup efficacy results and strong treatment effect difference that was demonstrated between the European and non-European subgroups.

Analysis
As previously stated under point #6 above, the Agency conducted an internal analysis looking at efficacy results between Europe and non-European subgroups for study 235. The results of this internal analysis revealed that the treatment effect from the non-European subgroup was clinically insignificant compared to Europe [MADRS score change compared to placebo -1.4 (SE 1.74) v. -7.0 (SE 1.68) respectively]. In addition, the absence of the Russian subgroup from the European data set in study 292 led to a dramatic reduction in treatment effect in the European dataset when compared to study 292 [MADRS score change compared to placebo -2.9 + 1.85 v. -7.0 (SE 1.68) respectively]. Therefore it is reasonable to believe that the European subgroup (particularly the Russian subgroup) is an outlier and not consistent with the results from the rest of the study.

During the review of this application, another internal analysis of the submitted datasets for the adjunctive study 235 indicated that two sites in particular, site 191 in Russia and 618 in the Czech Republic, showed an extremely large treatment effect in lurasidone subjects compared to placebo. For site 191, high baseline MADRS scores (30s) for several patients were noted to have a total cure of depressive symptomatology (scores of 0 to 1 on MADRS) during the 6 weeks of treatment. In addition, the lack of any reported adverse events from site 191 was questioned by a sponsor-directed audit of the site (according to audit summary reports). The response from the principal investigator at site 191 with regards to this query was to confirm that no adverse events took place with no additional explanation given for the investigator.

During the statistical review of the data from study 235, removal of the efficacy data from site 618 and 191 in the primary analysis resulted in the pooled efficacy results from study 235 showing that lurasidone lacked efficacy in the adjunctive treatment of bipolar depression. As a result of these findings, the division has requested clinical inspections of site 191 and 618 to verify the data integrity and ensure that policies and procedures were followed in accordance to

FDA regulations and policies. Unfortunately the Agency was not able to conduct these inspections prior to the PDUFA deadline.

Conclusions
Based on the strong treatment effect between European and non-European efficacy subgroups study 235 along with a dramatic reduction in treatment effect from the European subgroup with the absence of Russian data in study 292, these findings does little to provide "substantial evidence" that lurasidone is effective for the adjunctive treatment of bipolar depression the within the United States IAW 21 U.S.C. §355(d)(5). However one can reasonably conclude that data obtained from the Russian subgroup had a significant effect on the treatment effect that was seen from the European subgroup and the global endpoint in study 235.

In addition, the inability to obtain inspections of sites 191 and 618, combined with an inadequate analysis by the sponsor to examine factors that could explain efficacy for the European continent compared to all non-European derived data leads to the similar conclusion that at this time this application requires a Complete Response action by the Agency.

Issue #3
The last issue to consider whether or there is an unmet need for the treatment of bipolar depression within the United States. Currently there are two approved medications indicated for the treatment of bipolar depression, Seroquel XR and Symbyax. Lurasidone appears to have less of a metabolic signal compared to these two medication, but also appears to have a greater dose-related increase in akathisia and parkinsonism compared to the two approved drugs. Although a comparative efficacy analysis cannot be determined from the two submitted adjunctive studies for this NDA application, or is currently a decision factor in the approvability of a particular drug, the current approved labeling for Seroquel XR notes mean MADRS score changes of -4.1 to -6.5, with the Symbyax approved-labeling noting mean MADRS score changes of -6 to -8. Comparing these mean MADRS score changes to the results noted in the lurasidone monotherapy study 236 (mean MADRS score change of -4.6 $\pm$1.17) and adjunctive therapy study (mean MADRS score change of -3.6 (SE 1.25), it appears that lurasidone treatment is associated with a smaller mean change reduction of MADRS scores compared to existing products in treating bipolar depression.

One unmet need is the treatment of bipolar disorder in pregnant and lactating patients. Current guidelines for the treatment of this population are to consider discontinuation or medications or continue with lithium despite a higher fetal risk of Ebstein's anomaly if exposed to lithium in the first trimester.[8] For treatment of bipolar depression, selective serotonin reuptake inhibitors can be used with caution, with no evidence of teratogenicity with haloperidol for treatment of mania/psychosis. Electro convulsive therapy for severe depression and/or mania is less likely to pose risks than pharmacotherapy.

Lurasidone, a category B drug, may be useful to treat bipolar depression as monotherapy. Unfortunately, the lack of evidence to support the efficacy of lurasidone for the treatment of bipolar disorder as monotherapy significantly reduces the likelihood that lurasidone will be a clinically appropriate therapy for use in pregnancy, regardless of lurasidone's effects for bipolar depression. Since current practice guidelines recommend several options to treat bipolar disorder

[8] Hirschfeld RMA, Bowden CL et al: " Practice Guideline for the treatment of patients with bipolar disorder second edition". DOI: 10.1176/appi.books.9780890423363.50051 obtained from http://psychiatryonline.org on 6 May 2013.

and bipolar depression in pregnancy using currently existing therapies, there is low risk that withholding an approval for this NDA for the indication of bipolar depression will lead to lack of treatment options for the pregnant bipolar depressed or pregnant bipolar disorder populations respectively. While lurasidone can potentially be the sole option for treatment of both bipolar depression and bipolar disorder in pregnancy, this reviewer recommends that this reason by itself should compel the Agency to strongly recommend to the sponsor that bipolar disorder studies for lurasidone should be conducted.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, this reviewer has no recommendations for post market risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

Should the Agency approve either or both applications, it is this reviewer's recommendation that sponsor be required to conduct bipolar disorder trials to assess for the efficacy of lurasidone in the treatment of bipolar disorder. The fulfillment of this commitment is essential to the safe and effective use of lurasidone, especially if the monotherapy supplement obtains Agency approval.

All currently approved monotherapy treatments for bipolar disorder or bipolar depression have been initially shown to be effective as a mood stabilizer, since bipolar disorder is defined as patients who have demonstrated a history of at least one manic or hypomanic episode. Should lurasidone receive approval for monotherapy treatment of bipolar depression, a monotherapy claim infers that lurasidone is also effective for the treatment of bipolar disorder. To this reviewer's knowledge, it currently is not, nor has been, the policy of the Agency to grant de facto claims of efficacy without adequate and well-controlled data to substantiate claims of efficacy.

Based on lurasidone's pharmacology as an atypical antipsychotic and knowledge that other members of the class have been shown effective for the treatment of mania, it is likely that lurasidone may have mood stabilizing properties. However the lack of any available efficacy data for lurasidone in the treatment of mania will require the sponsor to conduct such studies in order to protect public health should the Agency grant the monotherapy claim.

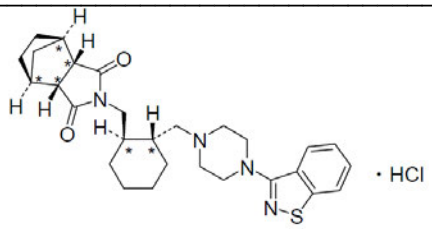
2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Lurasidone, an atypical antipsychotic, has been developed as an immediate release solid oral dosage form containing 20, 40, 80, and 120mg of lurasidone hydrochloride per tablet.

The chemical name and chemical structure for lurasidone is provided below for reference:

(3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4[(1,2-benzisothiazol-3-yl)piperazin-1-ylme]cyclohexymethyl}hexahydro-4,7-methano-2-isoindole-1,3-dione Hydrochloride.



Asterisks (*) indicate chiral carbons

The molecular weight of lurasidone HCL is 529.14 with the following molecular formula:

$$C_{28}H_{36}N_4O_2S*HCL$$

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently two (2) U.S. products approved for the treatment of bipolar depression as listed below.

Table 1: Current Products Available in the United States for the Treatment of Bipolar Depression*

Product	Sponsor	Indication
Seroquel XR® (Quetiapine fumarate extended release)	AstraZeneca	• Depressive Episodes associated with bipolar disorder (type I and type II)
Symbyax® (olanzapine and fluoxetine hydrochloride)	Eli Lilly	• Depressive episodes associated with bipolar I disorder in adults

*both products also are approved for the treatment of mania associated with bipolar disorder

2.3 Availability of Proposed Active Ingredients in the United States

Lurasidone hydrochloride has been approved in the United States for the treatment of schizophrenia. The initial U.S. approval for lurasidone in the treatment of schizophrenia was granted on 28 October 2010.

2.4 Important Safety Issues With Consideration to Related Drugs

The following are antipsychotic-class safety issues that are currently described in the product labeling of lurasidone and other antipsychotic medications.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

As an atypical antipsychotic, lurasidone has boxed warning language consistent with other antipsychotics to warn prescribing clinicians of a potential increased risk of death that has been associated with treating elderly patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS)
NMS is a rare and potentially fatal adverse event that has been reported with antipsychotic drug administration, to include lurasidone.

Tardive Dyskinesia
Serious and sometime permanent abnormal involuntary movements have been associated with antipsychotic-class of medications.

Metabolic Changes
Administration of antipsychotic-class medication has been associated with increases in blood glucose level, diabetes, increased serum levels of cholesterol and triglycerides, as well and weight gain.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Although the sponsor has made various clinical and non-clinical submissions during the bipolar depression clinical development program, this review will focus on the pertinent clinically-related submissions that occurred during the bipolar depression clinical development program.

On 19 June 2008, the sponsor requested to hold a Type-B pre-IND meeting for pIND 103,427. The Agency communicated with the sponsor on 9 July 2008 to submit materials and questions to the Agency for consideration. Consequently the sponsor submitted pre-IND materials to the schizophrenia IND 61,292 on 13 August 2008 for Agency comment in lieu of a face-to-face meeting.

In an Agency letter dated 14 October 2008 in response to the 13 Aug 2008 submitted materials, the Agency stated that post-hoc analysis of results from a schizophrenia study (D1050196) demonstrated significant change in depressive symptoms as assessed by the MADRS scale, thus prompting the sponsor to consider development of lurasidone for the treatment of bipolar depression. Studies 235 and 236 were proposed as part of the 13 August 2008 submission with the Agency noting that the two proposed draft protocols appear adequate on face to support an sNDA for lurasidone treatment of depressive disorders associated with bipolar disorder, both monotherapy and adjunctive therapy.

On 17 December 2008, the sponsor submitted an initial Investigational New Drug Application (IND 103,427) to the Agency for the treatment of bipolar depression. After review of the submitted FDA materials for IND 103,427, the sponsor was notified by email on 14 January 2009 from Doris Bates, PhD., that the study was allowed to proceed with the official letter to proceed being sent by the Agency on 6 February 2009 to the sponsor. The sponsor later submitted a draft statistical analysis plan for study 235 to the Agency on 19 December 2011 with Agency comments sent to the sponsor on 27 January 2012.

Ultimately the sponsor submitted a Type-B pre-NDA meeting request on 12 April 2012 that was granted by the Agency. The Agency and sponsor met via teleconference to discuss the results of study 235 and 236 in preparation for a possible sNDA submission for lurasidone for the treatment of bipolar depression, both monotherapy and adjunctive therapy. A review of briefing package for this meeting is noteworthy in that only summary efficacy results and tables were included into the briefing package showing that overall efficacy was demonstrated in lurasidone-treated patients compared to placebo. At no point in either the briefing package or in conversations reflected in meeting minutes did the sponsor disclose or inform the Agency that the efficacy data from the two studies 235 and 236 showed geographical variation, with lack of efficacy in North America, Asia, and Africa and efficacy only demonstrated in European data.

A review of the Agency minutes from the meeting date 24 May 2012 notes that four additional studies (two open label, two double-blind studies) were to contribute to the safety database of the sNDA. Specifically study 292 and study 296 (double-blind, placebo-controlled, parallel groups study of adjunctive lurasidone for the prevention of recurrence in subjects with bipolar 1 disorder) were mentioned to contribute to the safety database of the sNDA. Upon review of the summary efficacy and safety results from studies 235 and 236 that were submitted as part of the briefing package, the Agency stated that:

"…on face, there appears to be sufficient data to support submission of a sNDA for lurasidone in the treatment of depressive episodes associated with bipolar I disorder as monotherapy and adjunctive therapy to lithium or valproate. Whether the data from these pivotal trials are sufficient to support these indications is a matter for review."

On 31 August 2012, the sponsor submitted NDA 200-603 S-010 (monotherapy) and S-011 (adjunctive therapy) the Agency for review.

2.6 Other Relevant Background Information

There were four (4) protocol amendments that were submitted to the Agency for both studies (235 and 236). A brief summary of the pertinent changes is presented below.

- Amendment #1 18 Feb 2009- this amendment added the requirement to use an electronic version of the MINI to be used in making a bipolar diagnosis at screening (language specific version for other countries). In addition a secondary efficacy analysis was removed (proportion of patients with treatment emergent mania). Also blister cards were changed to allow 7 days plus 2 additional days of dosing.
- Amendment #2 6 Aug 2009- this amendment made several changes to each study as specified below:
    - Study 235: Sheehan Disability Scale was changed from electronic to paper based format. Subjects who required hospitalization at screening were excluded from the study. A rater quality control program (voice recordings) for the MADRS was implemented at all non-US sites.
    - Study 236: Inclusion criteria 5 was added that specified subjects must have both rater administered and computerized MADRS total scores at both screening and baseline of at least 20 or greater
- Amendment #3 16 Nov 2009- This amendment made a change to both studies that a confirmation of the diagnosis made by the MINI is required for study entry. For study 235, the lower limit of lithium serum concentrations at screening and during the study was set to 0.4mEq/L for subjects who cannot tolerate levels of 0.6 or greater. In addition, investigators will verify that lithium/divalproex was taken for at least 28 days via reliable informant or treating health professional. In addition, numerous new investigators were added to the protocol, to include Dr. Tochilov, site 191.
- Amendment #4 dated 02 Dec 2011- This protocol amended both studies to remove the key secondary endpoint of functional impairment assessed by the Sheehan Disability Scale total score to a secondary endpoint, as well as moving the C-SSRS from an efficacy to a safety variable.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) was provided a list of 7 U.S. sites for inspections on 2 November 2012 as shown below:

Table 2: Office of Compliance Inspections

Site Name and #	Number Subjects Monotherapy study	Number of subjects Adjunctive Study
Howard Hassman, Site 120	8	13
Rosario Hidalgo Site 100	4	12
Tram Tran-Johnson Site 103	6	10
Raymond Manning Site 094	14	20
Glen Dempsey Site 080	1	10
Richard Weisler Site 106	7	9
David Walling Site 105	9	18

A report of inspection findings from four of the seven sites (sites 100, 094, 105 and 120) was filed to the NDA on 11 Feb 2013. Overall there were no major violations noted and the data from all the sites were deemed reliable. A brief summary of the report is provided below.

Clinical inspections of Dr Hidalgo took place on 27 Nov-4 December 2012 from staff of the Office of Scientific Investigations. A Verbal Action Indicated (VAI) was given to for a minor deficiency for use of a prohibited medication. Data from sites 094 and 105 were also deemed reliable with no OAI or VAI given. At site 120, some minor deficiencies were noted but an NAI was given to this site.

During the review of the efficacy data submitted with this NDA, a noted geographical variation in efficacy results was seen in efficacy data from both the monotherapy and adjunctive bipolar study. Specifically, efficacy was not established in the United States, India, or South Africa. However efficacy was established only in patients treated in Europe. During an internal meeting with the statistical team in February 2012, it was noted that two particular sites, site 191 and site 618, had a very high efficacy response with virtually no adverse events being reported from these two sites. In addition, removal of the efficacy data from these two sites would lead to the overall adjunctive study (study 235) being not statistically significant on the primary endpoint.

On 4 March 2013, the division requested OSI to perform clinical inspections of sites 191 and 618. However the OSI team was unable to conduct such inspections before the PDUFA goal date.

3.2 Compliance with Good Clinical Practices

Studies 235, 236, and 292 were conducted according to the Declaration of Helsinki and amendments. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997.

3.3 Financial Disclosures

See Appendix for Financial Disclosure Template.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Chhagan Tele, Ph.D. of the Office of New Drugs and Quality Assurance (ONDQA) performed a review of the Chemistry, Manufacturing and Controls (CMC) section of the supplement on 02 October 2012. As there was no new CMC data or changes to existing formulations being proposed in this supplement, Dr. Tele recommended approval of the supplement from a CMC perspective.

4.2 Clinical Microbiology

Due to the absence of any clinical microbiological data, a review of such data is not applicable to this submission.

4.3 Preclinical Pharmacology/Toxicology

A pharmacology/toxicology review of this supplement was conducted by Sonia Tabacova, Ph.D. on 10 May 2013. A brief summary of this review indicates that no new non-clinical studies were submitted as part of this IND. As there was no additional information related to lurasidone as part of a literature search, it was Dr. Tabacova's recommendation that there are no new non-clinical data or concerns that affect the safety profile of lurasidone form the treatment of depressive episodes associated with bipolar I disorder.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action is currently unknown for lurasidone. However based on preclinical receptor studies and the known clinical efficacy of lurasidone for the treatment of schizophrenia, it is believed that lurasidone's actions as a dopamine 2 (D2) receptor and serotonin receptor $5HT_{2a}$ antagonist in the central nervous system are believed to be involved in the clinical actions in reduction of symptoms in schizophrenia.

4.4.2 Pharmacodynamics

In preclinical studies, lurasidone is a potent D2 and $5HT_{2a}$ receptor antagonist, with some $5HT_7$ receptor antagonistic properties. In addition, lurasidone has some partial agonist activity at the $5HT_{1a}$ receptor.

With regards to ECG effects, lurasidone had little effects on the QT interval during a thorough QT study that was conducted under the schizophrenia clinical development program.

Lurasidone treatment has been associated with a slight increase in serum creatinine levels in schizophrenia studies when compared to placebo treatment. Little effects on hepatic enzymes were noted during clinical trials.

4.4.3 Pharmacokinetics

Absorption
After oral administration, lurasidone is absorbed poorly, with only 9-19% of the oral dose being absorbed. Peak time of maximum absorption (T_{max}) has been shown to be 1-3 hours after administration. The extent of absorption of lurasidone, as measured by C_{max} and AUC, is affected with food administration, whereby AUC and C_{max} are increased 3 fold and 2 fold, respectively, with food administration compared to fasting conditions. Thus lurasidone is currently recommended to be taken with food.

Distribution
Due to the poor solubility of lurasidone, lurasidone is highly protein bound in serum, with over 99% being protein bound. The poor solubility and highly protein-bound nature of lurasidone is reflected in a very large apparent volume of distribution of 6137 liters.

Metabolism
Lurasidone is highly metabolized by phase 1 oxidative reactions in the liver by CYP3A4, with n-dealkylation and S-oxidation to two active and two inactive metabolites. The apparent half-life of lurasidone in humans is approximately 18 hours.

Elimination
Excretion of lurasidone and its' metabolites occurs primarily through alimentary elimination, with approximately 89% of radiolabeled lurasidone being recovered in feces and 9% recovered in urine after a single 40mg radiolabeled dose of lurasidone.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Table 3: Latuda® Table of Studies

Adjunctive Studies	
D1050235 Flexible Dose	A six-week outpatient, multicenter, international (10 countries), double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), flexible dose study of 348 patients (ages 18-75 years of age) with a current clinical diagnosis of bipolar I disorder most recent episode depressed (with or without rapid cycling) of at least 4 weeks duration but less than one year with baseline MADRS scores of 20 or greater and Young Mania Rating Scores of less than 12 at baseline who are taking

	either lithium (0.6-1.2mEq/L) or valproic acid (50-125mcg/mL) at time of screening and had at least 28 days of lithium or valproic acid that was verified. First Enrollment: 11 May 2009 Last Subject: 09 Jan 2012
D1050292 Flexible dose	A six-week outpatient, multicenter, international (10 countries), double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), flexible dose study of 356 patients (ages 18-75 years of age) with a current clinical diagnosis of bipolar I disorder most recent episode depressed (with or without rapid cycling) of at least 4 weeks duration but less than one year with baseline MADRS scores of 20 or greater and Young Mania Rating Scores of less than 12 at baseline who are taking either lithium (0.6-1.2mEq/L) or valproic acid (50-125mcg/mL) at time of screening OR were candidates for lithium or valproic acid and received at least 28 days of Lithium or valproic acid who still met inclusion criteria for depression severity at the end of run-in. First Enrollment: 13 December 2010 Last Subject: 07 Aug 2012
MONOTHERAPY STUDY	
D1050236 Flexible Dose	A six-week outpatient, multicenter, international (8 countries), double-blind, parallel-group, placebo controlled, randomized (1:1:1-Low dose 20-60mg: High Dose 80-120mg: placebo), flexible dose study of 505 patients (ages 18-75 years of age) with a current clinical diagnosis of bipolar I disorder most recent episode depressed (with or without rapid cycling) of at least 4 weeks duration but less than one year with baseline MADRS scores of 20 or greater and Young Mania Rating Scores of less than 12 at baseline First Enrollment: 29 April 2009 Last Subject: 01 Feb 2012
OPEN LABEL SAFETY STUDY (ONGOING)	
D1050256 Open Label	A 24 week, outpatient, multicenter, open label extension study of 504 adults (as of 12 Apr 2012) aged 18-75 years who have completed study 235 or 236, 203 patients of which were randomized to placebo from the antecedent studies.

5.2 Review Strategy

Table XX below provides a listing of documents that were reviewed during the NDA review process.

Table 4: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
August 31, 2012	• Study reports: 235, 236, 256 tables, Integrated Safety Summary

	• Clinical Safety Summary • Regulatory History • Review of pertinent SAEs and safety data from previously un-reviewed study 2305 • Proposed labeling • Financial Disclosure Certification • Application Summary • Case Report Tabulations (.xpt files) • Case Report Forms
February 28, 2013	• Study report 292 • Case Report Forms • Review of pertinent SAEs
March 20, 2013	• Partial submission for Agency Request for additional data dated 22 Feb 2013- Raw data and SAS programs for study 292; regulatory history study 292
March 25, 2013	• Full submission for Agency Request for additional data dated 22 Feb 2013 and revised request dated 25 Feb 2013: Efficacy trend and Dose response exploratory analyses of US v Non-US sites; Clinical Site Audits; Audit Reports of non-US sites; Clinical Rater Quality Control
May 7, 2013	• Response to Agency-requested analysis of pharmacokinetic data
May 20, 2013	• Response to Agency-requested analysis to explore the effect of differences in baseline concomitant psychiatric illnesses on study endpoint, U.S. vs. non-U.S. subgroup

5.3 Discussion of Individual Studies/Clinical Trials

Studies 235 and 292 form the basis of the review for the adjunctive treatment of bipolar depression claim for lurasidone. Study 292 was not planned by the sponsor at the pre-NDA meeting to be completed by the time of NDA submission. However the completion of the study during the review of this NDA, which was ultimately a failed efficacy study with a nearly identical study design as study 235, was included as part of the efficacy and safety data review process for the adjunctive therapy claim.

Data from study 236 was reviewed solely to support the monotherapy claim for lurasidone. The longer-term safety and tolerability of lurasidone treatment for bipolar depression was assessed through review of the integrated safety summary, which includes safety data from studies 235,236, 292 and 256, as well as non-Sunovion-sponsored studies.

6 REVIEW OF EFFICACY

Efficacy Summary

Lurasidone treatment was shown to be effective for the treatment of bipolar depression as monotherapy. Study 236 (the sole study in support of the monotherapy indication) demonstrated efficacy on the study's primary efficacy and key secondary endpoints with a trend towards efficacy within the U.S. subgroup. Therefore this reviewer considers this a positive study.

On face, lurasidone was shown to be effective when given adjunctively with lithium or valproic acid compared to placebo treatment. However the adjunctive therapy study 235, in contrast to study 236, demonstrated efficacy on the study's primary and key secondary endpoints but demonstrated WORSE MADRS scores compared to placebo in the U.S. subgroup. An Agency-requested analysis to explore factors that could explain the results between the U.S. and non-U.S. subgroups failed to elucidate factors that could explain this trend, with the sponsor ultimately concluding that known and/or unknown factors may be attributable for the trend towards worsening MADRS scores in the U.S. This reviewer considers study 235 as a negative study based on the unexplainable trend towards worse outcomes with lurasidone treatment in the U.S. subgroup. The sponsor completed a similar adjunctive study (study 292) during review of this NDA. Results from study 292 demonstrated the lurasidone treatment did not show efficacy on the studies primary endpoint, however a trend toward efficacy was seen in the U.S. subgroups, but not the South American subgroup. This reviewer considers study 292 as a negative study.

Since the monotherapy study 236 was the only positive study that demonstrates both efficacy on the primary endpoint and a trend towards efficacy in the U.S. subgroup, it is this reviewer's opinion that lurasidone has not been shown effective for the treatment of bipolar depression. It is this reviewer's recommendation that the sponsor must conduct an additional study that demonstrates efficacy on the study's primary endpoint, as well as a favorable trend towards efficacy in the U.S. subgroup.

6.1 Studies Pertinent to Claim 1

For the monotherapy bipolar depression indication (supplement S-010), the sponsor conducted one (1) efficacy study, study D1050236.

6.1.1 Rationale for Selection of Studies for Review

This is a single study that is being used to support the monotherapy indication for bipolar depression.

6.1.2 Study Summaries

Study 1

Methods/Study Design/Analysis Plan

Study D1050236 is a 6-week, randomized, double-blind, placebo-controlled, flexible dose, parallel group monotherapy study of flexible doses of lurasidone from 20mg to 120mg/day in patients with bipolar I depression. Patients were evaluated for eligibility during a 3-14 day

screening process where all patients were tapered off current medication and underwent screening evaluations to determine patient eligibility for randomization.

Diagnostic confirmation of bipolar occurred with use of a computerized diagnostic instrument, the Bipolarity Index (BPI) and an interviewer-administered structured interview (MINI) conducted by site study staff. Both the BPI and MINI were used to confirm the DSM-IV TR diagnosis of bipolar I disorder, most recent episode depressed, with or without rapid cycling. The current episode was protocol-specified to be confirmed by the investigator and also noted in the source records.

For the BPI assessment, patients will respond to questions on a computer laptop that will then be submitted via score data transfer and reviewed by experts at the Concordant Rater Systems office. Only subjects who have a confirmed previous manic or mixed episode will be entered in the trial. Any uncertainty must be resolved by investigators with CRS to establish diagnosis.

Once eligibility for randomization was confirmed, patients were then randomized in 1:1:1 fashion to one of three treatment arms as specified below:

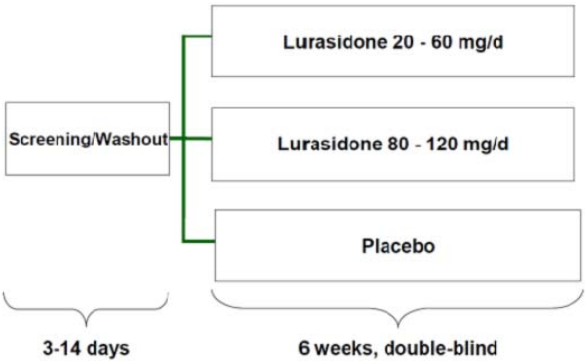
- 20-60mg/day dosing group: These patients were initiated to lurasidone treatment with 20mg/day for 7 days and then flexibly adjusted up to 60mg/day to optimize efficacy and tolerability after day 8.
- 80-120mg/day- These patients were initiated to lurasidone treatment at 20mg for days 1-2, 40mg/day for days 3-4, 60mg/day for days 5-6 and 80mg on day 7. Doses were then flexibly adjusted up to 120mg/day to optimize efficacy and tolerability after day 8.
- Placebo

After day 8, doses for each patient could be increased weekly; however dose reductions were permitted to occur less than weekly intervals for safety and tolerability consideration, with a maximum of two dose reductions being allowed.

During each protocol-specified on-site patient assessment, MADRS scores were entered into a computer system by a qualified rater. In addition, the patient also completed an interactive depressive symptom interview on the same laptop. The data derived from the clinician-administered MARDS and the self-reported patient depression interview was compared by Concordant Rater systems (CRS) as part of a remote rater management program to monitor the primary outcome measure at treatment phase assessments, as well as to provide ongoing feedback + remediation to the rater in the study. The only results transmitted to CRS were the patient's data and subject number. CRS was blinded to the treatment status of patients.

The study design schematic is presented below:

Figure 1: Study 236 Study Design Schematic



Patients

The trial protocol pre-specified that 500 patients meeting the following criteria were to be randomized:

- Subject age 18-75 years of age
- A history of at least one bipolar manic or mixed manic episode (strong recommendation that a reliable informant be available to confirm)
- Currently diagnosed in a major depressive episode of at least 4 weeks to no greater than 12 months
- Screening and baseline MADRS total score of at least 20 or greater
- Screening and baseline YMRS total scores of at 12 or less
- Non pregnant females using adequate contraception
- If on concomitant medications, stable doses of oral hypoglycemic, thyroid replacement and antihypertensive medications

Patients were excluded for the following pertinent reasons:

- Another primary Axis I or II diagnosis within three months of screening
- A score of at least 4 or greater on MADRS item 10 (suicidal thoughts) at screening or baseline
- History of non-response to an adequate 6 week trial of three or more antidepressants (with or without mood stabilizers during current episode
- Hospitalization within 60 days prior to randomization
- Treatment with antidepressants within 3 days (28 days for fluoxetine) or randomization, MAOI use within 21 days of randomization or clozapine use within 120 days prior to randomization
- Current history of significant neurological, metabolic, hepatic, renal, hematological, or other medical condition that might confound the study
- A demonstrated 25% or greater improvement (decrease) in MADRS score between screening and baseline or total MADRS score less than 20 at baseline
- Evidence of acute or chronic hepatic dysfunction, malignancies within the phase 5 years, history of organic CNS diseases
- History of NMKS, severe tardive dyskinesia or dystonia

- Alcohol or substance abuse within 3 months prior or dependence within 12 months prior to screening
- UDS positive at screening or baseline with cannabis users being evaluated on a case by case basis for ability to abstain from THC during study
- Diabetics who are uncontrolled (screening glucose >200, hemoglobin A1C greater than 7%)
- Screening prolactin of >100ng/ml or history of pituitary adenoma
- Abnormal ECG that is clinically significant, BMI greater than 40
- History of depot neuroleptics unless last injection was at least one treatment cycle before randomization
- Prior clinical trial exposure to lurasidone
- Received ECT within 90 days prior to randomization to is expected to require ECT during course of study

Primary Objective

The primary objective of the monotherapy study was to evaluate the efficacy of monotherapy lurasidone treatment compared to placebo treatment for the treatment of subjects with bipolar I disorder, most recent episode depressed, with or without rapid cycling (defined as at least 4 but less than 8 mood disturbances within past 12 months) and without psychotic features.

Key Secondary Objective

The sponsor initially identified two key secondary efficacy objectives for this study:

1. Evaluation of efficacy as measured by the Global severity, as assessed by the Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score
2. Evaluation of efficacy as measured by subject self-report of the functional impairment with bipolar depressive symptoms, assessed by the Sheehan Disability Scare total score

Primary Endpoint

The primary endpoint was *a priori* specified to be the mean change from baseline at week 6 on the MADRS total score in the lurasidone 20-60mg, 80-120mg and placebo treatment arms.

Key Secondary Endpoint

The key secondary endpoints *a priori* specified were the mean changes from baseline to week 6 in the lurasidone 20-60mg, 80-120mg and placebo treatment arms on the CGI-BP-S scale and SDS scale.

Results

Demographics

For the monotherapy study, the majority of patients were white females aged 41.7 and 41.2 years old for the combined lurasidone and placebo groups. The majority of patients randomized into this study were from sites outside of North America (58% for lurasidone patients; 64% of placebo patients), of which European patients constituted the largest proportion of subjects. The Czech

Republic randomized the majority of patients from the European continent, representing 12% of the entire randomized sample.

Table 5: Study 236 Demographics (ITT Population)

Category	Lurasidone 20-60mg (N=161)	Lurasidone 80-120mg (N=162)	Combined Lurasidone (N=323)	Placebo (N=162)	Total #
Age (years)	41.3 ±12.31	42.0 ±12.35	41.7 ± 12.31	41.5 ± 12.35	
White	66%	65%	66%	66%	
Male	43%	40%	41%	46%	
Geographic area					
North America	42%	43%	42%	36%	195 (40%)
Africa (South Africa)	12%	10%	11%	11%	54 (11%)
Asia (India)	14%	14%	14%	17%	73 (15%)
Europe*	32%	32%	32%	36%	165 (34%)
Czech Republic	11%	12%	11%	12%	
France	2%	2%	2%	3%	
Romania	2%	1%	2%	6%	
Russia	7%	6%	7%	6%	
Ukraine	10%	10%	10%	10%	
*includes Czech Republic, France, Romania, Russia, and Ukraine					

Baseline Characteristics

All patients had very similar baseline bipolar depression as based on the mean MADRS, CGI-BP-S and SDS total scores.

Table 6: Study 236 Baseline Bipolar Depression Characteristics (ITT)

Category	Lurasidone 20-60mg (N=161)	Lurasidone 80-120mg (N=162)	Combined Lurasidone (N=323)	Placebo (N=162)
Baseline MADRS Total Score (SD)	30.5 (4.95)	30.6 (4.93)	30.5 (4.97)	30.5 (4.95)
Baseline CGI-BP-S Depression Score	4.52 (0.623)	4.55 (0.641)	4.54 (0.631)	4.48 (0.613)
Baseline SDS total Score	19.7 (4.75)	19.8 (5.58)	19.7 (5.18)	19.8 (4.99)

The historical degree of mania associated with the baseline characteristics of the patients enrolled in the trial is similar amongst all the patients. The majority of patients had a diagnosis of bipolar I disorder without rapid cycling; were first diagnosed with bipolar I disorder at age 27 with an

approximate 14 year duration of bipolar I disorder and a mean 12 week duration of bipolar I depression. Slightly more than half of the patients were never hospitalized for bipolar depression, with 13-15% having 4 or more hospitalizations for bipolar depression. No patients had a diagnosis of ultra-rapid cycling (> 8 or more cycles in 12 mos.).

Table 7: Study 236 Baseline Psychiatric History (ITT)

Category	Lurasidone 20-60mg (N=161)	Lurasidone 80-120mg (N=162)	Combined Lurasidone (N=323)	Placebo (N=162)
Bipolar I disorder without rapid cycling (0-3 cycles in past 12 mos.)	92%	95%	93%	94%
Age at initial onset of Bipolar I (SD)	27.9 (11.92)	27.6 (10.82)	27.7 (11.37)	27.4 (10.76)
Duration of Bipolar I Disorder from initial onset to screening in years (SD)	13.4 (10.15)	14.4 (10.77)	13.9 (10.46)	13.8 (11.74)
Current duration of Bipolar depression in Weeks (SD)	12.0 (8.62)	11.8 (9.43)	11.9 (9.03)	10.6 (6.09)
No prior Hospitalizations for Bipolar Depression	54%	56%	55%	55%
4 or more hospitalizations for Bipolar I depression	13%	13%	13%	15%

However, the sponsor conducted an analysis of baseline psychiatric history between U.S. v. non-U.S. patients at the request of the Agency in order to explore factors related U.S. v. non-U.S. efficacy results. Results from this analysis show that U.S. patients had a longer duration of bipolar illness (19.1 years v. 10.4 years respectively), a longer duration of bipolar depression (14.2 weeks v. 9.7 weeks respectively) and 16% of all U.S. patients had a rapid-cycling diagnosis compared to 0% in the non-U.S. subgroup. Also, 17% of U.S patients had additional psychiatric illness compared to 0% for the rest of the world.

Table 8: Study 236 Baseline Psychiatric History, U.S. v. Non-U.S. Patients (ITT)

	Category	Lurasidone 20-60mg (N=67)	Lurasidone 80-120mg (N=70)	Placebo (N=58)	Total (N=195)
U.S. Patients	Proportion of Patients with rapid-cycling %	19%	11%	17%	16%
	Duration of Bipolar I Disorder from initial onset to screening in years (SD)	17.4 (11.1)	19.6 (11.4)	20.5 (12.5)	19.1 (11.6)
	Current duration of Bipolar depression in Weeks (SD)	14.3 (10.0)	15.2 (12.5)	12.8 (7.8)	14.2 (10.4)
	4 or more hospitalizations for Bipolar I depression	19%	11%	17%	16%
	Additional psychiatric diagnoses	19%	15%	17%	17%

	Category	Lurasidone 20-60mg (N=94)	Lurasidone 80-120mg (N=92)	Placebo (N=104)	Total (N=290)
Non-U.S. Patients	Proportion of Patients with rapid-cycling %	0%	0%	0%	0%
	Duration of Bipolar I Disorder from initial onset to screening in years (SD)	10.6 (8.4)	10.5 (8.4)	10.0 (9.5)	10.4 (8.8)
	Current duration of Bipolar depression in Weeks (SD)	10.3 (7.1)	9.3 (4.9)	9.4 (4.5)	9.7 (5.6)
	4 or more hospitalizations for Bipolar I depression	13%	15%	13%	13%
	Additional psychiatric diagnoses	0	0	0	0

Patient Disposition

Approximately 25% of all randomized patients in the trial were discontinued from the double-blind phase of the trial. The majority of patients that were discontinued from the trials were due to insufficient clinical response, followed by adverse events. Of the 374 patients that completed the entire study, 85% of these patients continued into the open label extension study 256.

Table 9: Study 236 Patient Disposition

Category	Lurasidone 20-60mg	Lurasidone 80-120mg	Combined Lurasidone	Placebo	Total
Subjects Screened					818
Screening failures					313 (38%)
Subjects Randomized	166	169	335	170	
Competed the Double-Blind Phase	123 (74%)	124 (73%)	247 (74%)	127 (75%)	374 (74%)
Rationale for Discontinuation					
Insufficient clinical response	12 (7%)	5 (3%)	17 (5%)	13 (8%)	
Discontinued for worsening of existing Condition on Adverse Event Page (AE)	3 (2%)	1	4 (1%)	5 (3%)	
Discontinued for worsening of existing Condition other than Worsening of Bipolar I disorder (AE)	8 (5%)	9 (5%)	17 (5%)	6 (4%)	
Lost to follow-up	7 (4%)	7(4%)	14(4%)	5(3%)	
Protocol Violation	7(4%)	4(2%)	11 (3%)	6 (4%)	
Withdrew Consent	3 (2%)	10 (6%)	13 (4%)	2 (1%)	
Administrative	3 (2%)	9 (5%)	12 (4%)	6 (4%)	
Subjects Discontinued due to insufficient Clinical Response or Worsening of Existing condition	15 (9%)	6 (4%)	21 (6%)	18 (11%)	
Continuing into extension study	109 (89%)	102 (82%)	211 (85%)	107 (84%)	318 (85%)

Prior Medication Use

Sixty nine percent (69%) of patients who entered the trial were taking one or more prior medications. The following list pertains to pertinent prior use of psychiatric medications in the ITT population:

Table 10: Study 236 Prior Medication Use (ITT)

Medication	Lurasidone group Combined N=323	Placebo N=162
One Or More Prior Medications	70%	68%
Antidepressants	29%	29%
Antiepileptic	15%	15%
Antipsychotics (incl. Lithium)	28%	31%
Anxiolytics	16%	23%
Hypnotics and sedatives	13%	11%

Concomitant Medication

The majority of patients in the monotherapy trial were taking concomitant medications (57% lurasidone combined v. 58% placebo patients). The majority of concomitant medication use was for drugs without a psychiatric indication. Only one patient was taking a concomitant antidepressant, antiepileptic (lamotrigine) or antipsychotic (quetiapine) during the trial. Patients continued to use concomitant anxiolytic agents during the trial, with the majority using lorazepam.

Table 11: Study 236 Concomitant Medication Use During Trial (ITT)

Medication	Lurasidone group Combined N=323	Placebo N=162
Any	57%	58%
Antidepressants	<1%	--
Antiepileptic	<1%	--
Antipsychotics (incl. Lithium)	<1%	--
Anxiolytics	13%	20%
Hypnotics and sedatives	13%	10%
Anticholinergic Agents	4%	2%

Important Protocol Deviations

The majority of protocol deviations were due to testing positive for illicit substances, prohibited use of medication and exposure less than 14 days.

Dosing

For the monotherapy trial, the mean daily dose for the 20-60mg/day lurasidone group for all subjects was 31.6mg $\pm$11.11 mg/day with completers having a mean daily dose of 33.4 $\pm$11.52mg/day. For the 80-120mg/day lurasidone group, mean daily dose for all subjects was 80.4 $\pm$16.14mg/day with completers having a mean daily dose of 85.1 $\pm$10.70 mg/day.

The mean modal dose for the 20-60mg/day lurasidone group for all subjects was 34.6mg +16.44 mg/day with completers having a mean modal dose of 37.4±16.98mg/day. For the 80-120mg/day lurasidone group, mean modal dose for all subjects was 90.6 ±19.15mg/day with completers having a mean modal dose of 93.9 ±15.34mg/day. For the combined lurasidone group, the mean modal dose for all subjects was 62.8 ± 33.22mg/day with completers having a mean modal dose of 65.7±32.57.

Efficacy Results

Primary Efficacy Endpoint

The primary efficacy analysis was based on the intent to treat (ITT) population, defined as all subjects who were randomized, received at least one dose of the study medication, and had at least one baseline and one post-baseline efficacy measurement for the MADRS or CGI-BP-S scales.

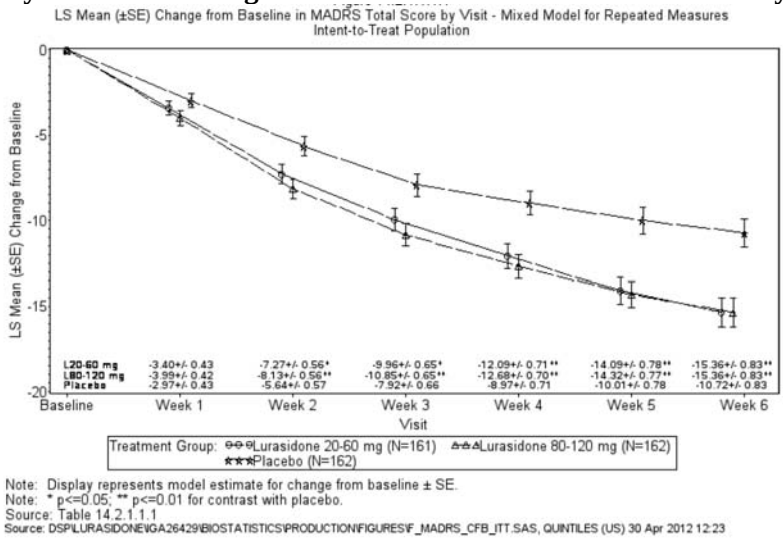
The primary efficacy analysis assessed the change from baseline scores on the MADRS total score at week 6 between each lurasidone dose group and combined lurasidone group, using an MMRM model. The following table delineates the weekly change from baseline scores in the three treatment groups.

Table 12: Study 236 Mean Change from Baseline MADRS Total Scores by Visit (ITT)

Treatment Group	Base-line	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Placebo N=162	30.5 (4.95)	-3.0 (0.43)	-5.6 (0.57)	-7.9 (0.66)	-9.0 (0.71)	-10.0 (.078)	-10.7 (0.83)
Lurasidone 20-60mg N=161	30.5 (4.95)	-3.4 (0.43)	-7.3 (0.56)	-10.0 (0.65)	-12.1 (0.71)	-14.1 (0.78)	-15.4 (0.83
Lurasidone 80-120mg N=162	30.6 (4.93)	-4.0 (0.42)	-8.1 (0.56)	-10.8 (0.65)	-12.7 (0.70)	-14.3 (0.77)	-15.4 (0.83)

Assessment of change on the MADRS-total score by week is graphically presented below:

Figure 2: Study 236 Mean Change from Baseline in MADRS Total Score by Visit (ITT)



For the primary efficacy analysis, the mean change from baseline at week 6 on the MADRS total scores revealed that both lurasidone 20-60mg/day and 80-120mg/day treatment groups statistically improved depressive symptomatology as measured by the MADRS when compared to placebo treatment. However there was no advantage, either statistically or numerically, in improvement of depressive symptomatology as measured by the MADRS-total score in patients who received the higher dosing of 80-120mg/day when compared to the 20-60mg/day dosing groups.

Table 13: Mean Change from Baseline in MADRS Total Score in Lurasidone 20-60mg/day Patients from Placebo Patients by Visit (ITT)

Week	Placebo	Lurasidone 20-60mg/day	Mean change Lurasidone-Placebo (SE)	P-value
Baseline	30.5 (4.95)	30.5 (4.95)	--	--
Week 1			-0.4 (0.59)	0.463
Week 2			-1.6 (0.79)	0.040
Week 3			-2.0 (0.92)	0.027
Week 4			-3.1 (1.00)	0.002
Week 5			-4.1 (1.09)	<0.001
Week 6			-4.6 (1.17)	**<0.001 <0.001***

*adjusted p-values using Hommel-based tree-gatekeeping procedures.

Table 14: Mean Change from Baseline in MADRS Total Score in Lurasidone 80-120 mg/day Patients from Placebo Patients by Visit (ITT)

Week	Placebo	Lurasidone 80-120mg/day	Mean change Lurasidone-Placebo (SE)	P-value
Baseline	30.5 (4.95)	30.6 (4.93)	--	--
Week 1			-1.0 (0.59)	0.085
Week 2			-2.5 (0.79)	0.002
Week 3			-2.9 (0.92)	0.001
Week 4			-3.7 (1.00)	<0.001
Week 5			-4.3 (1.09)	<0.001
Week 6			-4.6 (1.17)	**<0.001 <0.001***

*adjusted p-values using Hommel-based tree-gatekeeping procedures.

Table 15: Mean Change from Baseline in MADRS Total Score in Lurasidone 80-120 mg/day Patients from Lurasidone 20-60 mg/day at Week 6 (ITT)

Week	Lurasidone 20-60mg/day	Lurasidone 80-120mg/day	Mean change (SE)	P-Value
Week 6	-15.4 (0.83)	-15.4 (0.83)	0.0 (1.17)	0.998

Geographic Variation

Since study 236 was not powered to detect a statistically significant change in MADRS scores by region, this review will focus on the numerical trends in efficacy by region, with limited interpretation of statistical testing.

A review of the geographical efficacy results reveals that a consistent trend toward numerical improvement in MADRS scores in the lurasidone-treatment groups was seen, with the exception of the low dose lurasidone group in Africa. Even though study 236 was not powered to detect a significant difference in MADRS scores, a highly significant result in the European subgroup indicates that lurasidone treatment was associated with an unusually large treatment effect for this subpopulation.

Table 16: Mean Change from Baseline MADRS Total Score at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America N=195	Rest of the World* N=290
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-13.2 (1.53)	-8.9 (0.96)
Lurasidone 20-60mg (SE)	-17.1 (1.46)	-14.0 (1.00)
Lurasidone 80-120mg (SE)	-15.3 (1.45)	-15.4 (0.99)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-60mg (SE)	-3.9 (2.11) p=0.068	-5.2 (1.38) p<0.001
Lurasidone 80-120mg (SE)	-2.1 (2.11) p=0.330	-6.6 (1.37) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Romania, Russia and Ukraine)

Table 17: Mean Change from Baseline MADRS Total Score at Week 6 By Continent, excluding North America North America (ITT)

Treatment Group	Africa N=54	Asia N=73	Europe* N=163
Mean Change from Baseline MADRS at Week 6			
Placebo (SE)	-12.9 (1.60)	-12.6 (2.47)	-6.3 (1.25)
Lurasidone 20-60mg (SE)	-12.6 (1.60)	-16.2 (2.49)	-14.1 (1.33)
Lurasidone 80-120mg (SE)	-13.7 (1.70)	-15.4 (2.32)	-16.4 (1.32)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-60mg (SE)	0.4 (2.26) p=0.862	-3.6 (3.49) p=0.311	-7.8 (1.82) P<0.001
Lurasidone 80-120mg (SE)	-0.8 (2.33) p=0.749	-2.8 (3.40) p=0.418	-10.1 (1.82) P<0.001

*includes Czech Republic, France, Romania, Russia, and Ukraine

6.1.3 Crosscutting Issues

Subgroup Analyses

In February 2013, the Agency requested the sponsor to evaluate the paradoxical finding of improved efficacy with the lower dosing range of 20-60mg/day of lurasidone in US patients compared to the rest of the world where efficacy was improved at the 80-120mg/day lurasidone dose.

The sponsor conducted exploratory analyses to examine the effect of various factors that could explain the results. A summary of the findings are presented below:

- Baseline Demographics and Clinical Characteristics: The sponsor examined differences in patients mean age, gender, race, ethnicity, body weight, MADRS and CGI-BP-S scores, duration of bipolar illness, duration of current depressive episode, number of prior hospitalizations for bipolar depression and proportion of patients with rapid cycling bipolar disorder as to overall treatment effect each factor may have contributed to the geographical efficacy results seen. Results from the analysis revealed consistent demographic and clinical characteristics for both US and non-US patients in low and high dose lurasidone groups. Thus neither demographic nor clinical characteristics could explain the reversal of the dose-response trend in US patients. However, the sponsor did not statistically assess nor mention the effects of additional psychiatric diagnoses in 17% of U.S subjects compared to 0% of the non-U.S. subjects in this analysis.
- Subject disposition: Despite consistent and low overall dropout rates for patients in the US and non-US sites, drop-out rates for the higher dosing group in the US sites was numerically higher than in the non-US high dose group (33% v 22% respectively). In addition, drop-outs due to insufficient clinical response in the lower dosing group in US patients was 0% compared to the non-US dropout rate for insufficient clinical response in the low dose group of 12%. The sponsor concluded that both findings could have accounted for a weaker treatment effect in the high-dose group in the US data compared to non-US data.

- Dosage parameters: Mean daily and mean modal doses administered between the low and high dosing groups from both US and non-US sites were consistent. Thus dosing parameters were unlikely to account for the reversal dose-response in US patients:

Table 10: Study D1050236: Dose Parameters by Region (ITT Population)

	US		Non-US	
	Lurasidone 20-60 mg (N=67)	**Lurasidone 80-120 mg (N=70)**	**Lurasidone 20-60 mg (N=94)**	**Lurasidone 80-120 mg (N=92)**
Mean Dose (SD), mg/day	32.4 (11.1)	81.2 (15.3)	31.3 (11.1)	82.7 (11.8)
Modal Dose (%)	20 mg (47.8%)	80 mg (46.4%)	20 mg (51.1%)	80 mg (50.0%)
Mean Modal Dose (SD), mg/day	35.8 (16.9)	91.9 (18.3)	34.3 (16.2)	92.6 (15.0)

- Lurasidone exposure: Apparent clearance of lurasidone was similar for US v. non-US data. Therefore population pharmacokinetic differences were unlikely a cause for the apparent reduced efficacy in high-dosed patients in the US.

In conclusion, the sponsor stated that the relatively higher discontinuation rates in US high-dose patients compared to non-US patients, as well as lack of dropouts for insufficient clinical response in the low-dosed US patients may have contributed to a weaker treatment effect in the high-dosed US patient population. In addition, the lack of a fixed treatment design precludes any definitive dose-response determinations of efficacy.

The sponsor did not provide any explanation or separate analyses to elucidate the factors that may have contributed to efficacy results in the European subgroup when compared to the non-European subgroup.

Dose Response

Since the sponsor employed flexible dosing study design for the monotherapy study, an assessment of efficacy based on dose response cannot be determined from the data submitted. However the employment of fixed- flexible dosing arms does provide some evidence regarding dose response.

Evidence from the data suggests that doses above 60mg/day did not confer any additional benefit with regards to improved efficacy. Therefore this reviewer recommends that the Agency add language to the label to specifically address this finding should the application receive Agency approval.

Key Secondary Variables

Clinical Global Impressions-Severity: Bipolar version (depression) [CGI-BP-S]

The key secondary endpoint for this study was the mean change from baseline at week 6 in the clinician-measured Clinical Global Impressions-Severity: Bipolar version (depression). This clinician rated scale used a Likert scale from 1 (‘Normal, not ill’) to 7 (‘Very Severely Ill’) to assess the severity of the patient’s bipolar depression.

Assessment of efficacy based on the pooled analysis from all geographic regions showed that patients treated with lurasidone had statistically significantly less severe clinician-rated depression symptoms (reduced CGI-BP-S scores) compared to placebo treated subjects. However there were no differences between depression severity at week 6 between the 20-60mg treatment group and those taking the 80-120mg doses.

Table 18: Mean Change from Baseline in CGI-BP-S Score by Visit (ITT)

Treatment Group	Base-line	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Placebo N=162	4.48 (0.613)	-0.17 (0.043)	-0.46 (0.067)	-0.71 (0.078)	-0.80 (0.085	-0.98 (0.094	-1.14 (0.102)
Lurasidone 20-60mg N=161	4.52 (0.623)	-0.26 (0.043)	-0.71 (0.067)	-1.04 (0.078)	-1.32 (0.085)	-1.53 (0.094)	-1.83 (0.102)
Lurasidone 80-120mg N=162	4.55 (0.641)	-0.30 (0.043)	-0.77 (0.067)	-1.06 (0.077)	-1.28 (0.084)	-1.55 (0.093)	-1.71 (0.101)

The change from baseline CGI-BP-S scores by week is graphically represented below:

Figure 4: Change from Baseline (LS Mean ± SE) in Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S) in Subjects Treated with Lurasidone or Placebo (Intent-to-Treat Population)

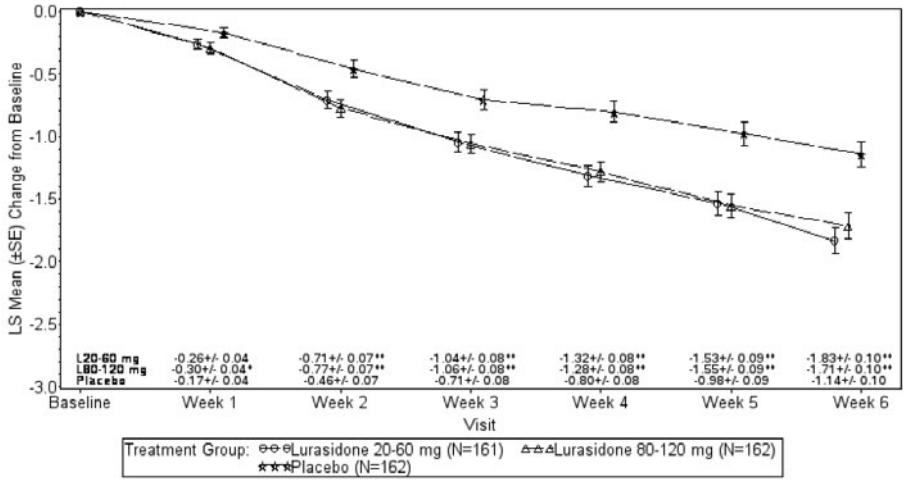


Table 19: Mean Change from Baseline in CGI-BP-S scores in Lurasidone 20-60mg/day Patients from Placebo Patients by Visit (ITT)

Week	Placebo	Lurasidone 20-60mg/day	Mean change L v. Placebo (SE)	P-value
Baseline	4.48 (0.613)	4.52 (0.623)	--	--
Week 1			-0.09 (0.060)	0.141
Week 2			-0.25 (0.094)	0.009
Week 3			-0.34 (0.110)	0.002
Week 4			-0.51 (0.119)	<0.001

Week 5			-0.56 (0.133)	<0.001
Week 6			-0.69 (0.143)	**<0.001** **<0.001***

*adjusted p-values using Hommel-based tree-gatekeeping procedures.

Table 20: Mean Change from Baseline in CGI-BP-S scores in Lurasidone 80-120 mg/day Patients from Placebo Patients by Visit (ITT)

Week	Placebo	Lurasidone 80-120mg/day	Mean change L v. Placebo (SE)	P-value
Baseline	4.48 (0.613)	4.55 (0.641)	--	--
Week 1			-0.12 (0.060)	0.041
Week 2			-0.31 (0.094)	<0.001
Week 3			-0.35 (0.109)	0.001
Week 4			-0.48 (0.119)	<0.001
Week 5			-0.58 (0.132)	<0.001
Week 6			-0.57 (0.143)	**<0.001** **<0.001***

*adjusted p-values using Hommel-based tree-gatekeeping procedures.

Though no statistically significant differences were noted in changes in the CGI-BP-S score between low and high dosed patients, patients in the lower dosing group did have a slight numerical improvement in scores compared to high dosed patients.

Table 21: Mean Change from Baseline in CGI-BP-S in Lurasidone 80-120 mg/day Patients from Lurasidone 20-60 mg/day at Week 6 (ITT)

Week	Lurasidone 20-60mg/day	Lurasidone 80-120mg/day	Mean change (SE)	P-Value
Week 6	-1.83 (0.102)	-1.71 (0.101)	0.12 (0.143)	0.403

Geographic Variation
With the exception of Africa, a trend towards numerical improvement in CGI-BP-S scores in all regions was noted, with highly statistically significant results from Europe indicating a very large European treatment effect.

Table 22: Mean Change from Baseline CGI-BP-S Scores at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America N=195	Rest of the World* N=290
Mean Change From Baseline CGI-BP-S at Week 6		
Placebo (SE)	-1.35 (0.179)	-0.99 (0.123)
Lurasidone 20-60mg (SE)	-2.01 (.0172)	-1.68 (0.127)
Lurasidone 80-120mg (SE)	-1.72 (0.172)	-1.72 (0.126)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-60mg (SE)	-0.66 (.247) p=0.008	-0.70 (0.177) p<0.001
Lurasidone 80-120mg (SE)	-0.36 (0.247) p=0.143	-0.73 (0.176) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Romania, Russia and Ukraine)

Table 23: Mean Change from Baseline CGI-BP-S Scores at Week 6 By Continent, excluding North America North America (ITT)

Treatment Group	Africa N=54	Asia N=73	Europe* N=163
Mean Change from Baseline CGI-BP-S at Week 6			
Placebo (SE)	-1.51 (0.236)	-1.52 (0.293)	-0.68 (0.160)
Lurasidone 20-60mg (SE)	-1.50 (0.236)	-2.04 (0.292)	-1.67 (0.169)
Lurasidone 80-120mg (SE)	-1.52 (0.251)	-1.71 (0.273)	-1.84 (0.169)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-60mg (SE)	0.01 (0.334) p=0.978	-0.51 (0.413) p=0.219	-0.99 (0.233) P<0.001
Lurasidone 80-120mg (SE)	0.00 (0.345) p=0.989	-0.19(0.400) p=0.635	-1.15 (0.233)P<0.001

*includes Czech Republic, France, Romania, Russia, and Ukraine

In the original protocol for the monotherapy study, the protocol pre-specified for two key secondary endpoints, the first being the clinician rated CGI-BP-S score with the second endpoint being the patient-rated Sheehan Disability Scale (SDS) total score. However as noted above in section 2.6 above, the SDS was removed as a co-key secondary endpoint with the implementation of protocol amendment #4. Nevertheless, the results from the SDS will be described in this section.

Sheehan Disability Scale (SDS)

The Sheehan Disability Scale is a self-reported measure of disability across three functional domains: work/school, social life and family life. Each domain contains one item that is self-rated by the patient on an 11-point visual scale from 0 to 10. The score from each item is then summated and the resulting score is the total score on the SDS, thus total scores can range from 0 (unimpaired) to 30 (highly impaired). The SDS has both internal and construct validity and has been approved to be used as a secondary endpoint in clinical trials by the Agency.

With the exception of Asia, results from the monotherapy study again show that that patients randomized to lurasidone showed a numerical trend towards improvement in SDS total scores at week six compared to baseline.

Table 24: Mean Change From Baseline At Week 6 in Sheehan Disability Score By Treatment Group (ITT)

Measurement	Placebo N=100	20-60mg/day N=88	80-120mg/day N=105	Low v. High
Baseline (SE)	19.8 (4.99)	19.7 (4.75)	19.8 (5.58)	---
Week 6 (SE)	12.8 (7.90)	9.6 (7.26)	9.2 (7.28)	---
Least Squares Mean change from Baseline (SE)	-7.5 (0.82)	-10.2 (7.59)	-10.7 (0.78)	-0.3 (1.05)

P-Value compared to placebo	---	P=0.002	P=0.002	P=0.745

Table 25: Mean Change From Baseline SDS total score at LOCF Endpoint, North America v. Rest of the World

Treatment Group	North America	Rest of the World*
Mean Change From Baseline SDS total score at LOCF Endpoint		
Placebo (SE)	-7.8 (1.96) N=22	-3.4 (1.12) N=78
Lurasidone 20-60mg (SE)	-9.7 (1.77) N=27	-9.2 (0.90) N=61
Lurasidone 80-120mg (SE)	-9.7 (1.63) N=32	-9.7 (0.80) N=73
Mean change Difference from Placebo at LOCF Endpoint		
Lurasidone 20-60mg (SE)	-1.9 (2.60) p=0.462	-3.4 (1.12) p=0.002
Lurasidone 80-120mg (SE)	-1.9 (2.51) p=0.441	-3.9 (1.07) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Romania, Russia and Ukraine)

Table 26: Mean Change From Baseline SDS total score at LOCF Endpoint by Continent, Excluding North America (ITT)

Treatment Group	Africa	Asia	Europe*
Mean Change from Baseline SDS total score at LOCF Endpoint			
Placebo (SE)	-5.9 (1.61) N=16	-9.1 (1.59) N=21	-3.9 (1.02) N=59
Lurasidone 20-60mg (SE)	-9.2 (1.87) N=10	-7.7 (1.84) N=15	-9.4 (1.17) N=36
Lurasidone 80-120mg (SE)	-8.9 (1.55) N=14	-8.1 (1.73) N=18	-10.0 (1.03) N=41
Mean change Difference from Placebo at LOCF Endpoint			
Lurasidone 20-60mg (SE)	-3.3 (2.38) p=0.173	1.4 (2.33) p=0.559	-5.5 (1.45) P<0.001
Lurasidone 80-120mg (SE)	-2.9 (2.25) p=0.200	1.0 (2.23) p=0.663	-6.1(1.40) P<0.001

*includes Czech Republic, France, Romania, Russia, and Ukraine

Effect Size

Lurasidone treatment was associated with a mean -4.6 point decrease in MADRS scores compared to placebo, regardless of dosing arm. This treatment effect is similar to the effects seen with existing therapies used to treat bipolar depression, where the current approved labeling for Seroquel XR notes mean MADRS score changes of -4.1 to -6.5, with the Symbyax approved-labeling noting mean MADRS score changes of -6 to -8.

Long-Term Efficacy
The sponsor has not provided any double-blind efficacy data beyond the 6 weeks of data submitted from the current study. Therefore long-term efficacy of monotherapy treatment beyond 6 weeks in patients with bipolar disorder cannot be determined at this time.

Pediatric Development
Pediatric bipolar disorder is noted to be a controversial diagnosis in the field of child psychiatry. The current DSM-IV TR diagnosis of bipolar disorder requires at least a four day to one week history of "…persistently elevated, expansive, or irritable mood…" as well as three or more symptoms of mania/hypomania in order to receive a bipolar diagnosis. One of the mania/hypomania symptoms includes distractibility.

Some psychiatrists have interpreted these criteria to include chronic irritable mood with three or more associated mania/hypomania features as a manic episode. Since persistent irritability is often associated with many childhood psychiatric disorders in children, particularly depression, anxiety and autism, there has been an effort to differentiate chronic irritability with associated features in children from a distinct, acute period of irritability with expansive mood and grandiosity which would classically be defined as a manic/hypomanic episode.
To add to the diagnostic complexity of a childhood bipolar diagnosis, irritability is quite often a feature of normal childhood development, particularly in children aged less than 10 years of age. Due to the diagnostic complexity of making a pediatric bipolar diagnosis, the true prevalence and incidence rate is difficult to determine, particularly in children less than 10 years old.

Given the unclear diagnostic criteria for bipolar disorder in children less than 10, a diagnosis of pediatric bipolar depression in this population is a very difficult, if not nearly impossible diagnosis to make. Therefore the sponsor has request a waiver of studies for bipolar depression in patients less than age 10 citing that such a study would be nearly impossible or highly impracticable given the very low incidence of this disease in this population.

The sponsor has requested a deferral of clinical bipolar depression studies in adolescents until initial registration studies in adults were completed. The sponsor is conducting a pediatric pharmacokinetic study as part of the written request dated 20 April 2012 to examine the effects of Latuda in pediatric patients with schizophrenia and autism. Once the pediatric pharmacokinetic study has been analyzed, appropriate pediatric dosing regimens would be adopted for the bipolar depression and pediatric schizophrenia programs.

The division agrees with the sponsor that studies for bipolar depression in patients aged less than 10 years old should be waived given the extremely complex and controversial diagnostic dilemma of making a bipolar diagnosis in this population. Such studies would be nearly impossible or highly impracticable given the current diagnostic dilemma in the field of child psychiatry. The division also supports the sponsor's request for deferral of studies for bipolar depression in adolescents until approval for bipolar depression has been granted in the adult population.

The Agency's Pediatric Research Committee (PeRC) reviewed the sponsor's rationale and justification for partial waiver and deferral of adolescent bipolar studies until approval is granted in adults. On 01 May 2013, PeRC agreed to waiver of pediatric studies in patients younger than age 10 and deferral of studies in patients aged 10-17 until the adult indication was approved.

PeRC has recommended that the sponsor modify the study submission date and change it to a date that is closer to the study completion date.

6.1.4 Efficacy Conclusions Regarding Claim 1

Study 236 demonstrated a statistically significant decrease in MADRS scores with lurasidone treatment compared to placebo on the study's primary endpoint. In addition, a review of geographical efficacy results from this international study indicates that a mostly consistent trend towards efficacy with lurasidone treatment was seen, with the U.S subgroup demonstrating a consistent trend towards efficacy. Based on these two criteria, this reviewer considers study 236 as a positive study in support of lurasidone treatment for bipolar disorder.

The lack of dose response in efficacy above doses of 60mg/day in the study should ultimately be mentioned in labeling should this supplement receive Agency approval. It is recommended that the following language be noted:

"Doses above 60mg/day of lurasidone was not associated with improved efficacy."

6.2 Studies Pertinent to Claim 2

For the adjunctive treatment of bipolar depression indication, the sponsor initially submitted one (1) efficacy study, study D1050235. However, during the course of this NDA review, the sponsor stated in an email on 19 December 2012 the following:

"On December 18, 2012, Sunovion submitted the Development Safety Update Report (DSUR) for IND 103,427, which noted Study D1050292 was recently completed. Study D1050292 was a six-week, randomized, double-blind, placebo-controlled study with lurasidone 20-120 mg/day, adjunctive to lithium or valproate, in patients with depressive episodes associated with bipolar I disorder. Results from this study were not included in the DSUR as they were not available during the DSUR reporting period (October 17, 2011-October 16 2012). However, preliminary results are now available and are briefly summarized here.

- Statistically significant differences were not demonstrated between the lurasidone (adjunctive to lithium or valproate) and placebo (adjunctive to lithium or valproate) treatment groups on the MADRS (primary) or CGI-BP-S (key secondary) at the Week 6 study endpoint.
- Statistical superiority for lurasidone vs. placebo was observed for MADRS and CGI-BP-S from Weeks 2 through 5
- Lurasidone adjunctive treatment was generally well-tolerated with a safety profile that was consistent with prior studies in bipolar depression
- Overall discontinuation rate was 18% for subjects in the lurasidone group and 20% for subjects in the placebo group.
- The most frequently reported adverse events for lurasidone were akathisia, somnolence, Parkinsonism, nausea and diarrhea.
- Minimal changes from Baseline in weight, lipids, measures of glycemic control and prolactin were observed for subjects in the lurasidone adjunctive treatment group.

The final clinical study report will be submitted to IND 103,427 with the 2013 DSUR; therefore, Sunovion does not plan to amend the sNDA (Supplement 011), which is currently under review, to include data from Study D1050292."

Since the study design of study 292 was nearly identical to study 235 yet had failed to achieve efficacy, the Agency requested that the sponsor submit this study and entire subgroups to the Agency for review under the current NDA. Consequently the entire subgroup and study report for this study was submitted in March 2013.

6.2.1 Rationale for Selection of Studies for Review

Initially study 235 was the sole study that is being used to support the adjunctive treatment indication for bipolar depression. However as stated above, study 292 was submitted at the request of the Agency for review as part of the adjunctive therapy claim to support the adjunctive therapy claim.

6.2.2 Study Summaries

Study 1

Methods/Study Design/Analysis Plan
Study D1050235 was a 6-week, randomized, double-blind, placebo-controlled, flexible dose, parallel group adjunctive treatment study to either lithium or divalproex that used flexible doses of lurasidone from 20mg to 120mg/day in patients with bipolar I depression. Patients were evaluated for eligibility during a 3-14 day screening process where all patients were tapered off current medication, with the exception of lithium and divalproex, while undergoing screening to determine eligibility into the study.

Lithium and divalproex levels must have been within the protocol-specified ranges at screening. The levels for each drug are noted below:

- Lithium- 0.6-1.2 mEq/L ($\geq$ 0.4 mEq/L was permitted with Medical Monitor Approval if 0.6 mEq/L or higher was judged to be intolerable or unsafe for an individual patient)
- Divalproex- 50-125 mcg/mL

Similar to the monotherapy study, diagnostic confirmation of bipolar occurred with use of a computerized diagnostic instrument, the Bipolarity Index (BPI) and an interviewer-administered structured interview (MINI) conducted by site study staff. The BPI and MINI were used to confirm the DSM-IV TR diagnosis of bipolar I disorder, most recent episode depressed, with or without rapid cycling. The current depressive episode must be confirmed by the investigator and noted in the source records.

For the BPI assessment, patients responded to questions on a computer laptop that was later submitted via score data transfer to Concordant Rater Systems and reviewed by experts CRS office. Only subjects who had a confirmed previous manic or mixed episode were eligible to be entered in the trial. Any uncertainty on a previous manic or mixed episode was to be resolved by investigators with CRS to establish diagnosis.

Once eligibility has been confirmed, patients were (in double-blind fashion) randomized 1:1 to one of two treatment arms:

- Lurasidone treatment with 20-120mg/day: patients were initiated treatment with 20mg/day for the first three days, 40mg for the next three days and receive a 60mg dose on day 7. Doses of lurasidone after day 7 were then adjusted to optimize efficacy and tolerability after day 8. Dose reductions were permitted to occur more frequently if required and more than one dose level reduction (maximum of two dosing reductions).

- Placebo

MADRS-Scores (US sites only)

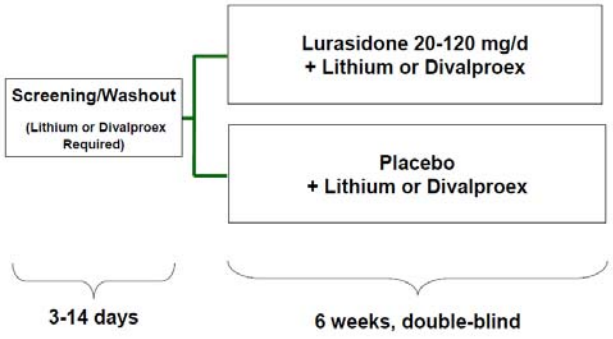
The procedure for obtaining MADRS scores in the adjunctive therapy study differed from the monotherapy study in that the adjunctive therapy study used a centralized rating system that was remotely administered via videoconferencing between the central raters and the patients from screening throughout the entire study. The sponsor contracted with MedAvante to provide centralized expert raters to obtain the MADRS scores for all patients. The process used in the US required a secure connection using videoconferencing equipment connected over an Internet Protocol Virtual Private Network. The rater then selected the remote site from a study directory of preconfigured Internet Protocol numbers and then rated subjects. After completion of the rating, the expert rater at MedAvante then received a fax or email with the MADRS item to the study site. Study site staff were then required to record the data manually into the eCRF.

MADRS Scores (Non-US sites)

The centralized rating system was only used in the United States since centralized ratings were not available at non-US sites. For the non-US sites, qualified site study raters were to administer the MADRS and record the data into the CRF. Quality control was performed via centralized rating of selected voice-recorded MADRS interviews performed by site staff by centralized rated from Quintiles. Scores were then compared between the Quintiles raters and the site raters and feedback was given via email.

The study design schematic is presented below:

Figure 3: Study 235 Study Design Schematic



NOTE: the protocol allowed the principal investigator to adjust the doses of lithium or divalproex based on serum levels of lithium or divalproex that were out of the protocol-specified therapeutic range at baseline (visit 2) to achieve protocol-specified levels. Serum levels may be repeated at the next scheduled visit or earlier at the investigators discretion. A maximum of two dosing adjustments of lithium or divalproex was permitted during the study WITHOUT Medical Monitor approval.

Patients

The trial protocol pre-specified that 340 patients (170 into each treatment arm) meeting the following criteria were to be randomized according to similar inclusion and exclusion criteria as the preceding monotherapy study 236. However the following criterion was specific to this adjunctive therapy study:

INCLUSION

- Patients must be currently taking lithium or divalproex and be required to have documented serum levels of lithium or divalproex within the protocol-defined therapeutic range (as noted above) at screening and at least 28 days prior to screening. Acceptable documentation includes laboratory reports, chart records or verbal communication with a health professional (but must be documented as such in the patient's source records).

Primary Objective

The primary objective of this study was to evaluate the efficacy of flexibly-dosed lurasidone treatment (20-120mg/day) in combination with lithium or divalproex compared to placebo treatment (in combination with lithium or divalproex) for the treatment of subjects with bipolar I disorder, most recent episode depressed, with to without rapid cycling (defined as at least 4 but less than 8 mood disturbances within past 12 months) and without psychotic features.

Key Secondary Objective

In identical fashion to the monotherapy study, the sponsor identified two key secondary efficacy objectives for this study:

1. Evaluation of efficacy of lurasidone (20-120mg/day) in combination with lithium or divalproex as measured by the Global severity, as assessed by the Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score
2. Evaluation of efficacy of lurasidone (20-120mg/day) in combination with lithium or divalproex as measured by subject self-report of the functional impairment with bipolar depressive symptoms, assessed by the Sheehan Disability Scare total score

However, as noted previously, amendment #4 changed the secondary efficacy endpoint to CGI-BP-S and moved the SDS endpoint to a secondary endpoint.

Primary Endpoint

The primary endpoint was a priori specified to be the mean change from baseline to week 6 on the MADRS total score in the lurasidone 20-120mg dosing group in combination with lithium or divalproex compared to the placebo dosing group + combination lithium or divalproex treatment.

Key Secondary Endpoint

The key secondary endpoints a priori specified were the mean changes from baseline to week 6 in the lurasidone 20-60mg, 80-120mg and placebo treatment arms on the CGI-BP-S scale and SDS scale. With amendment #4, the sole key secondary endpoint was change from baseline scores on the CGI-BP-S scale.

Results

Demographics

For this study, the majority of patients were white males aged 41 to 42.7 years old for the lurasidone and placebo groups respectively. 67% of patients randomized into this study were from sites outside of North America (68% for both lurasidone and placebo patients) of which patients from Europe constituted that largest proportion of subjects, followed by Asia (India). Compared to the monotherapy study, the greatest proportion of increase in non-US patients occurred in India, followed by Europe.

When looking at geographical variation by lithium or valproic acid treatment, patients from the US and Asia were more likely to receive treatment with lithium with 59% of US and 55% of subjects from Asia being treated with lithium respectively, compared to 39% of patients from Africa and only 36% of European patients receiving lithium.

Table 27: Study 235 Demographics By Treatment Group and Concomitant Mood Stabilizer (ITT)

Category	Lurasidone 20-120mg/day + Li/VPA (N=179)	Placebo +Li/VPA (N=161)	Total (N=340)
Age (years)	41.0 ± 11.49	42.7 ± 11.69	
White	60%	63%	61%
Male	51%	53%	52%
Geographic Variation-All Subjects			
North America	32%	32%	110 (32%)
Africa (South Africa)	6%	5%	18 (5%)
Asia (India)	24%	23%	80 (24%)
Europe*	38%	40%	132 (39%)
Czech Republic	27 (15%)	21 (13%)	48 (14%)
France	8 (4%)	8 (5%)	16 (5%)
Germany	2 (1%	4(2%)	6(2%)

Poland	9(5%)	6(4%)	15(4%)
Romania	2(1%)	3(2%)	5(1%)
Russia	9(5%)	10(6%)	19(6%)
Ukraine	11(6%)	12(7%)	23(7%)
Adjunctive Lithium Subjects			
North America	40%	39%	65 (40%)
Africa	4%	4%	7 (4%)
Asia	26%	28%	44 (27%)
Europe*	30%	28%	48 (29%)
Czech Republic	12(13%)	6(8%)	18(11%)
France	2(2%)	3(4%)	5(3%)
Germany	0	1(1%)	1(<1%)
Poland	4(4%)	3(4%)	7(4%)
Romania	1(1%)	1(1%)	2(1%)
Russia	3(3%)	4(5%)	7(4%)
Ukraine	5(6%)	3(4%)	8(5%)
Adjunctive Divalproex Subjects			
North America	25%	26%	45 (26%)
Africa	7%	6%	11 (6%)
Asia	22%	18%	36 (20%)
Europe*	46%	49%	84 (48%)
Czech Republic	15(17%)	15(17%)	30(17%)
France	6(7%)	5(6%)	11(6%)
Germany	2(2%)	3(3%)	5(3%)
Poland	5(6%)	3(3%)	8(5%)
Romania	1(1%)	2(2%)	3(2%)
Russia	6(7%)	6(7%)	12(7%)
Ukraine	6(7%)	9(10%)	15(9%)
*includes Czech Republic, France, Germany, Poland, Romania, Russia, Ukraine			

Similar to the geographic variation noted in baseline psychiatric history noted in study 236, there was again geographic variation in psychiatric history and baseline characteristics for study 235 with 8% of US patients having rapid cycling bipolar with initial age of onset at 27.2 +12.78 yrs. And duration of 17.1 +13.04 years compared to <1% having rapid cycling with mean age of onset of 29.4 + 9.7 yrs. With a duration of 11.1 +9.57 yrs. in non-U.S patients. Of particular note, 32% of U.S. subjects had additional psychiatric diagnoses at baseline compared to <1% for the rest of the world.

Table 28: Study 235 Baseline Psychiatric History (safety population)

Category	Lurasidone + Li/VPA (N=183)	Placebo+Li/VPA (N=163)	Total (N=346)
Bipolar I disorder without rapid cycling (0-3 cycles in past 12 mos.)	97%	96%	97%
Age at initial onset of Bipolar I (SD)	28.2(10.94)	29.3 (10.72)	28.7 (10.84)
Duration of Bipolar I Disorder from initial onset to screening in years (SD)	12.8 (10.95)	13.4 (11.47)	13.1 (11.18)
Current duration of Bipolar depression in Weeks (SD)	12.8 (9.15)	11.7 (7.63)	12.3 (8.47)
No prior Hospitalizations for Bipolar Depression	48%	50%	49%
4 or more hospitalizations for Bipolar I depression	14%	20%	16%

Table 29: Study 235 Baseline Psychiatric History (safety population) by United States Patients v. Rest of the World

Category	U.S Patients(L60, P54) (N=114)	Rest of the World (N=161)
Bipolar I disorder without rapid cycling (0-3 cycles in past 12 mos.)	92%	99%
Age at initial onset of Bipolar I (SD)	27.2(12.78)	29.4 (9.70)
Duration of Bipolar I Disorder from initial onset to screening in years (SD)	17.1 (13.04)	11.1 (9.57)
Current duration of Bipolar	14.7 (10.17)	11.1 (7.24)

depression in Weeks (SD)		
No prior Hospitalizations for Bipolar Depression	44%	52%
4 or more hospitalizations for Bipolar I depression	22%	14%
Additional psychiatric diagnoses at baseline	32%	<1%

Patient Disposition

Compared to the monotherapy study, there were more screening failures in the adjunctive study (38% v. 48% respectively). Approximately 20% of all patients randomized into the trial were discontinued from the double-blind phase of the trial. The majority of patients that were discontinued from the trial were due to insufficient clinical response, followed by adverse events. Of the 279 patients that completed the study, 92% of these patients continued into the open label extension study 256.

Table 30: Study 235 Patient Disposition

Category	**Lurasidone + Li/VPA**	**Placebo+Li/VPA**	**Total**
Subjects Screened			672
Screening failures			324 (48%)
Subjects Randomized	183	165	
Competed the Double-Blind Phase	143 (78%)	136 (82%)	279 (80%)
Reason for discontinuation			
Insufficient clinical response	9 (5%)	5 (3%)	
Discontinued for worsening of existing Condition on Adverse Event Page (AE)	3 (2%)	4 (2%)	
Discontinued for worsening of existing Condition other than	8 (4%)	8 (5%)	

Worsening of Bipolar I disorder (AE)			
Lost to follow-up	6(3%)	4(2%)	
Protocol Violation	7 (4%)	2 (1%)	
Withdrew Consent	3 (2%)	3 (2%)	
Administrative	4 (2%)	2 (1%)	
Subjects Discontinued due to insufficient Clinical Response or Worsening of Existing condition	12 (7%)	9 (5%)	
Continuing into extension study	131 (92%)	125 (92%)	256 (92%)

Prior Medication Use

Sixty two percent (62%) of patients who entered the trial were taking one or more prior medications (excluding Li/VPA). The following list pertains to pertinent prior use of psychiatric medications in the ITT population:

Table 31: Study 235 Prior Medication Use (ITT)

Medication	Lurasidone group N=179	Placebo N=161
Any excluding Li or VPA	60%	65%
Antidepressants	31%	27%
Antiepileptic (incl. VPA)	53%	55%
Antipsychotics (incl. Lithium)	60%	55%
Anxiolytics	21%	22%
Hypnotics and sedatives	9%	10%

Concomitant Medication

The majority of patients (safety population) in the trial were taking concomitant medications (60%). The majority of concomitant medication use were for antiepileptics and antipsychotics. However since this included patients who were taking VPA or Li, the number of patients taking excluded antiepileptic's or antipsychotics were <1%. Five patients were taking a concomitant antidepressant as noted in the table below. Patients continued to use concomitant anxiolytic agents during the trial, with the majority using lorazepam.

Table 32: Study 235 Concomitant Medication Use (ITT)

Medication	Lurasidone + Li/VPA group N=183	Placebo +Li/VPA N=162
Any (excl. Li/VPA)	60%	60%
Antidepressants	3 (2%): devenlafaxine,	2 (1%): duloxetine,

	escitalopram, mirtazapine	escitalopram
Antiepileptic (Incl. VPA)	49%	55%
Antipsychotics (incl. Lithium)	50%	46%
Anxiolytics	17%	20%
Hypnotics and sedatives	10%	7%
Anticholinergic Agents	7%	4%

Important Protocol Deviations

The majority of protocol deviations were due to testing positive for illicit substances (2%), prohibited use of medication (10%) and exposure less than 14 days (6%) to study drug.

Dosing

For the adjunctive trial, the mean daily dose for the lurasidone group for all subjects was 65.5mg ±18.42 mg/day with completers having a mean daily dose of 69.5 ±16.74mg/day.

The mean modal dose for the lurasidone group for all subjects was 74.2mg +24.77 mg/day with completers having a mean modal dose of 77.8±23.51mg/day.

For patients taking lithium, a small mean change in lithium doses was noted in patients randomized to lurasidone treatment compared to placebo treatment. However only one patient had his/her dose of lithium decreased by 25-50% from baseline levels at week 1, 4, and week 6. The changes in lithium dose for these patients, compared to the vast majority of patients with unchanged lithium doses, is unlikely affect the efficacy results for this study in this reviewer's opinion.

Table 33: Study 235 Change in Concomitant Lithium by Visit (ITT)

Metric	**Lurasidone + Lithium N=90**	**Placebo + Lithium N=74**
Screening Li dose (SD)	912.4 (298.32)	942.5 (321.74)
Baseline Li dose (SD)	897.2 (299.28)	947.3 (317.08)
Week 1 Mean Change from Baseline Li dose (SD)	-4.7 (43.39	0.0
Week 4 Mean Change from Baseline Li dose (SD)	-5.6 (47.47)	0.0
Week 6 Mean Change from Baseline Li dose (SD)	8.1 (125.84)	0.0
Patients with Total Daily dose Change from Baseline		
Week 1 <25-50% change N	1	--
Week 4 <25-50% change N	1	--
Week 6 <25-50% change N	1	
Lithium Concentrations		
Baseline mmol/L (SD)	0.72 (0.285)	0.71 (0.278)
Week 1 change from baseline (SD)	0.00 (0.321)	-0.03 (0.330)
Week 4 change from baseline (SD)	0.02 (0.341)	-0.06 (0.370)

Week 6 change from baseline (SD)	0.05 (0.359)	-0.03(0.369)
Change from baseline at LOCF endpoint (SD)	0.02 (0.372)	-0.05 (0.366)

For patients taking divalproex, small mean changes in VPA level from baseline were noted in patients taking VPA. However only one patient had his/her VPA level reduced (at week 4 and week 6) during the trial.

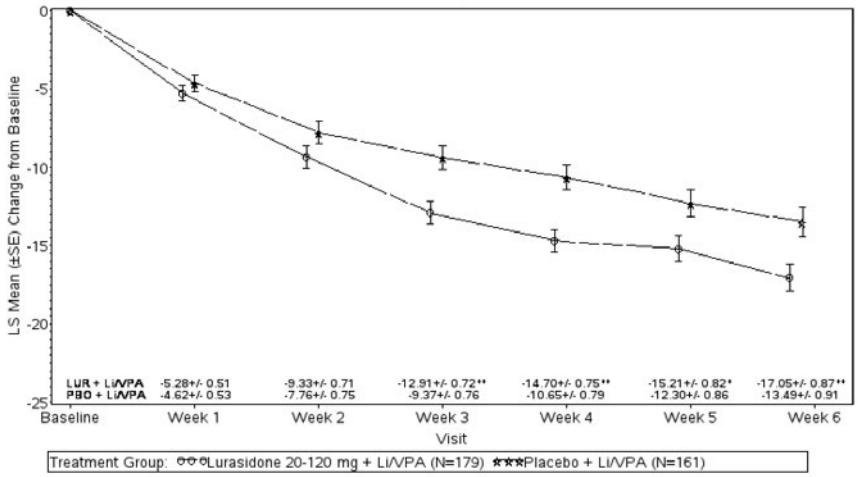
Table 34: Study 235 Change in Concomitant Valproic Acid by Visit (ITT)

Metric	**Lurasidone + VPA N=89**	**Placebo + VPA N=87**
Screening VPA dose (SD)	1067.3 (351.05)	1100.3 (341.90)
Baseline VPA dose (SD)	1058.3 (349.45)	1117.8 (333.99)
Week 1 Mean Change from Baseline VPA dose (SD)	0.0	0.0
Week 4 Mean Change from Baseline VPA dose (SD)	-3.4 (29.26)	0.0
Week 6 Mean Change from Baseline VPA dose (SD)	-4.0 (31.50)	0.0
Patients with Total Daily dose Change from Baseline		
Week 1 <25-50% change N	--	--
Week 4 <0-25% change N	1	--
Week 6 <0-25% change N	1	
VPA serum levels		
Baseline mg/L (SD)	75.01 (25.898)	72.03 (26.575)
Week 1 change from baseline (SD)	-5.70 (30.728)	0.57 (24.824)
Week 4 change from baseline (SD)	-4.33 (32.333)	-0.34 (31.148)
Week 6 change from baseline (SD)	-0.54 (31.788)	-1.09 (28.865)
Change from baseline at LOCF endpoint	-2.64 (32.396)	-1.28 (30.244)

Efficacy Results

As was found in the monotherapy study, the efficacy results for both the primary and key secondary endpoints demonstrated that treatment with lurasidone in combination with lithium or valproic acid was associated with a statistically significant decrease in MADRS and CGI-BP-Scores.

Figure 1: Change from Baseline (LS Mean ± SE) in Montgomery-Asberg Depression Rating Scale Total Score in Subjects Treated with Lurasidone or Placebo – Repeated Measures (Intent-to-Treat Population)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: LUR = lurasidone; LI – Lithum; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.
Source: Figure 14.2.1.1.1.1.

Table 35: Study 235 Mean Change from Baseline MADRS Total Score by Visit (ITT)

Treatment Group	Baseline	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Placebo +Li/VPA N=161	30.8 (4.81)	-4.6 (0.53)	-7.8 (0.75)	-9.4 (0.76)	-10.7 (0.79)	-12.3 (.86)	-13.5 (0.91)
Lurasidone +Li/VPA N=179	30.6 (5.30)	-5.3 (0.51)	-9.3 (0.71)	-12.9 (0.72)	-14.7 (0.75)	-15.2 (0.82)	-17.1 (0.87)

Table 36: Mean Change from Baseline in MADRS Total scores in Lurasidone Patients from Placebo Patients by Visit (ITT)

Week	Placebo+Li/VPA N=161	Lurasidone +Li/VPA N=179	Mean change L v. Placebo (SE)	P-value
Baseline	30.8 (4.81)	30.6 (5.30)	--	--
Week 1			-0.07 (0.72)	0.367
Week 2			-1.6 (1.02)	0.125
Week 3			-3.5 (1.03)	<0.001
Week 4			-4.0 (1.08)	<0.001
Week 5			-2.9 (1.19)	0.015
Week 6			-3.6 (1.25)	**0.005**

Geographical Variation

In contrast to the consistent trend towards efficacy in nearly all subgroups in study 236, lurasidone treatment was associated with WORSE MADRS scores in the U.S. subpopulation.

Table 37: Study 235 Mean Change from Baseline MADRS Total Score at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America N=110 (58L,52 P)	Rest of the World* N=230 (121L,109P)
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-13.8 (1.70)	-13.3(1.03)
Lurasidone 20-120mg (SE)	-12.7(1.66)	-19.1(0.98)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-120mg (SE)	1.1 (2.38) p=0.642	-5.8(1.41) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Germany, Poland, Romania, Russia and Ukraine)

Table 38: Study 235 Mean Change from Baseline MADRS Total Score at Week 6 by Continent, Excluding North America (ITT)

Treatment Group	Africa N=18 (10L,8P)	Asia N=80(43L,37P)	Europe* N=132(68L,64P)
Mean Change from Baseline MADRS at Week 6			
Placebo (SE)	-7.5 (3.07)	-17.6 (2.12)	-11.3 (1.21)
Lurasidone 20-120mg (SE)	-12.2 (2.82)	-21.2 (1.94)	-18.3 (1.18)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-120mg (SE)	-4.7(4.16) p=0.280	-3.7 (2.84) p=0.203	-7.0(1.68) p<0.001

*includes Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine

Additional Considerations

After initial review and analyses of subgroup from study 235 indicated a noted geographical variation in efficacy results, noting that the U.S. subgroup demonstrated worse outcomes with lurasidone treatment compared to the non-U.S. subgroup, the Agency requested the sponsor to conduct additional evaluations of the efficacy data from study 235 to evaluate potential factors/sources of data that could account for the geographical variation in results, specifically with regards to the unfavorable trend in US v non-US data.

On 25 March 2013, the sponsor formally responded to the Agency's request. The sponsor conducted several exploratory analyses of the data from study 235, the results of which are summarized below:

- Sample size: The sponsor noted that since 32% of the total study subjects were from North American, US-based data likely did not have sufficient power to detect a treatment effect. Consequently, data obtained from US sites had large confidence intervals thus making an interpretation of treatment effect difficult. The sponsor also mentioned that

the similarly-designed study 292, which enrolled 45% of the entire patient population from North America, did show a trend towards efficacy.

- Baseline Demographics and Clinical Characteristics: The sponsor examined differences in patients mean age, gender, race, ethnicity, body weight, MADRS and CGI-BP-S scores, duration of bipolar illness, duration of current depressive episode, number of prior hospitalizations for bipolar depression and proportion of patients with rapid cycling bipolar disorder as to overall treatment effect each factor may have contributed to the geographical efficacy results seen. Although minimal differences were noted in many of these factors, adding all these factors as covariates in the efficacy results between US vs. Non-US data did not account for the geographical variation of the efficacy results. Results from an analysis that examined factors that were significant differences in the non-US data (age, duration of bipolar depressive episode, rapid cycling states) revealed essentially unchanged efficacy results when factored into the analysis. However, the sponsor did not statistically assess nor mention the effects of additional psychiatric diagnoses in 32% of U.S subjects compared to <1% of the non-U.S. subjects in this analyses.
- Placebo Response: Mean change from baseline MADRS scores in placebo patients from both US and non-US sites were similar (-13.8 and -13.3 respectively). Placebo response rates from both US (44%) and non US data (41%) were also very similar. Thus placebo response was unlikely a contributor to the geographical variation in efficacy seen.
- Subject Disposition: There were similar discontinuation rates noted between US (23%) and non-US data (18%) with no differences noted in rationale for discontinuation. However discontinuations rates for lurasidone treated patients in the US (28%) was higher than in non-US data (19%), despite similar drop-out rates in the placebo group (US:17%, non-US 18%). The sponsor concluded that this discrepancy could contribute to the observed geographic variation in efficacy
- Time to Subject Discontinuation: Although the overall pattern of discontinuation was similar between US and non-US data, there were additional discontinuations from the US sties that occurred in the last two weeks of the study. The sponsor concluded that this may also contribute to the observed geographic variation in efficacy results.
- Lurasidone Exposure: although apparent clearance of lurasidone was lower in the Asian data (and currently labeled in package labeling), there were no apparent differences in clearance between US v. non-US sites. Thus population pharmacokinetic factors are unlikely to account for the geographical variation of the efficacy results.

The sponsor concluded that a small US sample size, a greater proportion of Lurasidone-treated US subjects dropping out, and a greater proportion of subjects being discontinued from the study in the last two weeks of the study in the US subgroup may have contributed to the geographical variation in efficacy results. Even though the sponsor attributes lack of power in the U.S. subset and the increase in dropout rates in U.S. v. non-U.S. patients during the last two weeks of study 235 and potentially contributing to the U.S. trend towards worse MADRS scores with lurasidone treatment, the sponsor ultimately concluded the following:

Overall, definitive factors were not identified that are clearly associated with the disparity in treatment outcomes across regions in Study D1050235. Thus, the observed heterogeneity in treatment outcome in this study may be attributable to unknown or unexplored factors, or combinations of these factors.

Of note, the sponsor did not examine a treatment by clinical site analysis of the data. Nor did the sponsor examine the factors related to European v. non-European data and the lack of efficacy noted in the non-European data set.

Analysis

Study 235 was initially the only adjunctive treatment study of lurasidone submitted as part of the original NDA submission. Results from study 235 indicate that 6 weeks of adjunctive treatment of lurasidone with either lithium or valproic acid was shown to be effective in improving depressive symptoms as measured by changes on the MADRS scale and the CGI-BP-S scale. However a relatively large and unexplainable geographical trend towards worsening MADRS scores with lurasidone treatment in the U.S. subgroup is quite problematic.

The sponsor suggests that a small US sample size, a greater proportion of Lurasidone-treated US subjects dropping out, and a greater proportion of lurasidone treated subjects being discontinued from the study in the last two weeks of the study in the US subgroup may have contributed to the geographical variation in efficacy results.

Sample Size
Although it is true that the U.S. population was only 32% of the entire study set and not powered to detect a treatment effect, one should be able to reasonably detect a direction of a treatment trend in a subpopulation of 32% unless variability within that population was exceedingly high. Results from an internal analysis of the heterogeneity of the results from the U.S subgroup indicates that some variability in the U.S data was seen. However the degree of variability would likely not be so high as to render an interpretation of a directional trend in efficacy invalid. In addition, higher variability in treatment differences was noted in Asia and Africa, with the largest subgroup Europe having a slightly smaller, yet highly variable rate of treatment differences. Therefore this factor is likely not an adequate explanation for the trend in U.S. efficacy results.

Increase in Lurasidone-treated Drop-outs in U.S. v. non-U.S. lurasidone-treated subjects
The sponsor also suggests that the an increase in lurasidone-treated U.S. compared to lurasidone-treated non-U.S. subjects (28% v. 19% respectively) with similar placebo response rates may have contributed to the finding of worse MADRS scores in lurasidone-treated U.S. subjects. Although this increase in dropouts may contribute to the variability in the U.S. lurasidone subgroup, these patients could have affected the primary endpoint if their efficacy data was excluded from the primary analysis. The primary endpoint used for hypothesis testing was the intent-to-treat population, defined as all patients who had a baseline and at least one post-baseline MADRS score assessment. The only patients excluded from the primary efficacy endpoint analysis were those patients who had substantial protocol deviations. Out of a total of 348 patients in study 235, 340 patients (98%) were defined as the ITT population and used for hypothesis testing on the primary endpoint. Thus it is unlikely that the increase in the number of lurasidone-treated U.S. subjects contributed to the trend in efficacy noted in the U.S population since the vast majority of these drop-outs contributed data to the primary efficacy endpoint.

Increased discontinuation of lurasidone-treated subjects in the U.S during last two weeks of study.
The final possible suggestion the sponsor has suggested that could partially explain the treatment trend in the U.S. subgroup is the additional subject discontinuation noted in lurasidone-treated U.S subjects in the last two weeks of the study. The primary efficacy analysis uses an MMRM

approach on the primary endpoint as compared to an LOCF approach that has been traditionally used. In an MMRM approach, all the data points are used to construct a least squares mean regression-like line for each of the two treatment arms. The more data points, the more precise the least squares mean line. In an LOCF approach, the last observation from a subject who has dropped out is "carried forward" to the study endpoint. Based on these two approaches, the LOCF method, in this reviewer's opinion, is more sensitive to change on the primary endpoint to dropouts than the MMRM approach. However both approaches should be less sensitive to change on the primary endpoint the closer the dropouts are to the primary endpoint. The results from the LOCF and MMRM analysis are similar on the global endpoint, thus it is unlikely that an LOCF analysis by regional subgroup on the primary endpoint would be significantly different.

Conclusion
Ultimately, this reviewer agrees with the sponsor that the observed trend for worse MADRS scores in the U.S. subpopulation with lurasidone treatment is likely attributable to known and/or unknown factors.

Since there is no apparent explanation at present to delineate the factors to describe the trend that U.S.-treated patients are worse with lurasidone treatment, this reviewer must conclude that the non-U.S. subgroup data is not totally applicable to the U.S subgroup. Hence this reviewer must conclude that the efficacy seen in study 235 is not applicable at this time to the U.S. population. Thus study 235 is considered a NEGATIVE study for the adjunctive treatment of bipolar depression.

Study 2 STUDY 292

Methods/Study Design/Analysis Plan

Study 292 was essentially an identical study to the previous study 235, with the main distinction being that patients who were not previously taking lithium or valproic acid were eligible to enter the trial, provided that patients were treated for at least 28 days with lithium or valproic acid and still met inclusion criteria for study entry at baseline.

Another key distinction for study 292 was found in the selection of non-U.S. clinical sites where the study was conducted. For study 292, the sponsor did not select any sites in Russia to conduct clinical trials. The sponsor did conduct clinical trials in other countries not previously selected to conduct trials in study 235, namely:

- Canada (4 sites)
- Japan (4 sites)
- Lithuania (5 sites)
- Peru (3 sites)
- Slovakia (8 Sites)

In addition, although site 618 was selected to conduct clinical trials under site 292, this site only randomized 4 patients compared to 17 under study 235.

Finally, study 292 did NOT collect pharmacokinetic samples, whereas study 235 and 236 collected pharmacokinetic samples during the trial.

Results

Demographics

Compared to study 235, the majority of the patients were white females (compared to males in 235) who were slightly older than patients in study 235 by about 2 years, aged 43 and 44 years old for the lurasidone and placebo groups respectively. For study 292, more patients were randomized from the United States than from outside the United States when compared to study 235 (45% US v. 55% rest of the world; study 235: 67% from rest of the world). As with study 235, patients from Europe constituted that largest proportion of subjects, followed by Asia (30% and 15% respectively).

Table 39: Study 292 Patient Demographics(ITT)

Category	Lurasidone 20-120mg/day + Li/VPA (N=177)	Placebo +Li/VPA (N=171)	Total (N=348)
Age (years)	43.0 ± 11.93	44.0 ± 11.95	
White	64%	64%	64%
Male	49%	44%	46%
Geographic Variation-All Subjects			
North America	45%	44%	155 (45%)
South America	10%	11%	36 (10%)
Asia	15%	15%	52 (15%)
Europe	30%	30%	105 (30%)

When compared to study 235, there were more patients with a history of rapid cycling randomized into study 292 (3% v. 16% respectively). Initial age of onset of a bipolar diagnosis and duration of bipolar illness to screening was slightly older compared to study 235 with an initial age of onset of 29.3 ± 12.41 and duration of 14.2 ± 11.47 years in study 292 compared to an initial age of onset 28.7 +10.84 yrs. and current duration of 13.1 +11.18 years in study 235.

Study 292 Baseline Psychiatric History (Safety population)

Category	Study 235 Total (N=346)	Study 292 Total (N=348)
Bipolar I disorder without rapid cycling (0-3 cycles in past 12 mos.)	97%	84%
Age at initial onset of Bipolar I (SD)	28.7 (10.84)	29.3 (12.41)
Duration of	13.1 (11.18)	14.2 (11.47)

Bipolar I Disorder from initial onset to screening in years (SD)		
Current duration of Bipolar depression in Weeks (SD)	12.3 (8.47)	13.4 (10.24)
No prior Hospitalizations for Bipolar Depression	49%	54%
4 or more hospitalizations for Bipolar I depression	16%	16%

Patient Disposition

Similar to study 235, the proportion of patients that were screening failures was 52%. Of note, 36% of those patients who required a run-in with Li/VPA were either discontinued or completed the run-in phase and not randomized.

Similar to study 235, approximately 20% of all patients randomized into the trial were discontinued from the double-blind phase of the trial. The majority of patients that were discontinued from the trials were for protocol violations. In contrast to study 235, study 292 allowed patients who were not currently taking lithium or valproic acid to enter into the study. The majority of patients randomized into the trial required a run-in with Lithium or Valproic acid (62%). However (as noted above), 36% of patients who required a run-in at screening were not randomized into the double-blind phase of the study.

Table 40: Study 292 Patient Disposition

Category	**Lurasidone + Li/VPA**	**Placebo+Li/VPA**	**Total**
Subjects Screened			748
Screening failures			390 (52%)
Subjects Randomized	180	176	
Subjects who required Li/VPA run-in phase at screening			343 (46%)
Number of Subjects Discontinuing the Li/VPA Run-in or Completing the			124 (36% of total patients who

Li/VPA run-in and not randomized			entered Run-in Phase)
Number of Subjects randomized with the Li/VPA Run-in	115 (64%)	104 (59%)	219 (62%)
Competed the Double-Blind Phase	148 (82%)	140 (80%)	288 (81%)
Reason for discontinuation			
Insufficient clinical response	2 (1%)	6 (3%)	
Discontinued for worsening of existing Condition on Adverse Event Page (AE)	5 (3%)	1 (<1%)	
Discontinued for worsening of existing Condition other than Worsening of Bipolar I disorder (AE)	6(3%)	4 (2%)	
Lost to follow-up	4(2%)	2(1%)	
Protocol Violation	8(4%)	9 (5%)	
Withdrew Consent	5 (3%)	9 (5%)	
Administrative	2 (1%)	5 (3%)	
Subjects Discontinued due to insufficient Clinical Response or Worsening of Existing condition	7 (4%)	7 (4%)	
Continuing into extension study	123 (83%)	119 (85%)	242 (84%)

Prior Medication Use

Compared to study 235, more patients in study 292 who entered the trial were taking one or more prior medications (excluding Li/VPA) (62% v. 78% respectively). Compared to study 235, more placebo patients were taking a prior antidepressant in study 292 (27% v. 36% respectively). In addition, more patients in study 292 previously took an antiepileptic compared to study 235 (54% study 235 v. 71% study 292). However, slightly less patients in study 292 previously took an antipsychotic (57% study 235 v. 54% study 292). More patients in study 292 previously took a

hypnotic/sedative than patients in study 235 (22% study 292 v. 9% study 235). The following list pertains to pertinent prior use of psychiatric medications in the ITT population:

Table 41: Study 292 Prior Medication Use (ITT)

Medication	Lurasidone group N=176	Placebo N=166
Any excluding Li or VPA	60%	65%
Antidepressants	32%	36%
Antiepileptic (incl. VPA)	71%	72%
Antipsychotics (incl. Lithium)	53%	55%
Anxiolytics	23%	27%
Hypnotics and sedatives	19%	25%

Concomitant Medication

Excluding Li/VPA, the majority of patients in the safety subgroup in study 292 were taking concomitant medications in similar proportions to study 235 (64% study 292 v. 60% study 235). The majority of concomitant medication use were for antiepileptics and antipsychotics. However since this included patients who were taking VPA or Li, the number of patients taking excluded antiepileptic's or antipsychotics were <1%. Only two patients were taking a concomitant antidepressant as noted in the table below. Patients continued to use concomitant hypnotic agents during the trial and in greater proportions in study 292 than compared to study 235 (25% study 292 v. 9% study 235), with the majority using zolpidem.

Table 42: Study 292 Concomitant Medication Use (ITT)

Medication	Lurasidone N=177	Placebo N=171
Any (excl. Li/VPA)	63%	65%
Antidepressants	1 (<1%): Venlafaxine	1 (<1%): Venlafaxine
Antiepileptic (Incl. VPA)	68%	67%
Antipsychotics (incl. Lithium)	33%	36%
Anxiolytics	18%	20%
Hypnotics and sedatives	22%	28%
Anticholinergic Agents	5%	2%

Important Protocol Deviations

Overall, 17% of patients were excluded from the ITT population for protocol violations in study 292. The most common protocol violations were "did not have 14 days or more of continuous exposure (6%). And "prohibited medication use or prohibited dose of allowed medication" (5%).

Dosing (safety population)

For study 292, the mean daily dose for the lurasidone group for all subjects was similar to study 235, with a mean daily dose of 64.4mg $\pm$15.37 mg/day and with completers having a mean daily dose of 67.3 $\pm$13.20mg/day.

The mean modal dose for the lurasidone group for all subjects was very similar to study 235, with a dose of 74.4mg +25.40 mg/day and completers having a mean modal dose of 77.4±24.61mg/day.

Similar to study 235 for patients taking lithium, a small mean change in lithium dose were noted in patients taking lurasidone compared to placebo patients. The changes in lithium dose for these patients, compared to the vast majority of patients with unchanged lithium doses, does not affect the efficacy results for this study.

Table 43: Study 292 Change in Concomitant Lithium by Visit
ITT population (all subjects)

Metric	Lurasidone + Lithium N=56	Placebo + Lithium N=57
Screening Li dose (SD)	812.2 (280.62)	843.8 (261.70)
Baseline Li dose (SD)	932.6 (250.50)	942.5 (242.84)
Week 3 Mean Change from Baseline Li dose (SD)	0.0	0.0
Week 6 Mean Change from Baseline Li dose (SD)	0.0	0.0
Lithium Concentrations		
Baseline mmol/L (SD)	0.73 (0.277)	0.82 (0.284)
Week 3 change from baseline (SD)	-0.06 (0.345)	-0.03 (0.319)
Week 6 change from baseline (SD)	-0.07 (0.398)	-0.02(0.402)
Change from baseline at LOCF endpoint (SD)	-0.07 (0.372)	-0.04 (0.359)

For patients taking divalproex, small mean changes in VPA level from baseline were noted in patients taking VPA. This is consistent with findings from study 235.

Table 44: Study 292 Change in Concomitant Valproic Acid by Visit
ITT population (all subjects)

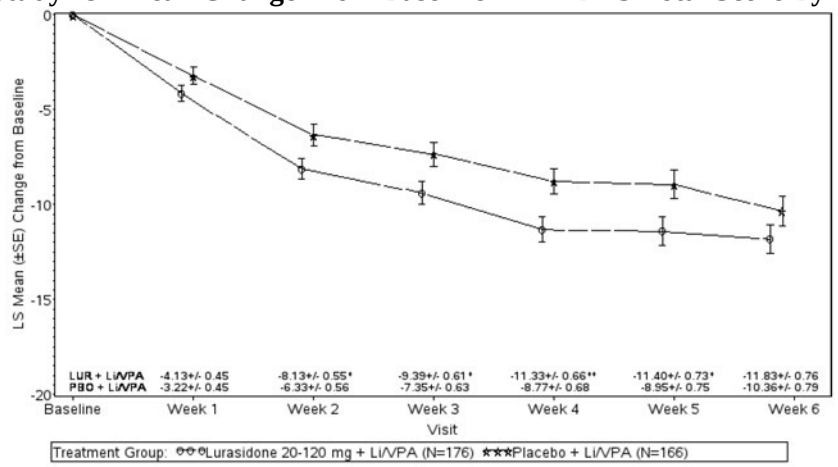
Metric	Lurasidone + VPA N=120	Placebo + VPA N=109
Screening VPA dose (SD)	1058.4 (376.96)	1051.3 (340.41)
Baseline VPA dose (SD)	1067.5 (358.96)	1077.7 (327.39)
Week 3 Mean Change from Baseline VPA dose (SD)	0.0	0.0
Week 6 Mean Change from Baseline VPA dose (SD)	0.0	0.0
VPA serum levels		
Baseline mg/L (SD)	68.71 (26.473)	73.59 (26.678)
Week 3 change from baseline (SD)	-4.07 (30.443)	-2.25 (24.431)
Week 6 change from baseline (SD)	-0.98 (34.349)	-3.30 (26.995)
Change from baseline at	-2.64 (32.396)	-1.28 (30.244)

LOCF endpoint		

Efficacy Results

In contrast to study 235 where a statistically significant decrease in MADRS scores was seen in lurasidone treated subjects, the pooled efficacy results for both the primary and key secondary endpoints did NOT demonstrate a statistically significant decrease in MADRS and CGI-BP-Scores in patients treated with lurasidone. Efficacy was noted in weeks 2-5 in lurasidone-treated patients. However efficacy was not sustained at week 6.

Figure 4: Study 292 Mean Change From Baseline in MADRS Total Score By Visit (ITT)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: LUR = lurasidone; LI = Lithium; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.

Table 45: Study 292 Mean Change from Baseline MADRS Total Score by Visit (ITT)

Treatment Group	Baseline	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Placebo +Li/VPA N=166	29.1 (4.66)	-3.2 (0.45)	-6.3 (0.56)	-7.3 (0.63)	-8.8 (0.68)	-8.9 (.75)	-10.4 (0.79)
Lurasidone +Li/VPA N=176	29.1 (4.92)	-4.1 (0.45)	-8.1 (0.55)	-9.4 (0.61)	-11.3 (0.66)	-11.4 (0.73)	-11.8 (0.76)

Table 46: Mean Change from Baseline in MADRS Total scores in Lurasidone Patients from Placebo Patients by Visit (ITT)

Week	Placebo+Li/VPA N=166	Lurasidone +Li/VPA N=176	Mean change L v. Placebo (SE)	P-value
Baseline	29.1 (4.66)	29.1 (4.92)	--	--
Week 1			-0.9 (0.61)	0.134
Week 2			-1.8 (0.76)	0.019
Week 3			-2.0 (0.86)	0.018

Week 4			-2.6 (0.92)	0.006
Week 5			-2.5 (1.03)	0.018
Week 6			-1.5 (1.08)	**0.176**

In contrast to study 235, there was no noted geographical variation of efficacy data from the U.S. subgroup. Of note, no Russian sites were used in study 292.

Table 47: Study 292 Mean Change from Baseline MADRS Total Score at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America* N=151 (80L,71 P)	Rest of the World** N=191 (96L,95P)
Mean Change From Baseline MADRS at Week 6		
Placebo (SE)	-8.7 (1.24)	-11.4(0.99)
Lurasidone 20-120mg (SE)	-10.4(1.19)	-12.9(0.97)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-120mg (SE)	-1.7(1.71) p=0.320	-1.5(1.35) p=0.282

*includes USA and Canada
**includes Africa, Asia (India and Japan), Europe (Czech Republic, Lithuania, Slovakia, and Ukraine), and South America (Colombia and Peru)

Geographical Variation

In contrast to study 235, the U.S. subpopulation in study 292 demonstrated a trend towards efficacy with lurasidone treatment. However a trend towards worse MADRS scores with lurasidone treatment was noted in the South American subgroup.

Table 48: Study 292 Mean Change from Baseline MADRS Total Score by Visit, North America V. Rest of the Word (ITT)

Week	North America Mean change from Baseline L v. Placebo (SE) N=151	P-value	Rest of the World Mean change from Baseline L v. Placebo (SE) N=191	P-value
Week 1	-0.2 (1.10)	0.883	-1.5 (0.67)	0.025
Week 2	-0.6 (1.21)	0.635	-2.8 (0.98)	0.005
Week 3	-0.8 (1.47)	0.572	-3.0 (1.03)	0.004
Week 4	-2.1 (1.54)	0.172	-2.9 (1.13)	0.010
Week 5	-2.2 (1.70)	0.207	-2.8 (1.24)	0.024
Week 6	-1.7 (1.71)	0.320	-1.5 (1.35)	**0.282**

Table 49: Study 292 Mean Change from Baseline MADRS Total Score at Week 6 by Continent, Excluding North America (ITT)

Treatment Group	South America N=35 (18L,17P)	Asia N=51(25L,26P)	Europe* N=105(53L,52P)
Mean Change from Baseline MADRS at Week 6			
Placebo (SE)	-16.0 (2.45)	-10.6 (1.82)	-10.7 (1.35)
Lurasidone 20-120mg (SE)	-14.5 (2.12)	-10.8 (1.88)	-13.5 (1.34)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-120mg (SE)	1.5 (3.09) p=0.629	-0.2 (2.60) p=0.952	-2.9(1.85) p=0.127

*includes Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine

With regards to efficacy based on Li/VPA run-in v. non-run-in status, there was no statistically significant improvement in depressive symptoms based on the run-in status. For patients who did not require a run-in, efficacy was noted in weeks two through five. However there was no statistically significant improvement in depressive symptoms at week 6 despite numerical improvement in depressive symptoms at week 6 compared to placebo-treated patients.

Table 50: Study 292 Mean Change from Baseline MADRS Total Score by Visit and Mean Change Difference by Treatment Group, Run-In With Li or VPA Required (ITT)

Treatment Group	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Lurasidone+ Li/VPA N=113	-3.9 (0.57)	-7.6 (0.65)	-8.2 (0.79)	-10.3 (0.83)	-9.7 (0.88)	-10.6 (0.98)
Placebo +Li/VPA N=97	-4.1 (0.62)	-6.7 (0.70)	-8.0 (0.86)	-9.4 (0.89)	-9.1 (0.95)	-10.4 (0.1.05)

Week	Mean change L v. Placebo (SE)	P-value
Baseline	--	--
Week 1	0.1 (0.80)	0.889
Week 2	-0.8 (0.92)	0.358
Week 3	-0.2 (1.13)	0.890
Week 4	-0.9 (1.18)	0.432
Week 5	-0.6 (1.26)	0.651
Week 6	-0.2 (1.04)	**0.862**

Table 51: Study 292 Mean Change from Baseline MADRS Total Score by Visit and Mean Change Difference by Treatment Group, NO Run-In With Li or VPA Required (ITT)

Treatment Group	Week 1 Change (SE)	Week 2 Change (SE)	Week 3 Change (SE)	Week 4 Change (SE)	Week 5 Change (SE)	Week 6 Change (SE)
Lurasidone+ Li/VPA N=63	-5.7 (0.80)	-10.4 (1.04)	-12.8 (1.03)	-14.3 (1.16)	-15.7 (1.30)	-15.1 (1.29)
Placebo +Li/VPA N=69	-3.9 (0.83)	-7.6 (1.05)	-8.3 (1.05)	-9.7 (1.17)	-10.6 (1.31)	-12.2 (1.30)

Week	Mean change L v. Placebo (SE)	P-value
Baseline	--	--
Week 1	-1.8 (0.96)	0.058
Week 2	-2.8 (1.33)	0.039*
Week 3	-4.6 (1.51)	0.003**
Week 4	-4.6 (1.51)	0.003**
Week 5	-5.1 (1.73)	0.004**
Week 6	-3.0 (1.72)	**0.089**

*p<0.05
**p<0.01

Additional Considerations

The sponsor submitted data from study 292 in response to the request for analysis of geographical variation noted in efficacy data. The sponsor notes that the effect size of lurasidone treatment is low and generally homogeneous across all the clinical sites for study 292 when compared to study 235. Thus the sponsor did not examine regional variability in treatment outcomes.

Conclusions

Study 292 is a recently completed and analyzed adjunctive study with a nearly identical study as the submitted NDA study 235. The key distinction between study 235 and 292 being that patients in study 292 who were not taking lithium or valproic acid at the time of screening were allowed to enter the study after a 28 day run-in with either lithium or valproic acid and still met study inclusion criteria for randomization. In addition, there were no centralized MADRS ratings conducted in study 292, compared to all centralized MADRS ratings in the U.S. only for study 235.

In contrast to study 235, no patients were recruited from Russia or Africa, however patients were recruited from South America. Of note, a larger proportion of patients recruited from study 292 were from North America (45% study 292 v. 33% in study 235). In addition, patients in study 292 were slightly older with a slight female predominance with more patients having a diagnosis of rapid-cycling bipolar I disorder compared to study 235.

Both study 235 and 292 had similar number of protocol deviations and baseline MADRS and CGI-BP-S scores for randomized patients. In addition, mean daily and mean modal doses of lurasidone used in study 292 were comparable to mean daily and mean modal doses used in study 235. Thus upon review of the demographic data from studies 235 and 292, both studies recruited very similar patients with similar severity of bipolar depression and used very similar doses of lurasidone with both studies adopting a nearly identical study design.

In contrast to the positive efficacy result noted in study 235 however, efficacy results from study 292 clearly show that lurasidone treatment was not shown to be effective in the treatment of bipolar depression after 6 weeks of adjunctive treatment when compared to placebo on both the primary and key secondary endpoint. Although efficacy results from study 292 indicate adjunctive lurasidone treatment was associated with possible efficacy at weeks 2 through 5 of treatment, efficacy was not sustained by week 6.

The lack of efficacy noted in study 292 could be explained by the inclusion of patients who require a 4 week run-in of lithium or valproic acid, which could theoretically allow placebo patients (who were not quite stabilized) to enter the trial with patients who were allowed to then take lurasidone. Indeed efficacy results indicate that patients who required a run-in had virtually the same MADRS scores at each week compared to placebo patients, whereas efficacy was noted at weeks 2 through 5 in those patients who were already stabilized on lithium or valproic acid prior to screening.

Also, the lack of geographic variation noted in within the U.S. subgroup on the primary endpoint efficacy results indicates that the recruitment of more North American patients, with the additional exclusion of Russian sites in study 292, may have contributed to the lack of efficacy in study 292 when compared to study 235. The exclusion of Russian sites is noteworthy in that a comparison of mean change from MADRS scores at study endpoint from study 235 in the European subgroup demonstrated a very significant decrease in treatment effect in study 292 compared to study 235 where Russian data was included in the European dataset (-7.0 study 235 v. -2.9 study 292). This suggests that the Russian subpopulation had a very large effect over the positive efficacy results seen in the European dataset in study 235 and, ultimately, the primary endpoint efficacy results.

In this reviewer's opinion, the lack of efficacy seen on the primary endpoint for study 292, despite a trend towards a treatment effect in the U.S subgroup with lurasidone treatment, renders study 292 a NEGATIVE study with regards to adjunctive treatment of bipolar disorder.

6.2.3 Crosscutting Issues

Subgroup Analyses

Subgroup analyses were conducted and discussed previously under *Additional Considerations* for each study. Please refer back to this section.

Dose Response

Since the sponsor employed flexible dosing study designs the adjunctive therapy studies, an assessment of efficacy based on dose response cannot be determined from the data submitted.

Key Secondary Variables

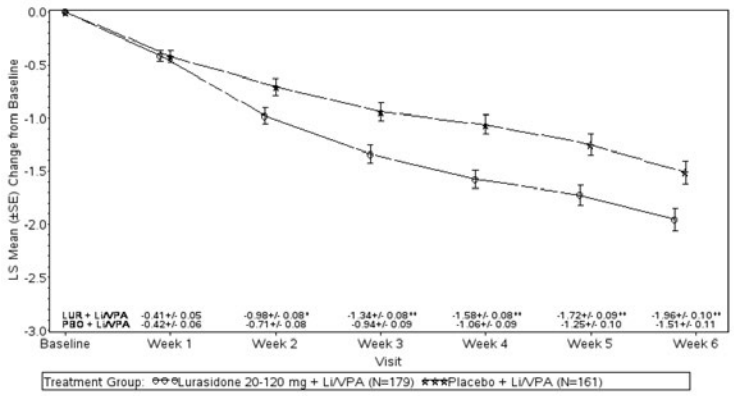
Study 235

Key Secondary CGI-BP-S

Assessment of efficacy based on the pooled analysis from all geographic regions showed that patients treated with lurasidone had statistically significantly less severe clinician-rated depression symptoms (reduced CGI-BP-S scores) compared to placebo treated subjects.

Figure 5: Study 235 Mean Change From Baseline CGI-BP-S Scores By Visit

Figure 4: Change from Baseline (LSM ± SE) in Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S) in Subjects Treated with Lurasidone or Placebo (Intent-to-Treat Population)



Note: * p ≤ 0.05; ** p ≤ 0.01 for contrast with placebo.
Abbreviations: LUR = lurasidone; LI – Lithum; LS = least square; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.
Source: Figure 14.2.2.1.1.1.

Table 52: Study 235 Mean Change from Baseline in CGI-BP-S scores in Lurasidone Patients from Placebo Patients by Visit (ITT)

Week	Placebo+ Li/VPA N=161	Lurasidone +Li/VPA N=179	Mean change L v. Placebo (SE)	P-value
Baseline	4.60 (0.625)	4.47 (0.648)	--	--
Week 1			0.01 (0.078)	0.933
Week 2			-0.27 (0.108)	0.013
Week 3			-0.40 (0.118)	<0.001
Week 4			-0.52 (0.122)	<0.001
Week 5			-0.47 (0.136)	<0.001
Week 6			-0.44 (0.150)	**0.003**

As was the case with the MADRS, geographical variation was seen in response to the CGI-BP-S in the South American subgroup, with North America showing a small change favoring placebo-treated patients on CGI-BP-S scores between lurasidone and placebo-treated patients, but a larger, statistically significant mean change difference between lurasidone and placebo-treated patients in Europe.

Table 53: Study 235 Mean Change from Baseline CGI-BP-S Scores at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America N=110 (58L,52 P)	Rest of the World* N=230 (121L,109P)
Mean Change From Baseline CGI-BP-S at Week 6		
Placebo (SE)	-1.59(0.185)	-1.46(0.130)
Lurasidone 20-120mg (SE)	-1.43(0.180)	-2.19(0.124)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-120mg (SE)	0.17(0.258) p=0.522	-0.73(0.178) p<0.001

*includes Africa, Asia and Europe (Czech Republic, France, Germany, Poland, Romania, Russia and Ukraine)

Table 54: Study 235 Mean Change from Baseline CGI-BP-S Scores at Week 6 by Continent, Excluding North America (ITT)

Treatment Group	Africa N=18 (10L,8P)	Asia N=80(43L,37P)	Europe* N=132(68L,64P)
Mean Change from Baseline CGI-BP-S at Week 6			
Placebo (SE)	-1.25 (0.414)	-1.85 (0.244)	-1.24 (0.166)
Lurasidone 20-120mg (SE)	-1.30(0.350)	-2.27 (0.222)	-2.21 (0.162)
Mean change Difference from Placebo at Week 6			
Lurasidone 20-120mg (SE)	-0.05(0.541) p=0.993	-0.42 (0.327) p=0.204	-0.97(0.231) p<0.001

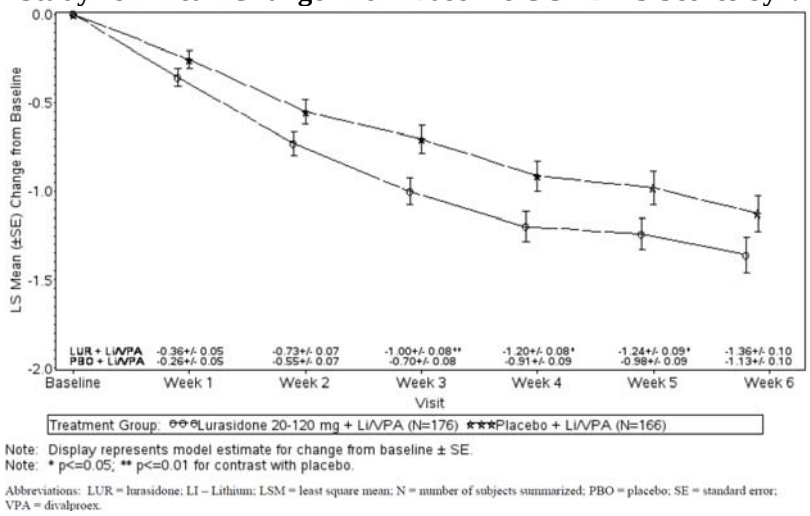
*includes Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine

Study 292

Key Secondary CGI-BP-S

Assessment of efficacy based on the pooled analysis from all geographic regions showed that patients treated with lurasidone had statistically significantly less severe clinician-rated depression symptoms (reduced CGI-BP-S scores) compared to placebo treated subjects.

Figure 6: Study 292 Mean Change From Baseline CGI-BP-S Scores by Visit (ITT)



Note: Display represents model estimate for change from baseline ± SE.
Note: * p<=0.05; ** p<=0.01 for contrast with placebo.

Abbreviations: LUR = lurasidone; LI – Lithium; LSM = least square mean; N = number of subjects summarized; PBO = placebo; SE = standard error; VPA = divalproex.

Table 55: Study 292 Mean Change from Baseline in CGI-BP-S scores in Lurasidone Patients from Placebo Patients by Visit (ITT)

Week	Placebo+Li/VPA N=166	Lurasidone +Li/VPA N=176	Mean change L v. Placebo (SE)	P-value
Baseline	4.43 (0.575)	4.50 (0.659)	--	--
Week 1			-0.10 (0.070)	0.151
Week 2			-0.18 (0.095)	0.057
Week 3			-0.30 (0.107)	0.006
Week 4			-0.29 (0.117)	0.015
Week 5			-0.26 (0.127)	0.043
Week 6			-0.24 (0.141)	**0.095**

For study 292, a trend towards efficacy was noted in the North American data set and the pooled non-U.S. data set. However a notable trend towards worse CGI-BP-S scores was seen in the South American subgroup (CGI-BP-S mean change form baseline score 0.05 $\pm$0.403)

Table 56: Study 292 Mean Change from Baseline CGI-BP-S Scores at Week 6, North America V. Rest of the Word (ITT)

Treatment Group	North America* N=151 (80L,71 P)	Rest of the World** N=191 (96L,95P)
Mean Change From Baseline CGI-BP-S at Week 6		
Placebo (SE)	-0.94 (0.167)	-1.26(0.125)
Lurasidone 20-120mg (SE)	-1.20 (0.160)	-1.49(0.122)
Mean change Difference from Placebo at Week 6		
Lurasidone 20-120mg (SE)	-0.26(0.230) p=0.253	-0.23(0.171) p=0.186

*includes USA and Canada
**includes Africa, Asia (India and Japan), Europe (Czech Republic, Lithuania, Slovakia, and Ukraine), and South America (Colombia and Peru)

Effect Size

Each of the adjunctive therapy studies were powered to detect a mean MADRS score change of 3.25 on the global endpoint. For comparison, Seroquel XR (approved for bipolar depression) had mean MADRS score changes -4.1 to -6.5 in the phase 3 clinical program for bipolar depression. In addition, Symbyax (also approved for bipolar depression) had mean MADRS score changes of -6 to -8 for the phase 3 trials that led to approval for bipolar depression.

An internal analysis of efficacy results from the non-European subgroup for study 235 indicates that the treatment effect for the non-European subgroup was minimal and no clinically significant [-1.4 (SE=1.74); CI -4.8, 2.1 p=0.4362]. Again when compared to the European result of -7.0 (SE 1.68) CI: -10.3, -3.7; p<0.0001 and the global mean change of -3.6 for study 235, this suggests that some factor(s) that are specific to Europe had an unusually large treatment effect that was not seen anywhere else in the world. In addition, the comparison also suggests that the

majority of the subgroups demonstrated a very small, not clinically significant MADRS score change.

Long-Term Efficacy
The sponsor has not provided any double-blind, randomized efficacy data beyond 6 weeks for either the monotherapy or adjunctive therapy bipolar depression program. Therefore efficacy beyond 6 weeks is unable to be determined at this time.

Pediatric Development

Please see 5.1.3 for full details.

6.2.4 Efficacy Conclusions Regarding Claim 2

The results from studies 235 and 292 indicate that patients who require adjunctive treatment with lurasidone to treat depressive symptoms of bipolar disorder are an unique population of bipolar depressed patients when compared to patients who received monotherapy treatment for bipolar depression. Patients who fail to respond to initial therapy who then require additional treatments adjunctively are considered partially treatment resistant compared to patients who have not been treated with initial treatments. For study 235 and 292, the sponsor elected to specifically examine efficacy of lurasidone in partially resistant bipolar depressed patients. In this reviewer's opinion, efficacy results from the monotherapy study 235 cannot be used to support efficacy for patients who require adjunctive treatment in order to improve the depression of bipolar disorder.

After review of the efficacy data from the negative study 235, the worsening of MADRS scores with lurasidone treatment within the U.S. subpopulation despite overall positive efficacy on the global endpoint noted in study 235, combined with a trend towards efficacy in the U.S. subgroup in the negative study 292 but overall lack of efficacy on the study endpoint and worsening MADRS scores in South America, does not provide "substantial evidence" to support a claim of adjunctive treatment of bipolar depression within the United States.

7 REVIEW OF SAFETY

Safety Summary

Generally lurasidone was well tolerated. Discontinuation rates due to adverse events were similar between placebo and lurasidone-treated subjects. Adverse events for the monotherapy and adjunctive studies were generally mild, with nausea, headache, somnolence, akathisia and parkinsonism being common adverse events in study 236 and with somnolence also being reported as a common adverse event in study 235.

Due to the flexible study designs of the studies submitted, dose-dependency of adverse events cannot be definitively determined. However the monotherapy study provides some evidence of dose dependency as a result of the use of flexible dosing ranges. Nausea, parkinsonism, akathisia, and somnolence were dose-related adverse events observed from study 236.

There were minimal changes in laboratory parameters, with the exception of prolactin levels and some notable shifts from low/normal creatinine levels to "high" in lurasidone patients. Overall metabolic changes were minimal, as well as weight and BMI changes. Although the sponsor has

previously conducted a thorough QT study under the schizophrenia clinical development program, a review of the consult from the Agency's QT-interval recommends that the previous study was inadequate.

It is recommended that the sponsor conduct an in vitro study to examine the effects of lurasidone on creatinine secretion that is modulated by renal organic anion and cation transporters. In addition, it is recommended that the sponsor conduct an additional through QT study of lurasidone, as recommended the Agency's QT team.

7.1 Methods

The integrated summary of safety report (ISS), which includes safety data obtained from the two double-blind, placebo-controlled studies, safety and tolerability data from studies 236, 235 and 292, and data from the open label extension study D1050256 as well as serious adverse events from three additional ongoing studies (studies D1050292, D1050296, D1050298) were reviewed as part of the safety summary. In addition, safety results from the individual studies were also reviewed for the summary of safety.

The cut-off date for safety data used in the integrated summary of safety was 6 April 2012.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Please refer to section 7.1.

7.1.2 Categorization of Adverse Events

Adverse events were characterized by system and preferred term according the most recent MedDRA update. Adverse events were then displayed by system organ class and by preferred term by proportion of patients receiving lurasidone or placebo who reported the MedDRA-coded adverse event term.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the Integrative Safety Summary (ISS), the sponsor did not pool data from any other study as the two originally submitted studies were different study designs, one being monotherapy and the other adjunctive therapy.

The sponsor submitted data from the recently completed adjunctive study 292 in February 2013. However no update to the ISS was performed to examine the pooled safety data from study 235 and study 292.

7.2 Adequacy of Safety Assessments

A review of the safety assessments was conducted for all of the submitted efficacy and safety studies. In addition, a review of QT-IRT team's consult recommendations that was reviewed as part of the original NDA for schizophrenia was reviewed. After review of the data, it appears that the QT-study conducted by the sponsor and currently noted in labeling was insufficient to detect a potential QT effect of lurasidone due to a.) lack of a placebo control arm and b.) the use of ziprasidine instead of moxifloxacin as the positive control.

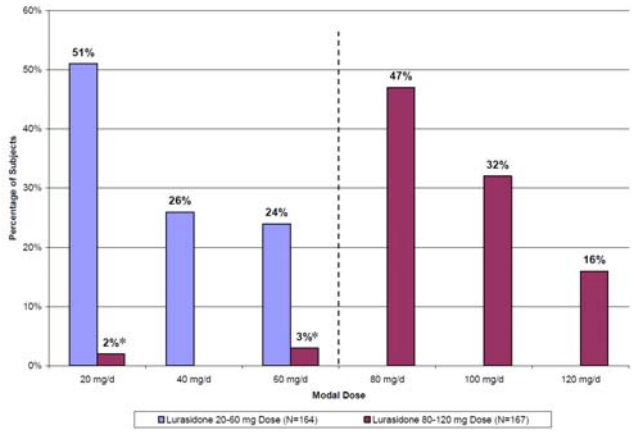
This reviewer recommends that the sponsor conduct another QT study that is accepted to Agency standards.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For all three studies, a flexible dosing scheme was used. However the mean duration of exposure to lurasidone for the monotherapy study was 35.6 ± 10.94 days with 20mg being the most common modal dose (see sponsor figure 1 below) in the low dosing group leading to a mean daily dose of 31.6 ±11.11 mg. For the higher dosing group, the 80mg/day dose was the most common modal dose leading to a mean daily dose of 90.4 ±16.14mg (refer to sponsor figure 2).

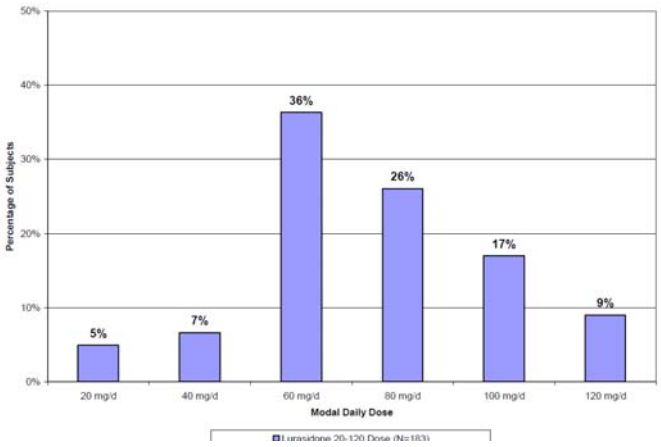
Please refer to the efficacy section of this review for an in-depth review of the demographics of the patient populations for each study.

Figure 1: Modal Daily Dose - Monotherapy Study (D1050236) All Subjects (Safety Population)



For the adjunctive study 235, the most common modal dose was 60mg/day leading to a mean daily dose of 65.5±18.42mg.

Figure 2: Modal Daily Dose - Adjunctive Therapy Study (D1050235) All Subjects (Safety Population)



7.2.2 Explorations for Dose Response

An exploration of dose response for adverse events related to lurasidone administration is confounded by the flexible dosing strategy employed for all the double blind controlled studies. However safety data obtained from the monotherapy study provides some evidence for dose-related adverse events.

In the monotherapy study, nausea, somnolence, akathisia and parkinsonism were noted to be dose related.

Table 57: Study 236 Dose-Related Adverse Events (Safety Population)

Adverse Event	Placebo N=168	Lurasidone 20-60mg/day N=164	Lurasidone 80-120mg/day N=167
Nausea	7.7%	10.4%	17.4%
Somnolence*	6.5%	7.3%	13.8%
Akathisia	2.4%	7.9%	10.8%
Parkinsonism**	2.4%	4.9%	9.0%

*includes hypersomnia, sedation and somnolence
** includes drooling, muscle rigidity, parkinsonism, and tremor

7.2.3 Special Animal and/or In Vitro Testing

The sponsor did not conduct animal or in vitro testing of lurasidone for this supplemental NDA.

7.2.4 Routine Clinical Testing

After reviewing the clinical protocols of the submitted studies and clinical study reports, this reviewer is of the opinion that clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no studies addressing metabolic, clearance, or drug interactions that were submitted as part of this NDA submission. Although having such studies is clinical useful, metabolic studies were conducted as part of the initial registration studies for the adult schizophrenia indication.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The use of the antipsychotic class of medications has been associated with extrapyramidal adverse events, such as involuntary movements, akathisia and parkinsonism-related movements. In addition, clinical trials in psychiatry often involve treating patients who are at risk of expressing suicidal ideations or make suicidal attempts. The sponsor measured changes in each of these domains during the trials.

In summary, the emergency or lurasidone-induced akathisia and suicidality (increase suicidal thinking) was noted in the data from studies 236, 235 and 292 when compared to placebo treated patients. This reviewer recommends that the lurasidone labeling discuss the findings from the

BARS and adopt the anti-depressant suicidality language should these applications receive Agency approval.

Simpson-Angus Scale (SAS)
The SAS is a rating scale used to monitor for drug-induced parkinsonism which contains 10 items that are rated 0(normal) to 4(extreme). Thus the scale can rate a patient from 0-40. The SAS results from each study are reviewed below.

Study 236
Over the course of the study, 8.4% of combined-lurasidone treated patients shifted from a normal to abnormal SAS score by the LOCF endpoint compared to 4.3% of placebo-treated patients.

Looking at the trends in SAS scores at LOCF endpoint (stratified by concomitant medication use), patients in the 20-60mg lurasidone group had a 0.04 $\pm$ 0.033 increase in SAS scores, compared to 0.03 $\pm$ 0.036 in the 80-120 mg dose group and 0.01 $\pm$ 0.079 change in the placebo group.

One patient in the placebo group (subject 23614813) discontinued the study due to Parkinson-related tremors. There were a total of 3 lurasidone patients who had a treatment-emergent adverse event related to drug-induced parkinsonism, defined as a >0.3 mean screen and coded as an AE.

Study 235
There were eight lurasidone-treated subjects (4.4%) who met criteria for abnormal SAS (defined as SAS mean score >0.3). Four patients had parkinsonism coded as an AE.

Study 292
There were negligible changes in SAS scores overtime between placebo and lurasidone-treated subjects for this study.

Abnormal Involuntary Movements Scale (AIMS)
The AIMS is a 12-item rating scale used to monitor dyskinetic movements. The highest possible total AIMS score is 28.

Study 236
In study 236, mean total AIMS scores showed an absence of involuntary movements, with no change in AIMS median scores at LOCF for all treatment groups. There were no involuntary movements coded as an AE, with the exception of restless leg syndrome in a patient taking concomitant medications.

Study 235

No mean changes in AIMS scores were noted at LOCF, with the absence of involuntary movements note. One patient who was receiving lithium and 120mg of lurasidone plus benztropine developed dystonia (subject 23510605). The dystonia was judged to be related to the benztropine.

Study 292
According to the AIMS global score categorical change from baseline to LOCF endpoint, 7 lurasidone patients (4%) compared to 1 in the placebo group (1%) had worse scores at LOCF. There were minimal changes in AIMS score from baseline which were not clinically significant. At LOCF, 5.1% of lurasidone treated patients v. 1.8% had minimal symptoms of involuntary movements. There were no severe involuntary movements noted.

Barnes Akathisia Rating Scale (BARS)
The (BARS) is an objective and subjective rating scale used to assess the severity of drug-related akathisia. The objective scoring is ranged on a 0-3 scale. A total score is the summation of all objective items, with a global score rating separately on a 6 point scale.

Study 236
There were minimal mean changes from baseline scores noted amongst the treatment groups. However there were six patients (all receiving lurasidone) who were discontinued from the study due to an adverse event of akathisia. The proportion of patients who had worsened BARS scores at LOCF from baseline was dose-related, with 8.1% in low dose, 8.6% in high dose and 5.6% taking placebo.

Study 235
Although mean BARS scores had minimal change at LOCF, 12% of lurasidone patients had worse BARS scores at LOCF, with 9 reporting the event as an adverse event.

Study 292
There was a small increase in baseline BARS scores at LOCF for patients taking lurasidone compared to placebo (0.1 $\pm$ 0.03 v. 0.0 $\pm$0.03 respectively). The proportion of subjects who worsened from baseline to LOCF on the BARS was larger in lurasidone patients compared to placebo (8.5% v. 1.8% respectively).

Columbia- Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an instrument that is administered in clinical trial to assess for potential drug-induced suicidality, defined as an increase in suicidal thoughts or suicidal behaviors.

Study 236

In Study 236, there were no suicidal behaviors after baseline noted for lurasidone or placebo-treated subjects.

When looking at the emergence of suicidal ideation within the lurasidone and placebo treatment arms, the proportion of patients who developed suicidality was similar between the two groups. There was one patient who received lurasidone who developed an active suicidal plan. However this patient was a 41 yo woman who two days earlier lost her child to an automobile accident while he played in the yard of the patient. This patient was hospitalized and stabilized.

Table 58: Study 236 C-SSRS Score Summary By Treatment Group (safety population)

C-SSRS Item	L 20-60mg N=164	L 80-120mg N=167	Combined L N=331	Placebo N=168
At least one episode of suicidal ideation after baseline (Suicidality)	22 (13.7%)	24 (14.8%)	46 (14.2%)	22 (13.6%)
Most Severe Suicidal Ideation after Baseline				
1-wish to be dead	16	15	31	18
2-non-specific active suicidal thoughts	2	4	6	3
3-active suicidal ideation with any method (without plan) without intention to act	3	5	8	1
4-active suicidal ideation with intent to act, no specific plan	0	0	0	0
5-active suicidal ideation with plan and intention to act	1	0	1	0

Study 235

As with study 236, no patients displayed any suicidal behaviors after baseline. There was a small signal for increases in post-baseline suicidal ideation in the lurasidone group vs. placebo patients, primarily as a result of some lurasidone-treated patients expressing non-specific active suicidal thoughts. This reviewer recommends that the Agency adopt the antidepressant class labeling suicidality language for lurasidone should these two supplemental NDA applications receive approval.

Table 59: Study 235 C-SSRS Score Summary By Treatment Group (safety population)

C-SSRS Item	Lurasidone + Li/VPA N=183	Placebo + Li/VPA N=163
At least one episode of suicidal ideation after baseline (Suicidality)	17 (9.7%)	20 (12%)
Most Severe Suicidal Ideation After Baseline		
1-wish to be dead	22	17
2-non-specific active suicidal thoughts	4	0
3-active suicidal ideation with	0	1

any method (without plan) without intention to act		
4-active suicidal ideation with intent to act, no specific plan	0	0
5-active suicidal ideation with plan and intention to act	0	1

Study 292

Again, there were no post-baseline suicidal behaviors reported for any patients in study 292. Unlike study 235, placebo-treated subjects in study 292 had a smaller increased rate of suicidality when compared to lurasidone-treated subjects, particularly with more placebo patients expressing active suicidal thoughts without intent or plan compared to lurasidone treated patients. Nevertheless, there appears to be an increase in lurasidone patients expressing non-specific active suicidal thoughts, which is consistent with the findings in study 235. However the data generated by the sponsor is not consistent with C-SSRS findings from the previous two studies and therefore the C-SSRS data obtained from study 292 is unable to be used for regulatory actions on suicidality language. Therefore this reviewer continues to recommend the Agency adopt antidepressant suicidality language should approval be granted for these two applications.

Table 60: Study 292 C-SSRS Score Summary By Treatment Group (safety population)

C-SSRS Item	Lurasidone + Li/VPA N=111	Placebo + Li/VPA N=171
At least one episode of suicidal ideation after baseline (Suicidality)	26 (14.5%)	19 (11.8)
Most Severe Suicidal Ideation After Baseline		
1-wish to be dead	126	145
2-non-specific active suicidal thoughts	43	13
3-active suicidal ideation with any method (without plan) without intention to act	8	13
4-active suicidal ideation with intent to act, no specific plan	0	0
5-active suicidal ideation with plan and intention to act	0	0

7.3 Major Safety Results

Lurasidone was generally well tolerated by most patients during the bipolar depression pivotal trials. Serious adverse events and discontinuations due to adverse events in lurasidone-treated subjects were generally proportional to those seen in placebo-treated subjects. Akathisia, vomiting, somnolence and tremors/parkinsonism-related adverse events were more commonly reported in lurasidone-treated subjects. Elevated prolactin levels were consistently noted in lurasidone-treated subjects compared to placebo. With regards to metabolic and weight/BMI changes, small changes were noted in some metabolic parameters with some changes in weight noted for lurasidone-treated subjects compared to placebo, with some individual lurasidone patients noting larger changes in weight compared to placebo patients. However the metabolic

and weight changes in lurasidone patients overall compared to placebo were generally less severe than those generally seen with other atypical antipsychotics.

There was a noted shift from low/normal creatinine to high creatinine noted in laboratory testing. IT is recommended that the sponsor conduct an in vitro study to examine the effect of lurasidone on the renal cell anion/cation transporter that facilitates the secretion of creatinine in the renal tubule.

There were few events of treatment-emergent mania noted. However there were numerically more treatment-emergent mania events noted in the monotherapy trial compared to both adjunctive treatment trials. There were more suicidality events noted in lurasidone-treated subjects in the adjunctive trial 235 than in placebo.

It is this reviewer's opinion, antidepressant class labeling for suicidality is recommended to be included to product label should this application receive Agency approval. In addition, the ≥2% adverse events tables and common adverse events table, along with metabolic change and weight change information is recommended to be included into product labeling should the application receive approval.

7.3.1 Deaths

No deaths occurred in the short-term, double-blind, placebo controlled studies.

Two (2) deaths occurred in the open-label extension study:

- Subject 25615610 (b) (6) was a 20 year old healthy Indian male with history of bipolar depression and no history of concomitant medications was enrolled in the 24 week open-label study and began treatment with 60mg of lurasidone open-label on (b) (6). On (b) (6), 8 days after the first dose of 60mg lurasidone, the patient committed suicide by hanging from a tree. The site was expecting the patient to report to the site on (b) (6) for a follow-up visit and after several failed phone calls to the patient, the coordinator of the study went to the his house who was informed by the patients' brother that the subject committed suicide several 21 days earlier. The original protocol specified that visits were to occur every month during the open label trial.
- Subject 25615809 (b) (6) was a 22 year old Indian male with bipolar depression, who began treatment with 60mg lurasidone on (b) (6) and was also taking 1000mg of valproic acid daily. On (b) (6), 11 days after the first dose of lurasidone, the patient was involved in motor vehicle accident as a passenger and was killed. While en route to a religious service in a passenger car with 13 other relatives, the car turned upside down while making a sharp turn, with the patient having the steering wheel severely injure his testicles with severe bleeding and scrotal tears. At autopsy, cause of death was related to neurogenic shock due to vital organ (testis) and multiple body injuries.

It is clear that there is no association between the motor vehicle accident death and lurasidone administration for subject (b) (6), since the patient was not in control of the vehicle as a passenger in the vehicle and the cause of death was exsanguination and multiple bodily injuries.

Although an association between lurasidone administration and suicide for subject (b) (6) cannot be ruled out, it is known that depression is a significant risk factor for suicide. In addition,

pharmacological treatment of depression generally requires 4 to 6 weeks of treatment prior to improvement in symptoms. Current boxed warnings for selective serotonin reuptake inhibitors do report an association between increased suicidal thoughts and treatment initiation. However given that lurasidone is pharmacologically not an SSRI, as well as not currently been shown to be effective as an antidepressant, it possible but unlikely that increased suicidality with lurasidone administration was a proximate cause to this subject's suicide. Given that this patient had only received 8 days of lurasidone prior to his suicide, it is unlikely that there is an association between lurasidone treatment and this patient's suicide.

7.3.2 Nonfatal Serious Adverse Events

In general, serious adverse events rates were similar between lurasidone and placebo patients groups. This reviewer recommends that reports of anaphylaxis and angioedema with lurasidone use be incorporated into the product labeling. A review of the SAEs from each study are presented below.

Study 236
For the monotherapy study, nine (9) total serious adverse events occurred during the study. The majority of the serious adverse events were non-psychiatrically-related and not due to the study drug.

Table 61: Study 236 Serious Adverse Events by Treatment Group

Preferred Term	Lurasidone 20-60mg (N=164)	Lurasidone 80-120mg (N=167)	Placebo (N=168)
Total SAEs	**3 (1.8%)**	**5 (3.0%)**	**1 (<1%)**
Duodenal Ulcer			1
HIV Infection		1	
Subcutaneous Abscess		1	
Foot Fracture		1	
Restless legs Syndrome		1	
Depression	2		
Panic Attack	1	1	

A review of the psychiatric serious adverse events leading to discontinuation are from study 236 are provided below.

- Subject 23607612 was a 40 yo white male from the U.S. who was randomized to lurasidone 20-60mg/day and started the study on (b) (6). The patients had 18 year history of bipolar disorder. During the trial, the patient reported feeling increased depression and patient was discontinued from the study medication. On the same day, the patient admitted himself to the hospital for treatment of moderate to severe depression. The patient was discharged from the hospital on (b) (6) and from the study on 02 November 2010. His discharge medications at time of discharge from the hospital were lithium 300mg twice daily and Seroquel 100mg at bedtime.
- Subject 23610309 was a 46 yo white male from the U.S. who was NOT randomized to take medication, was discontinued from the study for severe suicidal ideation. The patient was taken to the hospital and admitted and consequently discontinued from the study.

- Subject 23615706 was a 28 yo Asian male from India who was randomized to take lurasidone 20-60mg/day. This patient had a 9 year history of bipolar disorder and was not taking any medications prior to entry into the study. After 21 days of treatment with 60mg of lurasidone, the patient expressed suicidal ideations and worsening depression. He was subseq2uently discontinued from the study medications and hospitalized for his depression. After 10 days of inpatient treatment, the subject was discharged taking fluoxetine, divalproex, amitriptyline and chlordiaezopoxide. His depression remitted approximately 6 weeks after being admitted to the hospital.
- Subject 23641411 was a 55 yo white female from South Africa who had a 14 year history of bipolar disorder, reported to the principal investigator after taking lurasidone 20mg for 4 days of panic symptoms and an inability to sleep for three nights despite taking zolpidem. She was admitted to the hospital and received treatment overnight. The next day the subject's panic symptoms were resolved and she was discharged from the hospital.

Adjunctive study 235
For the adjunctive study, four (4) total serious adverse events occurred during the study. Three of the four serious adverse events were psychiatrically-related with only one SAE that occurred in the placebo group being non-psychiatrically related femur fracture that occurred in the study.

A review of the three psychiatric SAEs are provided below.

- Subject 23507407 was a 33 yo white female from the U.S. who was randomized to lurasidone plus adjunctive lithium and started the study on (b) (6). The patient had 5 year history of bipolar disorder. Three days after taking lurasidone, the patient reported severe suicidal ideation. It was reported that the patient's 2 year old son was struck and killed by a truck the same day the patient started taking lurasidone. She was admitted to the psychiatric hospital and discharged approximately 10 days later.
- Subject 23515013 was a 35 yo Indian female from India who was randomized to lurasidone plus adjunctive lithium and started the study on (b) (6) The patient had 6 year history of bipolar disorder. On day 13 of lurasidone treatment, the patient reported severe worsening depression with a wish to die. It was also noted that the patient had moderate akathisia that was coded as an adverse event but not noted as an SAE. She was admitted to the psychiatric hospital and discharged approximately 7 days later. The SAE is coded for depression with no mention of akathisia.
- Subject 23534404 was a 33 yo white male from France who was randomized to placebo plus adjunctive lithium and started the study on (b) (6) The patient had 10 year history of bipolar disorder. After 22 days of taking adjunctive placebo, the patient reported severe suicidal ideation. He was admitted to the psychiatric hospital the following day for suicidal ideation and discharged approximately 10 days later.

Adjunctive study 292

For the adjunctive study 292, there were eight (8) serious adverse events, five (5) occurring in patients who took lurasidone (2.8%) and three who were randomized to placebo (1.8%). The pertinent SAEs of those patients who were taking lurasidone are discussed below.

Trial 292 (double-blind, adjunctive treatment of lurasidone)

- Subject 29210108 was a 26 yo female from the U.S. who was randomized to lurasidone plus adjunctive lithium and an 11 year history of bipolar disorder. After 8

days of taking adjunctive blinded study medication, the patient reported severe suicidal ideation and a moderate intentional overdose. She was admitted to the psychiatric hospital the following day for suicidal ideation and discharged approximately 10 days later.

- Subject 29224802 was a 50 yo female from the Ukraine who was randomized to lurasidone treatment plus adjunctive valproic acid. After 30 days of taking adjunctive blinded study medication, the patient reported severe bipolar depression and was hospitalized. She was admitted to the psychiatric hospital the following day for her depression with the depression still ongoing at time of report.
- Subject 29216201 was a 46 year old Indian patient who was randomized to lurasidone 40mg/day treatment plus adjunctive valproic acid, was hospitalized 12 days after last dose of lurasidone (subject completed the 41 day trial) for severe anaphylactic shock which required hospitalization. He was taking concomitant ACE inhibitors, calcium channel blockers and torasemide. The patient was stabilized and discharged from the hospital 4 days later in stable condition.
- Subject 29262408 was a 39 yo woman from the Czech republic who was randomized to lurasidone 60mg plus concomitant valproic acid who developed severe depression and suicidal ideation and hospitalized for suicidal ideation after taking lurasidone for 20 days.
- Subject 29265834 was a 32 yo female from the U.S. who was randomized to lurasidone treatment plus adjunctive valproic acid. Other concomitant medications were Ativan. She was reported to have allergies to Benadryl (itching and agitation), penicillin and latex (hives). After taking the first dose of taking adjunctive lurasidone study medication, the patient developed moderate angioedema with puffy eyes, and then took a second dose the next day whereby her eyes were swollen shut. Patient was recommended to go to the ER but did not follow recommendation and took ibuprofen for treatment on the third day. Patient did not receive any other treatments.

Study 296 (randomized double-blind, placebo controlled, flexible dose, parallel-group study of adjunctive lurasidone to li/vpa for prevention of recurrence in subjects with bipolar 1 disorder)

- Subject 296006009 was a 26 yo female from the U.S. who was randomized to lurasidone plus adjunctive valproic acid. The patient started to take lurasidone for approximately 26 days. One month after initiating dosing with lurasidone, urine pregnancy test was positive on the follow up visit, with serum hcg level confirming pregnancy. After cessation of all medications, patient followed up with her physician 4 months later for a suspected UTI. Two days later, she was found to have premature rupture of amniotic membranes and hospitalized with induction of labor. A stillborn female of 21 weeks gestation was delivered.
- Subject 296019007 was a 57 yo female from the U.S. who was randomized to lurasidone plus adjunctive Depakote. After 39 days of taking adjunctive lurasidone, the patient reported increased depressive symptoms and admitted to the psychiatric hospital the same day for worsening depression.
- Subject 296022009 was a 39 yo female from the U.S. who was randomized to lurasidone plus adjunctive lithium and a history of 3 prior suicide attempts by overdose and hospitalizations. After 27 days of taking adjunctive lurasidone, the patient reportedly took an overdose of her lurasidone and valproic acid. She was

admitted to the hospital for medical treatment and quickly stabilized and transferred to the psychiatric hospital the same day. UDS was positive for cocaine.

Study 256-open label extension study

- Subject 25619003 was a 53 yo female patient enrolled in the antecedent study 236 and was taking lurasidone 60mg/day, experienced a depressive episode that required hospitalization 109 days after initiating lurasidone treatment.
- Subject 25615206 was a 41 yo male from India who received open label lurasidone plus adjunctive lithium. The patient was previously enrolled in the adjunctive study 235 and randomized to placebo. After 2 days of taking open label lurasidone at 60mg, the patient reported suicidal ideation of plans to cut throat with a sickle with a superficial cut to anterior neck and was recommended to be hospitalized but patient's brother refused and patient was treated with fluoxetine and olanzapine with daily follow-up. Over the next several days patient improved and after several months, patient was no longer suicidal.
- Subject 25616003 was a 43 yo male from India who received open label lurasidone plus adjunctive lamotrigine. The patient was previously enrolled in the monotherapy study 236 and randomized to placebo, however it appears that this patients was also taking lamotrigine during the entire monotherapy study. After 183 days of taking lurasidone at 80mg, the patient reported depression was hospitalized. He was treated and subsequently discharged 10 days later.
- Subject 25624010 was a 48 year old female who received placebo during the antecedent study 235 and completed the trial. On the 27th day of the open label extension study taking lurasidone 60mg, she experienced a moderate exacerbation of her depression and was hospitalized.
- Subject 2567401 was a 43 yo female who also received placebo in the preceding study 235 and completed the trial. Four months later the patient was enrolled into the open label extension study and started treatment with lurasidone 60mg/day. After 8 days of open label treatment, the patient experienced a major depressive episode and was hospitalized.
- Subject 2564403 was a 36 yo female who received lurasidone 100mg during the double blind phase of study 235. After 65 days total on lurasidone (23 days in open label treatment), the patient had suicidal ideation and was hospitalized.
- Subject 25662101 was a 39 yo male who received lurasidone 20mg during the double blind phase of study 235. After 183 days total of lurasidone treatment (142 of open label treatment), the patients experienced a moderate depressive episode and was hospitalized.

7.3.3 Dropouts and/or Discontinuations

Overall the rates of dropouts and discontinuations were similar between lurasidone-treated subjects compared to placebo patients for each of the studies reviewed.

A review of dropouts/discontinuations are presented below for each study.

Monotherapy study 236

During the course of the monotherapy study, a total of 29 patients discontinued from the study due to an adverse event, of which 20 patients (6%) were from the lurasidone group and 9 (5.4%) were randomized to placebo. A comparison between the discontinuation rates between the combined lurasidone and placebo groups reveals that lurasidone patients were twice as likely to discontinue the study due to nervous system adverse events compared to placebo, 2.4% to 1.2% respectively. Of the nervous system adverse events, akathisia was the leading cause of discontinuations for patients taking lurasidone (1.8% lurasidone to 0% placebo).

Table 62: Study 236 Discontinuations by Adverse Event

Preferred Term	Lurasidone 20-60mg N=164 N (%)	Lurasidone 80-120mg N=167 N (%)	Lurasidone combined N=331 N (%)	Placebo N=168 N (%)
GI Disorder	--	--	--	**1 (<1)**
Duodenal Ulcer	--	--	--	1 (<1)
Infections and infestations	**2 (1.2)**	--	**2 (<1)**	--
Bronchitis	1 (<1)	--	1(<1)	--
Staphylococcal infection	1 (<1)	--	1(<1)	--
Investigations	**1(<1)**	--	**1(<1)**	--
Blood creatine phosphokinase increased	1(<1)	--	1(<1)	--
Musculoskeletal	--	**1(<1)**	**1(<1)**	--
Myositis	--	1(<1)	1(<1)	--
Nervous system disorders	**2(1.2)**	**6(3.6)**	**8(2.4)**	**2(1.2)**
Akathisia	1(<1)	5(3.0)	6(1.8)	--
Dyskinesia	--	--	--	1(<1)
Headache	1(<1)	--	1(<1)	--
Parkinsonism	--	--	--	1(<1)
Restless leg syndrome	--	1(<1)	1(<1)	--
Psychiatric Disorders	**5(3.0)**	**1(<1)**	**6(1.8)**	**5(3.0)**
Bipolar I	--	1(<1)	1(<1)	1(<1)
Depression	2(1.2)	--	2(<1)	3(1.8)
Logorrhea	1(<1)	--	1(<1)	--
Mania	1(<1)	--	1(<1)	1(<1)
Panic Attack	1(<1)	--	1(<1)	--
Respiratory, thoracic and mediastinal disorders	--	**1(<1)**	**1(<1)**	--
Hypopnea	--	1(<1)	1(<1)	--

Skin and Subcutaneous Tissue disorders	**1(<1)**	**--**	**1(<1)**	**--**
Rash popular	1(<1)	--	1(<1)	--
TOTAL	**11(6.7)**	**9(5.4)**	**20 (6.0)**	**9(5.4)**

Adjunctive study 235

Similar to the findings seen in the monotherapy study, only 22 patients [of which 11 patients (6%) were from the lurasidone group and 11 (6.7%) were randomized to placebo] were discontinued from the trial due to an adverse event. In contrast to the monotherapy study, a comparison between the discontinuation rates between the combined lurasidone and placebo groups reveals that lurasidone patients discontinued the study due to GI adverse events compared to placebo, 2.2% to <1% respectively.

Table 63: Study 235 Discontinuations by Adverse Event

Preferred Term	**Lurasidone 20-120mg+Li/VPA N=183 N (%)**	**Placebo + Li/VPA N=163 N (%)**
GI Disorder	**4(2.2)**	**1 (<1)**
Nausea	2(1.1)	--
Upper abdominal pain	1(<1)	--
Vomiting	1(<1)	--
Salivary Hyper secretion	--	1(<1)
General disorders and administration site conditions	**--**	**1(<1)**
Drug withdrawal syndrome	--	1(<1)
Injury, poisoning and procedural complications	**--**	**1(<1)**
Femur Fracture	--	1(<1)
Investigations	**1(<1)**	**--**
Weight increased	1(<1)	--
Nervous system disorders	**--**	**1(<1)**
Dysaesthesia	--	1(<1)
Psychiatric Disorders	**5(2.7)**	**7(4.3)**
Agitation	1(<1)	1(<1)
Depressed mood	1(<1)	--
Depressive symptom	1(<1)	--
Hypomania	1(<1)	1(<1)

Suicidal ideation	1(<1)	1(<1)
Anxiety	--	1(<1)
Depression	--	3(1.8)
Vascular disorders	**1(<1)**	**--**
Hypertension	1(<1)	--
TOTAL	**11 (6.0)**	**11(6.7)**

Adjunctive study 292

A total of 15 patients were discontinued from study 292 due to adverse events as seen in the table below. Although there were nearly double the proportion of patients from the lurasidone groups that were discontinued from the study due to an adverse event compared to placebo, the number of patients from both groups is small.

Table 64: Study 292 Discontinuations by Adverse Event

Preferred Term	**Lurasidone 20-120mg+Li/VPA N=177 N (%)**	**Placebo + Li/VPA N=171 N (%)**
Eye Disorder	**1(<1)**	**--**
Visual acuity reduced	1(<1)	--
General disorders and administration site conditions	**4(2.3)**	**1(<1)**
Disease Progression	3(1.7)	--
Fatigue	1(<1)	1(<1)
Investigations	**--**	**1(<1)**
ECG T wave inversion	--	1(<1)
Nervous system disorders	**1(<1)**	**2(1.2)**
Somnolence	1(<1)	--
Akathisia	--	1(<1)
Dizziness	--	1(<1)
Psychiatric Disorders	**3(1.7)**	**1(<1)**
Depression suicidal	1(<1)	--
Suicidal ideation	1(<1)	--
Tension	1(<1)	--
Mania	--	1(<1)
Skin and subcutaneous tissue disorders	**1(<1)**	**--**
Angioedema	1(<1)	--
TOTAL	**10 (5.6)**	**5(2.9)**

7.3.4 Significant Adverse Events

Generally patients treated with lurasidone tolerated the medication well and with few side effects. However some events from both the monotherapy study and two adjunctive studies occurred more frequently compared to placebo treated subject. This reviewer recommends that the labeling for lurasidone include a greater than 2% table of adverse events and greater than placebo be included into labeling should this application be approved.

Monotherapy study 236

A majority of patients receiving both lurasidone and placebo had at least one treatment emergence adverse event (TEAE) during the study (63.1% and 57.1% respectively). Of those adverse events considered "drug related", defined as possibly, probably or definitely drug related as judged by the clinical investigator, 51% of lurasidone-treated patients and 44% of placebo patients experienced a drug related TEAE.

The number of patients taking lurasidone who have reported an adverse event at least 2% or greater and more frequently then placebo patients indicates that vomiting, diarrhea, nasopharyingitis, akathisia, sedation, tremor, parkinsonism and anxiety are twice as likely to be reported in lurasidone patients than compared to placebo patients. Nausea is also more frequently reported in patients taking lurasidone compared to placebo patients, although the proportion of lurasidone-treated patients who report nausea is not quite twice the rate of placebo patients.

Table 65: Study 236 Adverse Events Occurring in ≥2% of Lurasidone-Treated Patients and more frequently than Placebo

Adverse Event	Lurasidone 20-60mg N=164	Lurasidone 80-120mg N=167	Lurasidone Combined N=331	Placebo N=168
Gastrointestinal Disorders	**27.4%**	**27.5%**	**27.5%**	**19.6%**
Nausea	10.4%	17.4%	13.9%	7.7%
Dry Mouth	6.1%	3.6%	4.8%	4.2%
Vomiting	2.4%	6.0%	4.2%	1.8%
Diarrhea	4.9%	3.0%	3.9%	1.8%
Infections and Infestations	14.6%	13.8%	14.2%	11.3%
Nasopharyingitis	4.3%	3.6%	3.9%	1.2%
Nervous System Disorder	**32.3%**	**32.9%**	**32.6%**	**27.4%**
Akathisia	7.9%	10.8%	9.4%	2.4%
Somnolence	4.3%	6.6%	5.4%	4.2%
Tremor	2.4%	4.8%	3.6%	1.2%
Parkinsonism	2.4%	3.0%	2.7%	1.2%
Psychiatric Disorders	**16.5%**	**17.4%**	**16.9%**	**15.5%**
Anxiety	3.7%	4.8%	4.2%	1.2%

Adjunctive study 235

Similar to the monotherapy study, the majority of patients in the adjunctive treatment study had reported at least one TEAE (lurasidone 63.9%; Placebo 57.7%). The table below delineates the proportion of patients with TEAEs reported in 2% or greater in the lurasidone group[s and more frequently than in the placebo group.

Table 66: Study 235 Adverse Events Occurring in ≥2% of Lurasidone-Treated Patients and more frequently than Placebo

Adverse event	Lurasidone + Li/VPA N=183	Placebo + Li/VPA N=163
Eye Disorder	**5.5%**	**1.2%**
Vision blurred	3.3%	--
GI Disorders	**29%**	**21.5%**
Nausea	17.5%	11%
Vomiting	4.9%	2.5%
Constipation	2.2%	1.8%
General Disorders of administration site conditions	**6.6%**	**9.8%**
Fatigue	2.7%	1.8%
Infections and infestations	**11.5%**	**12.3%**
Nasopharyngitis	3.3%	1.8%
Metabolism and nutrition disorders	**5.5%**	**6.1%**
Increased appetite	3.3%	1.8%
Musculoskeletal and connective tissue disorders	**9.3%**	**9.8%**
Musculoskeletal stiffness	2.7%	1.2%
Muscle rigidity	2.2%	--
Nervous System Disorder	**35.5%**	**31.3%**
Somnolence	8.7%	4.3%
Tremor	8.2%	4.3%
Akathisia	7.7%	4.3%
Parkinsonism	4.4%	4.3%
Sedation	2.2%	1.2%
Psychiatric Disorders	**20.2%**	**14.7%**
Insomnia	7.1%	5.5%
Restlessness	3.8%	1.2%
Agitation	2.2%	1.2%
Renal and urinary disorders	**3.3%**	**--**
Pollakiuria	2.2%	--

The only adverse event that was considered common (i.e. ≥5% in the lurasidone groups and at least twice the rate of placebo) was somnolence. However those events as noted above occurring greater than twice the rate of placebo were blurry vision, musculoskeletal stiffness, muscle rigidity, restlessness and Pollakiuria.

Adjunctive study 292

A similar adverse event profile was noted for the additional adjunctive study that was submitted at the request of the Agency. The following table provides that incidence of TEAEs that were reported in ≥3% of subjects in either treatment group:

Table 67: Study 236 Adverse Events Occurring in ≥3% of Lurasidone-Treated Patients

Adverse event	Lurasidone + Li/VPA N=177	Placebo + Li/VPA N=171
Eye Disorder	**1.7%**	**4.1%**
Vision blurred	1.1%	3.5%
GI Disorders	**22.6%**	**24.6%**
Nausea	10.2%	9.4%
Diarrhea	7.9%	5.8%
General Disorders of administration site conditions	**7.3%**	**4.1%**
Fatigue	3.4%	1.2%
Infections and infestations	**10.7%**	**8.8%**
Nasopharyngitis	4%	2.3%
Investigations	**9%**	**3.5%**
Weight Increased	4%	--
Nervous System Disorder	**37.3%**	**26.9%**
Akathisia	14.1%	5.3%
Somnolence	11.9%	4.7%
Parkinsonism	11.3%	7.6%
Headache	8.5%	8.8%
Dizziness	5.1%	5.3%
Psychiatric Disorders	**22%**	**24%**
Insomnia	8.5%	10.5%
Restlessness	3.4%	<1%
Anxiety	2.8%	4.7%

Those adverse events that were considered common (at least 5% or greater in the lurasidone group and twice the rate of placebo) were akathisia and somnolence (to include hypersomnia, sedation and somnolence).

7.3.5 Submission Specific Primary Safety Concerns

The sponsor performed an analysis of treatment-emergent mania and changes in anxiety symptoms for study 236, 235 and 292. The results of these analyses are formally reviewed under section 7.5 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This reviewer recommends including common adverse events that occurred in the monotherapy study and adjunctive studies be included into product labeling should this NDA obtain approval. A summary of common adverse events for each study in briefly reviewed below.

Monotherapy Study 236

Those adverse events which occurred in at least 2% or greater of lurasidone-treated patients (combining low and high dose groups) AND at least twice the rate of placebo were vomiting, diarrhea, Nasopharyngitis, akathisia, sedation, tremor, parkinsonism and anxiety.

Table 68: Study 236 Adverse Events Occurring ≥2% and Twice the Rate of Placebo

Adverse Event	Placebo N=168	Lurasidone Combined N=331
Vomiting	1.8%	4.2%
Diarrhea	1.8%	3.9%
Nasopharyngitis	1.2%	3.9%
Akathisia	2.4%	9.4%
Sedation	1.8%	5.1%
Tremor	1.2%	3.6%
Parkinsonism	1.2%	2.7%

Adjunctive Study 235
For the adjunctive study 235, common adverse events were blurry vision, vomiting, musculoskeletal stiffness, muscle rigidity, somnolence, restlessness, and pollakiuria.

Table 69: Study 235 Adverse Events Occurring ≥2% and Twice the Rate of Placebo

Adverse Event	Placebo + Li/VPA N=163	Lurasidone +Li/VPA N=183
Blurry Vision	--	3.3%
Vomiting	2.5%	4.9%
Musculoskeletal stiffness	1.2%	2.7%
Muscle rigidity	--	2.2%
Somnolence	4.3%	8.7%
Restlessness	1.2%	3.8%
Pollakiuria	--	2.2%

Adjunctive Study 292

Common and drug-related adverse events that occurred in study 292 were fatigue, weight increased, akathisia, somnolence, and restlessness

Table 70: Study 292 Adverse Events Occurring ≥2% and Twice the Rate of Placebo

Adverse Event	Placebo + Li/VPA N=171	Lurasidone +Li/VPA N=177
Fatigue	1.2%	3.4%
Weight Increased	--	4.0%
Akathisia	5.3%	14.1%
Somnolence	4.7%	11.9%
Restlessness	<1%	3.4%

7.4.2 Laboratory Findings

For studies 235, 235 and 292, very small and clinically insignificant mean changes from baseline and very few markedly abnormal values in laboratory parameters were noted. A noteworthy small, but consistent shift from baseline in creatinine from low/normal to high in lurasidone treated subject compared to placebo is noted. This reviewer recommends that this shift be noted in labeling for lurasidone. In addition, it is recommended that the sponsor conducts an in vitro study to examine the effects of lurasidone on renal tubule creatinine secretion.

A summary of pertinent laboratory findings (hematological and clinical laboratory) are presented below for each study.

Hematological Findings

Study 236
For changes in hematological parameters, the following tablets delineate direction change from baseline values. Overall, very small mean change from baseline values were noted in both groups. Nevertheless, the small changes are likely to have little clinical significance.

Table 71: Study 236 Directional Change in Hematological Parameters from Baseline at LOCF Endpoint (Safety Population)

Test At baseline	Lurasidone Combined N=331			Placebo N=168		
	Test at LOCF Endpoint					
Basophils Absolute N=332						
	Low	Normal	High	Low	Normal	High
Low	--	--	--	--	--	--

Normal	--	313 (97.2%)	2(<1%)	--	157 (98.1%)	1 (<1%)
High	--	6 (1.9%)	1 (<1%)	--	1 (<1%)	1 (<1%)
Basophil %						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--
Normal	--	286 (88.8%)	12 (3.7%)	--	147 (91.9%)	5 (3.1%)
High	--	17 (5.3%)	7 (2.2%)	--	7 (4.4%)	1 (<1%)
Eosinophil Absolute						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--
Normal	--	302 (93.8%)	9 (2.8%)	--	153 (95.6 %)	2(1.3%)
High	--	3 (<1%)	8 (2.5%)	--	2 (1.3%)	3 (1.9%)
Test At baseline	**Lurasidone Combined N=331**			**Placebo N=168**		
	Test at LOCF Endpoint					
Eosinophil % N=322						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--

Normal	--	254 (78.9%)	12 (3.7%)	--	137 (85.6%)	5 (3.1%)
High	--	25 (7.8%)	31 (9.6%)	--	9 (5.6%)	9 (5.6%)
Hemoglobin						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	16 (5%)	6 (1.9%)	--	9 (5.6%)	3 (1.9%)	--
Normal	8 (2.5%)	286 (88.8%)	1 (<1%)	5 (3.1%)	145 (89.5%)	--
High	--	1 (<1%)	4 (1.2%)	--	--	--
Lymphocyte Absolute						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	5 (1.6%)	--	3 (1.9%)	2(1.3%)	--
Normal	6 (1.9%)	310 (96.3%)	1 (<1%)	1(<1%)	153 (95.6%)	1 (<1%)
High	--	--	--	--	--	--

Test At baseline	**Lurasidone Combined N=331**			**Placebo N=168**		
	Test At LOCF Endpoint					
MCV N=332						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**

Low	11 (3.4%)	3(<1%)	--	14 (8.6%)	--	--
Normal	6 (1.9%)	291 (90.4%)	4 (1.2%)	3 (1.9%)	142 (87.7%)	1 (<1%)
High	--	3 (<1%)	4 (1.2%)	--	--	2 (1.2%)
Neutrophils Absolute						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	2 (<1%)	3 (<1%)	--	--	1 (<1%)	--
Normal	2 (<1%)	293 (91%)	13 (4%)	3 (1.9%)	134 (83.8%)	7 (4.4%)
High	--	5 (1.6%)	4 (1.2%)	--	10 (6.3%)	5 (3.1%)
Platelet Count						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	1(<1%)	3 (<1%)	--	3 (1.9%)	1 (<1%)	--
Normal	1 (<1%)	285 (88.8%)	11 (3.4%)	--	147 (90.7%)	4 (2.5%)
High	--	9 (2.8%)	11 (3.4%)	--	2 (1.2%)	5 (5.1%)

Test **At baseline**	**Lurasidone Combined** **N=331**	**Placebo** **N=168**
	Test At LOCF Endpoint	
Red Blood Cell Count **N=332**		

	Low	Normal	High	Low	Normal	High
Low	20(6.2%)	17 (5.3%)	--	11 (6.8%)	4 (2.5%)	--
Normal	15 (4.7%)	259 (80.4%)	2 (<1%)	3 (1.9%)	137 (84.6%)	1 (<1%)
High	--	4 (1.2%)	5 (1.6%)	--	3 (1.9%)	3 (1.9%)
White Blood Cell Count						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	10 (3.1%)	17 (5.3%)	--	4 (2.5%)	6 (3.7%)	--
Normal	12 (3.7%)	265 (82.3%)	10 (3.1%)	9 (5.6%)	121 (75.2%)	4 (2.5%)
High	--	4 (1.2%)	4 (1.2%)	--	11 (6.8%)	6 (3.7%)

Study 235

For changes in hematological parameters, the following tablets delineate direction change from baseline values. Overall very small mean change from baseline values were noted in both groups. However the small changes appear to have little clinical significance. Pertinent hematological changes are noted below:

Table 72: Study 235 Directional Change in Pertinent Hematological Parameters from Baseline at LOCF Endpoint (Safety Population)

Parameter/Value at Baseline	**Lurasidone + Li/VPA (N=183)**		**Placebo + Li/VPA (N=163)**	
	N	**LOCF Value**	**N**	**LOCF Value**
Eosinophils absolute		**High**		**High**
Low or Normal	171	9 (5.5%)	145	3 (2.1%)
Lymphocytes-Absolute		**LOW**		**LOW**
High or Normal	174	5 (2.9%)	149	1 (0.7%)
Neutrophils-Absolute		**High**		**High**
Low or Normal	158	11 (7%)	150	7 (4.7%)

The proportion of patients with markedly abnormal hematological values was very low in study 235, with slightly more placebo patients having higher eosinophil percentage than lurasidone (6.3% v. 4.5% respectively).

Study 292

For study 292, a review of the summary of mean change from baseline values on hematological parameters reveals very small and consistent changes between lurasidone and placebo-treated patients which is similar to findings form study 235.

For shifts from baseline to LOCF endpoint, the following table displays pertinent findings. Overall shifts were small and consistent to those seen in study 235.

Table 73: Study 292 Directional Change in Pertinent Hematological Parameters from Baseline at LOCF Endpoint (Safety Population)

Parameter/Value at Baseline	Lurasidone + Li/VPA (N=177)		Placebo + Li/VPA (N=171)	
	N	LOCF Value	N	LOCF Value
Basophils absolute		**High**		**High**
Low or Normal	169	4 (2.4%)	157	0
Monocytes-Absolute		**High**		**High**
Low to normal	169	2 (1.2%)	159	00

For markedly abnormal hematological values during the study, the markedly abnormal values were similar to those found in study 235, with comparable rates between lurasidone and placebo-treated subjects.

Table 74: Study 292 Markedly Abnormal Laboratory Values by Treatment Group (safety population)

Test and Criteria	Lurasidone +Li/VPA N=177	Placebo +Li/VPA N=171
Eosinophils >10%	4/169 (2.4%)	2/159 (1.3%)
WBC Count <2800	1/169 (<1%)	0
WBC Count >16,000	2/169 (1.2%)	0

Clinical Chemistry

Overall changes in clinical laboratory findings were minimal. However a noted shift in normal/low creatinine to high at LOCF in lurasidone patients compared to placebo may be due to interactions with the renal organic ion transporter that modulated creatinine secretion. It is recommended that the sponsor conduct an in vitro study to examine this potential interaction.

Study 236
For changes in clinical chemistry parameters, the following tables delineate direction change from baseline values for selected clinical chemistry parameters which may have some significance. Overall very small mean change from baseline values were noted in both groups. However the small changes appear to have little clinical significance.

Of note, 2.8% of patients had a shift from normal/low creatinine levels to high at LOCF endpoint compared to placebo. It is possible that lurasidone may be interfering with creatinine secretion that is modulated by the renal organic cation and anion transporter.

Table 75: Study 236 Directional Change in Clinical Chemistry Values from Baseline at LOCF Endpoint (Safety Population)

Test At baseline	Lurasidone Combined N=331			Placebo N=168		
	Test at LOCF Endpoint					
Albumin						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	1 (<1%)	--	--
Normal	1 (<1%)	149 (92.5%)	4 (2.5%)	--	148 (91.9%)	4 (2.5%)
High	--	5 (3.1%)	2 (1.2%)	--	6 (3.7%)	2 (1.2%)
ALT						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--
Normal	--	310 (96.3%)	7 (2.2%)	--	157 (96.9%)	2 (<1%)
High	--	3 (<1%)	2 (<1%)	--	1 (<1%)	1 (<1%)
AST						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--
Normal	--	302 (93.8%)	9 (2.8%)	--	153 (95.6 %)	2(1.3%)
High	--	3 (<1%)	8 (2.5%)	--	2 (1.3%)	3 (1.9%)
Test At	**Lurasidone Combined N=331**			**Placebo N=168**		

baseline	Test at LOCF Endpoint					
C-Reactive Protein N=283						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	--	--	--	--	--	--
Normal	--	221 (78.1%)	22 (7.8%)	--	117 (81.3%)	5 (3.5%)
High	--	12 (4.2%)	28 (9.9%)	--	11 (7.6%)	11 (7.6%)
Creatinine						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	3 (<1%)	9 (2.8%)	--	2 (1.2%)	5 (3.1%)	--
Normal	5 (1.6%)	285 (88.5%)	9 (2.8%)	5 (3.1%)	146 (90.1%)	1 (<1%)
High	--	7 (2.2%)	4 (1.2%)	--	3 (1.9%)	--
Prolactin						
	Low	**Normal**	**High**	**Low**	**Normal**	**High**
Low	1 (<1%)	7 (2.5%)	2 (<1%)	1 (<1%)	6 (4.1%)	--
Normal	3 (1.1%)	230 (81%)	27 (9.5%)	2 (1.4%)	121 (82.3%)	7 (4.8%)
High	--	11 (3.9%)	3 (1.1%)	--	6 (4.1%)	4 (2.7%)
Test At baseline	**Lurasidone Combined N=331**			**Placebo N=168**		
	Test At LOCF Endpoint					
Triglycerides Overall						

	Low	Normal	High	Low	Normal	High
Low	8 (2.8%)	14 (4.9%)	1 (<1%)	1 (<1%)	4 (2.7%)	--
Normal	13 (4.6%)	187 (65.8%)	21 (7.4%)	4 (2.7%)	111 (75.5%)	6 (4.1%)
High	--	21 (7.4%)	19 (6.7%)	--	9 (6.1%)	12 (8.2%)

With regards to outlier criteria, the following are pertinent markedly abnormal post-baseline laboratory values of note. Overall rates of markedly abnormal laboratory values were low, even when compared to placebo. Thus this reviewer recommends no additional labeling or monitoring for laboratory testing in patients.

Table 76: Study 236 Markedly Abnormal Laboratory Values by Treatment Group

Test and Criteria	Combined Lurasidone N=331)	Placebo N=168
C-reactive protein >0.79 mg/dL	52/284 (18.3%)	17/146 (11.6%)
Calcium <8.4 mg/dL	17/322 (5.3%)	4/162 (2.5%)
Fasting Cholesterol >300 mg/dL	6/262 (2.3%)	2/133 (1.2%)
Creatine Phosphokinase ≥ 300 X ULN	12-322 (3.7%)	2/162 (1.2%)
Fasting Triglycerides >300 mg/dL	10/262 (3.8%)	3/133 (2.3%)

Study 235
The trend for shift from baseline values in patients taking concomitant lurasidone was virtually unchanged compared to concomitant placebo patients, with the exception of shift from normal to high values at LOCF endpoint for glucose level (11.5% lurasidone patient shift normal to high v. 8.9% shift from normal to high placebo), total protein (3.9% in lurasidone patients v. <1% in placebo patients shifting from normal to high levels)

Overall very small mean change from baseline values were noted in both groups. However the small changes appear to have little clinical significance. Pertinent parameters of changes generally affected the placebo group greater than lurasidone treated subjects.

With regards to outlier criteria, two lurasidone patients had total bilirubin levels >2.0mg/dL compared to one in placebo. Otherwise no clinically significant abnormalities were noted.

Table 77: Study 235 Markedly Abnormal Laboratory Values by Treatment Group

Test and Criteria	Lurasidone +Li/VPA N=183	Placebo +Li/VPA N=163
C-reactive protein >0.79 mg/dL	13/157 (8.3%)	11/147 (7.5%)
Potassium >5.5 mmol/L	3/179 (1.7%)	1/157 (<1%)
Total bilirubin =>2.0mg/dL	2/179 (1.1%)	1/157 (<1%)
Triglycerides (fasting) =>300mg/dL	12/143 (8.4%)	9/136 (6.6%)

Study 292

Overall the trend for small shifts in laboratory parameters were noted in the open-label safety study. In general, patients who were previously taking placebo in the preceding study had larger shifts than those previously on lurasidone. As seen in study 236, there was a noted shift in lurasidone patients who had normal/low creatinine to high at LOCF endpoint compared to placebo.

For directions change from baseline, the following pertinent changes were noted. Overall changes were very small and of comparable between lurasidone and placebo-treated subjects.

Table 78: Study 292 Directional Change in Pertinent Chemistry Parameters from Baseline at LOCF Endpoint (Safety Population)

Parameter/Value at Baseline	Lurasidone + Li/VPA (N=177)		Placebo + Li/VPA (N=171)	
	N	LOCF Value	N	LOCF Value
ALT		**High**		**High**
Low or Normal	168	13 (7.7%)	159	9 (5.7%)
Calcium		**High**		**High**
Low to Normal	169	6 (3.6%)	158	2 (1.3%)
Creatinine		**High**		**High**
Low to Normal	169	7 (4.1%)	159	2 (1.3%)
Glucose Overall		**High**		**High**
Low to Normal	162	29 (17.9%)	156	16 (10.3%)
Insulin Overall		**High**		**High**
Low to Normal	141	15 (10.6%)	147	5 (3.4%)
Prolactin		**High**		**High**
Low to Normal	163	24 (14.7%)	154	5 (3.2%)

There were very few markedly abnormal post-baseline clinical chemistry values. Only fasting triglycerides >=300mg/dL was slightly more prevalent in the lurasidone groups compared to placebo patients (5.2% v. 4.9% respectively).

Study 256

Overall, changes in laboratory parameters thus far are very small and clinically insignificant.

7.4.3 Vital Signs

In general, very small changes were noted to blood pressure, pulse, temperature and respiratory rates were noted for studies 235, 236 and 292. The changes were consistent with those seen in placebo patients and were not clinically significant. This reviewer recommends no changes to current labeling for blood pressure and pulse adverse events should the application receive approval.

Blood Pressure and Pulse

Study 236

Overall there were minimal changes to pulse and blood pressures over the course of the study.

Table 79: Study 236 Mean Change from Baseline Parameters in Vital Signs (safety Population)

Measurement	L 20-60 (n=164)	L 80-120 N=167	L combined N=331	Placebo N=168
Sitting Pulse (BPM)				
Baseline Mean (SD)	74.2 (10.36)	73.8 (10.72)	74.0 (10.53)	74.7 (10.69)
Change from Baseline at LOCF (SD)	0.2 (9.88)	0.5 (9.83)	0.4 (9.84)	-0.2 (8.59)
Sitting Systolic Blood Pressure (mmHg)				
Baseline Mean (SD)	122.5 (12.30) (10.36)	120.9 (12.54)	121.7 (12.43)	120.7 (11.26)
Change from Baseline at LOCF (SD)	-0.8 (10.58)	-0.2 (9.03)	-0.5 (9.82)	-0.3 (9.66)
Sitting Diastolic Blood Pressure (mmHg)				
Baseline Mean (SD)	74.2 (10.36)	73.8 (10.72)	74.0 (10.53)	74.7 (10.69)
Change from Baseline at LOCF (SD)	0.2 (9.88)	0.5 (9.83)	0.4 (9.84)	-0.2 (8.59)

Study 235

Blood pressure changes overtime were minimal, with lurasidone patients having a -1.4 $\pm$8.86 mmHg decrease in systolic blood pressure and -1.6 $\pm$ 7.41 mmHg decrease in diastolic at week 6 compared to -0.1 $\pm$ 8.66 mmHg systolic and -1.3 $\pm$ 7.26 mmHg diastolic decrease in blood pressure at week 6 for placebo patients.

There were no apparent differences in pulse between the lurasidone and placebo patients. One patient (41 yo white female), developed tachycardia on day 11 while taking 60mg/day of lurasidone. The event resolved the same day with no clinical sequelae noted.

Study 292
Changes to blood pressure values overtime were similar to those seen in study 235.

Weight

Generally speaking, lurasidone treatment was associated with minimal changes in weight and BMI. Although a smaller proportion of patients taking lurasidone gained >7% of body weight, the rates are generally smaller than is seen with other drugs in this particular class. This reviewer recommends standard, class metabolic labeling for lurasidone with the addition of data from the specific studies to the labeling if these supplements are approved. A review of weight data from each trial is presented below.

Monotherapy 236

Overall, small changes in weight and BMI were noted. Although an increased proportion of patients treated with lurasidone shifted from normal to overweight during the trial when compared to placebo, a much smaller proportion of patients gained >7% of body weight over the trial.

Table 80: Study 236 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Weight (Safety Population)

Measurement/ Visit	**Statistic**	**Lurasidone 20-60mg N=164**	**Lurasidone 80-120mg N=167**	**Placebo N=168**
Weight (Kg)				
	Baseline Mean (SD)	78.29 (17.784)	76.03 (15.975)	77.20 (18.254)
Change From Baseline				
	LOCF Endpoint (SD)	0.56 (1.924)	0.02 (2.090)	-0.04 (1.815)
BMI (Kg/m^2)				
	Baseline Mean (SD)	27.72 (5.570)	27.17 (5.273)	27.17 (5.475)
Change From Baseline				
	LOCF Endpoint (SD)	0.20 (0.666)	0.01 (0.765)	-0.03 (0.649)

Table 81: BMI Shift at LOCF from Baseline (Safety population)

Parameter at Baseline	Lurasidone 20-60mg N=164 Weight Value at LOCF				Lurasidone 80-120mg N=167 Weight Value at LOCF			
BMI	**Under**	**Nml.**	**Over**	**Obese**	**Under**	**Nml**	**Over**	**obese**
Underweight	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Normal	1 (<1%)	39 (27.3%)	6 (4.2%)	0	1 (<1%)	55 (37.4%)	2 (1.4%)	0
Overweight	0	1 (<1%)	47 (32.9%	1 (<1%)	0	2 (1.4%)	27 (32%)	0
Obese	0	0	3 (2.1%)	43 (30.1%)	0	0	2 (1.4%)	36 (24.5%)

Table 82: Study 236 Significant Mean Change from Baseline Values at LOCF Endpoint (Safety population)

Weight (Kg)	Lurasidone 20-60mg N=164	Lurasidone 80-120mg N=167	Combined Lurasidone N=331	Placebo N=168
High (≥ 7% increase)	6/143 (4.2%)	1/147 (<1%)	7/290 (2.4%)	1/151 (<1%)
Low (≥7% decrease)	0/143	2/147 (1.4%)	2/290 (<1%)	2/151 (1.3%)

Largest increase in weight was a 8.1kg increase in six weeks. Subject 23610024, randomized to low dose lurasidone, gained 8.1 kg while taking 60mg/day of lurasidone. This event was not coded as an adverse event.

Adjunctive study 235

Weight and BMI findings from the adjunctive study are quite similar to finding found in the monotherapy study.

Table 83: Study 235 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Weight (Safety Population)

Measurement	Statistic	Lurasidone + Li/VPA N=183	Placebo +Li/VPA N=163
Weight (Kg)			
	Baseline mean(SD)	77.60 (17.117)	76.92 (16.357)
Mean Change From Baseline			
	LOCF Endpoint (SD)	0.23 (2.014)	0.14 (1.718)
BMI (Kg/m^2)			
	Baseline mean(SD)	26.78 (4.706)	26.78 (4.889)
Mean Change From Baseline			
	LOCF Endpoint (SD)	0.08 (0.723)	0.05 (0.600)

Table 84: Study 235 BMI Shift at LOCF from Baseline (Safety population)

Parameter at Baseline	Lurasidone 20-120mg + Li/VPA N=183 Weight Value at LOCF				Placebo + Li/VPA N=163 Weight Value at LOCF			
BMI	**Under**	**Nml.**	**Over**	**Obese**	**Under**	**Nml**	**Over**	**obese**
Underweight	4 (2.5%)	0	0	0	2 (1.3%	1 (<1%)	0	0
Normal	2 (1.2%)	42 (25.9%)	5 (3.1%)	0	0	54 (36%)	1 (<1%)	0
Overweight	0	3 (1.9%)	65 (40.1%)	4 (2.5%)	0	0	55 (36.7%)	3 (2%)
Obese	0	0	3 (1.9%)	34 (21%)	0	0	0	34 (22.7%)

Table 85: Study 235 Significant Mean Change from Baseline Values at LOCF Endpoint (Safety population)

Weight (Kg)	Lurasidone+ Li/VPA N=183	Placebo +Li/VPA N=163
High (≥ 7% increase)	5/162 (3.1%)	1/150 (<1%)
Low (≥7% decrease)	4/162 (2.5%)	0/150

Largest increase in weight was a 6kg increase in six weeks. Subject 23516013, randomized to lurasidone, gained 6 kg while taking 60mg/day of lurasidone. This event was not coded as an adverse event.

Study 292
Weight and vital sign findings from study 292 are small and similar to those seen in study 235.

Table 86: Study 292 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Weight (Safety Population)

Measurement	Statistic	Lurasidone + Li/VPA N=177	Placebo +Li/VPA N=171
Weight (Kg)			
	Baseline mean(SD)	79.80 (18.112)	79.08 (17.367)
Mean Change From Baseline			
	LOCF Endpoint (SD)	0.00 (2.357)	0.19 (1.683)
BMI (Kg/m^2)			
	Baseline mean(SD)	28.10 (5.273)	27.47 (5.026)
Mean Change From Baseline			
	LOCF Endpoint (SD)	0.01 (0.855)	0.05 (0.579)

Table 87: Study 292 Significant Mean Change from Baseline Values at LOCF Endpoint (Safety population)

Weight (Kg)	Lurasidone+ Li/VPA N=177	Placebo +Li/VPA N=171
High (≥ 7% increase)	5/165 (3.0%)	0/157
Low (≥7% decrease)	5/165 (3.0%)	0/157

7.4.4 Electrocardiograms (ECG's)

For all the studies submitted, ECGs were obtained on site and read via a centralized reading system. In general there were very minimal and clinically insignificant ECG-related changes that were noted in each of the studies. Therefore this reviewer recommends no additional labeling changes are needed with regards to ECG changes or adverse events.

A thorough QT study was conducted for lurasidone prior to initial approval for schizophrenia. A review of the QT team's review of the study indicates that the original QT study was inadequate to assess the QT prolongation potential of lurasidone since a.) there was lack of a placebo arm and b.) ziprasidone (not moxifloxacin) was used as the positive control. Therefore this reviewer recommends that the sponsor conduct another QT study consistent with Agency standards.

Monotherapy Study 236

Overall there were 12/289 (4.2%) patients in the lurasidone group-combined who shifted from normal to abnormal ECGs at the LOCF endpoint compared to 6/149 (4%) of placebo patients. However, there were no clinically significant ECG changes (defined as heart rate >100bpm, PR interval >210msec, QRS >120msec, and uncorrected QT >500msec), or markedly abnormal changes in ECG noted, with the exception of one patient who had a QTcB of >480msec on one ECG. There were no ECG or serious arrhythmias reports as an AE during the study.

Adjunctive study 235

Similar to study 236, there were no clinically significant ECG changes, ECG-related adverse events or arrhythmias noted during the trial. At the time of LOCF endpoint, 9/156 (5.8%) of patients in the lurasidone group v. 10/147 (6.8%) of placebo patients had an ECG read that shifted from normal to abnormal.

Study 292

No clinically significant or ECG-related adverse events were reported during this trial.

7.4.5 Special Safety Studies/Clinical Trials

Changes in metabolic parameters associated with antipsychotic administration, specifically changes in serum glucose, lipids and triglycerides, have received special attention in recent years. The sponsor conducted specific analysis on metabolic parameters for all the studies conducted. Overall small changes in metabolic parameters were noted with lurasidone administration compared to placebo. However consistent elevation in prolactin and triglyceride levels were a

consistent finding with lurasidone administration. The following is a summary of results from the individual studies.

This reviewer recommends the label indicate the individual changes in the laboratory parameters in the label should this NDA obtain approval.

Monotherapy study 236

Overall there were minor changes from baseline in various metabolic parameters that were likely of little clinical significance. However consistent elevations in prolactin were noted. Given the pharmacological mechanism of dopamine antagonism of lurasidone however, such elevations are not unexpected. Standard language for antipsychotic metabolic parameter monitoring is recommended, to include data obtained from the submitted studies.

Table 88: Study 236 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Metabolic Parameters (Safety Population)

Test	Metric	Lurasidone 20-60mg N=164	Lurasidone 80-120mg N=167	Combined Lurasidone N=167	Placebo N=168
Prolactin (ng/ml)-Overall					
LOCF Endpoint	N	140	144	284	147
	Baseline Mean (SD)	7.83 (5.545)	10.57 (13.990)	9.22 (10.765)	12.04 (28.160)
	Mean Change (SD)	5.31 (18.537)	5.29 (18.795)	5.30 (18.635)	-1.96 (28.226)
Prolactin (ng/ml)-Male					
LOCF Endpoint	N	62	56	118	65
	Baseline Mean (SD)	7.12 (5.726)	7.11 (6.392)	7.11 (6.025)	9.18 (10.262)
	Mean Change (SD)	2.57 (9.302)	4.81 (14.134)	3.63 (11.844)	0085 (14.894
Prolactin (ng/ml)-Female					
LOCF Endpoint	N	78	88	166	82
	Baseline Mean (SD)	8.40 (5.366)	12.78 (16.829)	10.72 (12.945)	14.31 (36.530)
	Mean Change (SD)	7.50 (23.256)	5.60 (21.309)	6.49 (22.197)	-4.18 (35.347
C-reactive Protein (mg/dl)-Overall					
LOCF Endpoint	N	140	143	283	144
	Baseline Mean (SD)	0.482 (0.7323)	0.454 (0.5941)	0.468 (0.6650)	0.429 (0.4630)
	Mean	0.177	0.043	0.109	0.031

	Change (SD)	(1.2186)	(0.7088)	(0.9948)	(0.8632)
Cholesterol-Total (mg/dL)-Overall					
LOCF Endpoint	N	140	144	284	147
	Baseline Mean (SD)	196.0 (44.59)	202.2 (48.12)	199.1 (46.43)	197.4 (47.15)
	Mean Change (SD)	1.2 (25.42)	-4.6 (30.18)	-1.7 (28.04)	-3.2 (27.14)
Glucose (mg/dL)-Overall					
LOCF Endpoint	N	140	143	283	148
	Baseline Mean (SD)	94.3 (13.48)	947.7 (11.85)	94.5 (12.66)	94.5 (14.38)
	Mean Change (SD)	-0.8 (14.86)	1.8 (17.55)	0.5 (16.30)	1.8 (18.42)
High Density Lipoprotein (mg/dL)-Overall					
LOCF Endpoint	N	139	144	283	147
	Baseline Mean (SD)	49.4 (15.63)	51.8 (16.13)	50.6 (15.90)	50.1 (14.69)
	Mean Change (SD)	1.0 (7.23)	-0.3 (10.53)	0.3 (9.06)	-0.3 (6.78)
HOMA-IR-Overall					
LOCF Endpoint	N	139	141	280	144
	Baseline Mean (SD)	3.88 (5.892)	2.64 (2.570)	3.25 (4.568)	3.37 (3.827)
	Mean Change (SD)	0.89 (7.491)	1.27 (6.375)	1.08 (6.942)	1.19 (8.156)
Insulin (mU/L)-Overall					
LOCF Endpoint	N	140	143	283	144
	Baseline Mean (SD)	15.91 (18.849)	10.73 (9.107)	13.29 (14.954)	13.62 (13.305)
	Mean Change (SD)	2.84 (24.782)	4.26 (21.154)	3.56 (22.991)	2.95 (19.927)
LDL (mg/dL)-Overall					
	N	140	144	284	147

LOCF Endpoint					
	Baseline Mean (SD)	132.4 (80.17)	133.9 (96.17)	133.2 (88.49)	125.2 (67.24)
	Mean Change (SD)	5.6 (65.35)	0.4 (65.69)	3.0 (65.46)	6.0 (55.71)
Prolactin (ng/ml)-Overall					
LOCF Endpoint	N	140	144	284	147
	Baseline Mean (SD)	7.83 (5.545)	10.57 (13.990)	9.22 (10.765)	12.04 (28.160)
	Mean Change (SD)	5.31 (18.537)	5.29 (18.795)	5.30 (18.635)	-1.96 (28.226)

Study 235
Similar to study 236, there were minor changes from baseline in various metabolic parameters that were likely of little clinical significance. Standard language for antipsychotic metabolic parameter monitoring is recommended.

Table 89: Study 235 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Metabolic Parameters (Safety Population)

Parameter/Visit	Statistic	Lurasidone + Li/VPA (N=183)	Placebo + Li/VPA (N=163)
Glucose-Overall (55-99mm/dL)	**N**	**157**	**146**
	Baseline Mean (SD)	88.8 (11.22)	92.1 (15.68)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	0.9 (12.35)	-0.3 (15.87)
HbA1c (4-6%)	**N**	**156**	**145**
LOCF Endpoint	Baseline Mean (SD)	5.44 (0.465)	5.53 (0.425)
	Change from Baseline		
	Mean (SD)	-0.03 (0.267)	-0.06 (0.242)
Insulin-overall (3-25mcIU/ml)	**N**	**158**	**147**
	Baseline Mean (SD)	11.29 (11.873)	14.55 (24.099)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	1.66 (16.178)	-0.16 (23.437)
HOMA-IR	**N**	**153**	**145**
	Baseline Mean (SD)	2.58 (3.239)	3.58 (6.922)
	Change from Baseline		

LOCF Endpoint	Mean (SD)	0.26 (3.967)	-0.07 (7.295)
Total Cholesterol (overall) 119-200mg/dL	**N**	**158**	**147**
	Baseline Mean (SD)	190.5 (43.98)	195.7 (45.16)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	-3.0 (25.99)	-3.8 (29.97)
HDL-overall (>35mg/dL)	**N**	**158**	**147**
	Baseline Mean (SD)	47.7 (16.91)	50.8 (18.14)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	-0.5 (13.75)	-0.4 (12.12)
LDL-overall (0-129 mg/dL)	**N**	**158**	**147**
	Baseline Mean (SD)	118.3 (33.11)	118.8 (36.33)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	-3.2 (22.07)	-2.0 (23.02)
Triglycerides-Overall (53-203 mg/dL)	**N**	**158**	**147**
	Baseline Mean (SD)	140.8 (100.35)	147.2 (95.75)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	9.0 (73.54)	-6.2 (80.64)
Prolactin All Subjects	**N**	**158**	**147**
	Baseline Mean (SD)	9.04 (8.540)	8.88 (9.924)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	5.93 (14.003)	0.18 (7.301)

Regarding shifts from low or normal to high levels during the study, the following table describes the pertinent changes from baseline to LOCF endpoint. In general the shifts in lurasidone-treated subjects are similar to those seen in placebo patients.

Table 90: Study 235 Directional Change in Metabolic Parameters from Baseline at LOCF Endpoint (Safety Population)

Parameter/Value at Baseline	**Lurasidone + Li/VPA (N=183)**		**Placebo + Li/VPA (N=163)**	
	N	**LOCF Value**	**N**	**LOCF Value**
Cholesterol (fasting)		**High**		**High**
Low or Normal	100	13 (13%)	90	14 (15.6%)
LDL (fasting)		**High**		**High**
Low or Normal	104	8(7.7%)	102	15 (14.7%)
Triglycerides (fasting)		**High**		**High**
Low or Normal	131	15 (11.5%)	120	9 (7.5%)
Prolactin		**High**		**High**
Low or Normal	158	25 (15.8%)	147	4 (2.7%)

For Markedly abnormal metabolic parameters, generally rates were similar and very in both lurasidone and placebo groups.

Table 91: Study 235 Markedly Abnormal Laboratory Values

Test and Criteria	Lurasidone N=183	Placebo N=163
C-reactive protein	13/157 (8.3%)	11/147 (7.5%)
Total Cholesterol >300 mg/dL	2/143 (1.4%)	3/136 (2.2%)
LDL >200mg/dL	1/143 (<1%)	5/136 (3.7%)
Triglycerides >300mg/dL	12/143 (8.4%)	9/136 (6.6%)

Study 292

As with study 235, a similar trend in small, but clinically insignificant shifts in metabolic parameters was noted.

Table 92: Study 292 Mean Change from Baseline Parameters at LOCF Endpoint by Treatment Group; Metabolic Parameters (Safety Population)

Parameter/Visit	Statistic	Lurasidone + Li/VPA (N=177)	Placebo + Li/VPA (N=171)
Glucose-Overall (55-99mm/dL)	**N**	**162**	**156**
	Baseline Mean (SD)	92.6 (12.01)	93.1 (12.52)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	1.4 (14.85)	-1.4 (14.36)
Insulin-overall (3-25mcIU/ml)	**N**	**141**	**147**
	Baseline Mean (SD)	9.47 (7.845)	11.92 (17.752)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	1.85 (12.197)	-2.51 (15.884)
HOMA-IR	**N**	**141**	**145**
	Baseline Mean (SD)	2.27 (2.138)	2.99 (5.659)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	0.57 (3.794)	-0.81 (5.195)
Total Cholesterol (overall) 119-200mg/dL	**N**	**163**	**156**
	Baseline Mean (SD)	190.0 (44.97)	192.8 (39.17)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	-3.3 (26.94)	-2.0 (29.15)
HDL-overall (>35mg/dL)	**N**	**158**	**147**
	Baseline Mean (SD)	47.7 (16.91)	50.8 (18.14)
	Change from Baseline		

LOCF Endpoint	Mean (SD)	-0.5 (13.75)	-0.4 (12.12)
LDL-overall (0-129 mg/dL)	**N**	**162**	**152**
	Baseline Mean (SD)	107.9 36.48)	111.6 (32.33)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	-3.4 (23.22)	-2.5 (24.73)
Triglycerides-Overall (53-203 mg/dL)	**N**	**163**	**156**
	Baseline Mean (SD)	143.5 (79.75)	145.9 (79.95)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	0.4 (56.29)	-3.1 (72.12)
Prolactin All Subjects	**N**	**163**	**154**
	Baseline Mean (SD)	10.07 (9.571)	10.09 (11.727)
	Change from Baseline		
LOCF Endpoint	Mean (SD)	4.25 (13.851)	-0.58 (10.255)

Ongoing Open Label Study 256

Table 111: Mean Baseline and Change from Open-Label Baseline to LOCF Endpoint for Key Parameters - D1050256 Safety Population

Laboratory Test/ Visit	Statistic	Treatment Group			
		D1050235		D1050236	
		Previous Lurasidone (N = 113)	Previous Placebo (N = 110)	Previous Lurasidone (N = 184)	Previous Placebo (N = 93)
Glucose (Overall) (59-99 mg/dL)					
LOCF Endpoint	n	103	98	157	82
	Baseline Mean (SD)	88.3 (9.58)	91.0 (13.34)	94.6 (15.48)	96.1 (18.40)
	Mean Change(SD)	3.1 (20.23)	0.2 (16.42)	1.4 (16.88)	0.0 (14.79)
	Median Change	1.0	0.5	2.0	0.0
	Min, Max	-31, 173	-63, 56	-54, 58	-39, 58

Laboratory Test/ Visit	Statistic	Treatment Group			
		D1050235		D1050236	
		Previous Lurasidone (N = 113)	Previous Placebo (N = 110)	Previous Lurasidone (N = 184)	Previous Placebo (N = 93)
Total Cholesterol (Overall) (119-200 mg/dL)					
LOCF Endpoint	n	105	98	158	82
	Baseline Mean (SD)	186.1 (40.68)	195.0 (44.01)	199.5 (47.32)	197.5 (39.81)
	Mean Change(SD)	-0.7 (27.46)	0.3 (31.13)	-0.7 (27.08)	0.1 (33.00)
	Median Change	-4.0	0.0	0.0	0.0
	Min, Max	-111, 73	-120, 92	-84, 65	-139, 65
Triglycerides (Overall) (53-203 mg/dL)					
LOCF Endpoint	n	105	98	158	82
	Baseline Mean (SD)	137.2 (88.70)	139.2 (73.02)	139.9 (105.80)	125.9 (70.84)
	Mean Change(SD)	5.5 (59.70)	10.4 (69.51)	0.4 (86.23)	9.2 (59.16)
	Median Change	5.0	-4.0	4.0	4.0
	Min, Max	-302, 145	-174, 260	-436, 230	-188, 233

Abbreviations: LOCF = last observation carried forward; n = total number of subjects with a value.

7.4.6 Immunogenicity

Testing for immunogenicity was not conducted under these efficacy supplements.

7.5 Other Safety Explorations

Treatment Emergent Mania

The sponsor performed an analysis of treatment-emergent mania for each study conducted. Treatment-emergent mania was defined as a total Young Mania Rating Scale (YMRS) of ≥16 at any two consecutive post-baseline visits or at the final assessment, or an adverse event of mania or hypomania. The YMRS is a validated and Agency-supported instrument that has been used to assess for changes in mania symptoms in clinical trials.

Overall there were no statistically significant differences in rates of treatment-emergent mania in any of the studies. There was a small numerical increase, but not statistically significant, in treatment-emergent mania events in the monotherapy study 236 in patients taking lurasidone v. placebo (OR 1.48 95% CI 0.39-5.53). It must be noted that the level of mania symptoms was very low for all patients in these studies. Therefore there is no ability to determine whether monotherapy lurasidone is effective for the treatment of mania or hypomanic episodes associated with bipolar I or Bipolar II disorder.

A review of the YMRS scores from each study is summarized below:

Monotherapy Study 236

In the Monotherapy study 236, there were 9 subjects from the total lurasidone group [6(4%) low dose 95% CI 0.5-8.3; 3 (2%) high dose 95% CI 0.2-5.2] compared to three patients (2%) who received placebo who were categorized as having a treatment-emergent mania episode (ITT population). Although the sponsor did not provide an Odds-Ratio with 95% CI for the combined low-dose, high dose groups, this review has calculated the odds-ratio for the combined low-dose/high dose group to be 1.48 95% CI 0.39-5.53. Mean change from baseline YMRS scores were not statistically significantly different between treatments.

Table 93: Study 236 Mean Change from Baseline Score on YMRS-Total Score at Week 6 Endpoint by Treatment Group (ITT)

Week	Lurasidone 20-60mg N=161	Lurasidone 80-120mg N=162	Placebo N=162
Baseline (SD)	4.4 (2.72)	4.1 (2.53)	4.3 (2.95)
Week 6 (SD)	2.3 (2.61)	2.7 (2.83)	2.9 (2.60)
Mean Change from Baseline (SD)	-2.0 (2.88)	-1.0 (2.65)	-1.4 (2.71)
Treatment Difference from placebo (95% CI)	-0.7 (-1.2, -0.1)	0.0 (-0.6, 0.6	

Adjunctive Therapy 235

Treatment-emergent mania was reported for two (2) subjects for both the lurasidone and placebo treatment groups respective. Thus the odds-ratio for treatment emergent mania in the adjunctive study was 0.9 95% CI 0.1-6.5. Overall mean change from baseline changes on the YMRS scores were comparable in the lurasidone group compared to placebo patients and not statistically significant between treatment groups.

Table 94: Study 235 Mean Change from Baseline Score on YMRS-Total Score at Week 6 (ITT)

Week	Lurasidone + Li/VPA N=179	Placebo + Li/VPA N=161
Baseline Score (SD)	3.4 (2.67)	3.4 (2.63)
Week 6 (SD)	2.1 (2.65)	2.1 (2.77)
Mean Change From Baseline (SD)	-1.2 (2.18)	-1.3 (2.65)
Treatment Difference (95% CI)	0.1 (-0.4, 0.6)	

Adjunctive Study 292
There was one patient in the lurasidone group compared to three patients (2%) in the placebo group who developed treatment-emergent mania. Similar to study 235, there were no statistically significant changes from baseline in YMRS scores at week 6 for any treatment group.

Table 95: Study 292 Mean Change from Baseline Score on YMRS-Total Score at Week 6 (ITT)

Week	Lurasidone + Li/VPA N=176	Placebo + Li/VPA N=166
Baseline Score (SD)	3.6 (2.65)	3.8 (2.86)
Week 6 (SD)	2.6 (2.97)	2.8 (2.85)
Mean Change From Baseline (SD)	-1.0 (2.43)	-1.0 (2.75)
Treatment Difference (95% CI)	-0.1 (-0.6, 0.5)	

Hamilton Rating Scale for Anxiety (HAM-A)

In addition to examining lurasidone-treatment effects on treatment-emergent mania episodes, the sponsor also assessed for the effects of lurasidone treatment effects on symptoms of anxiety, as assessed by changes on the HAM-A, and validated and Agency-supported instrument to assess for changes in anxiety symptoms in clinical trials. Although all treatment groups had lower HAM-A scores at week 6, lurasidone treatment for all lurasidone treatment-groups was associated with a statistically significant decrease in HAM-A scores when compared to placebo. Caution must be used in interpretation of these findings as the level anxiety symptoms in all patients were consistently mild. In addition, the study was designed to detect changes in HAM-A scores. Further clinical trials are indicated in patients with moderate to severe anxiety symptoms to confirm these results.

Monotherapy Study 236
IN study 236, Mean change from baseline HAM-A scores decreased over with teach treatment groups. However treatment with lurasidone at both low and high-doses was associated with a statistically significant decrease in HAM-A scores when compared to placebo treatment. Caution is required in interpretation of these findings as anxiety symptoms were generally mild for each treatment group, with changes in anxiety levels not being a primary outcome for this study.

Table 96: Study 236 Mean Change from Baseline Score on HAM-A Score at Week 6 Endpoint by Treatment Group (ITT)

Week	Lurasidone 20-60mg N=161	Lurasidone 80-120mg N=162	Placebo N=162
Baseline (SD)	16.3 (6.71)	15.6 (5.61)	16.2 (6.38)
Week 6 (SD)	8.0 (6.55)	7.7 (6.01)	10.4 (6.49)
Mean Change from Baseline (SD)	-8.2 (5.82)	-7.3 (5.86)	-5.9 (6.87)
Treatment Difference v. placebo (95%CI)	-2.5 (-3.7, -1.2) P<0.001	-2.0 (-3.2, -0.7) P=0.002	

Adjunctive Study 235 and Study 292

In similar fashion to study 236, both studies 235 and 292 mean change from baseline HAM-A scores decreased over with all treatment groups. However adjunctive treatment with lurasidone was associated with a statistically significant decrease in HAM-A scores when compared to placebo treatment. Again, caution is required in interpretation of these findings as anxiety symptoms were generally mild for each treatment group, with changes in anxiety levels not being a primary outcome for this study.

Table 97: Study 235 Mean Change from Baseline Score on HAM-A Score at Week 6 (ITT)

Week	Lurasidone + Li/VPA N=179	Placebo + Li/VPA N=161
Baseline Score (SD)	15.0 (5.91)	15.7 (6.57)
Week 6 (SD)	6.8 (5.51)	8.9 (6.40)
Mean Change From Baseline (SD)	-8.5 (6.55)	-7.1 (7.20)
Treatment Difference (95% CI)	-1.8 (-3.0, -0.5) P=0.006	

Table 98: Study 292 Mean Change from Baseline Score on HAM-A Score at Week 6 (ITT)

Week	Lurasidone + Li/VPA N=176	Placebo + Li/VPA N=166
Baseline Score (SD)	15.8 (5.60)	15.8 (5.74)
Week 6 (SD)	8.6 (5.81)	10.6 (6.55)
Mean Change From Baseline (SD)	-6.9 (6.45)	-4.9 (6.17)
Treatment Difference (95% CI)	-1.8 (-3.0, -0.6) P=0.005	

7.5.1 Dose Dependency for Adverse Events

Adverse events results from the monotherapy study provide some data to explore dose-related adverse events. However since the study employed a fixed-flexible dosing scheme, an accurate analysis of dose-dependent adverse events is not possible at this time. However, when comparing the low dose groups (20-60mg/day) to the high-dose groups (80-120mg/day) compared to placebo, the following adverse events appear to be related to increasing doses of lurasidone:

- Nausea (Placebo: 7.7%, Low dose: 10.4%, high dose: 17.4%)
- Somnolence, to include hypersomnia, sedation, and somnolence (Placebo: 6.5%, Low dose: 7.3%, high dose: 13.8%)
- Akathisia (Placebo: 2.4, Low dose: 7.9%, high dose: 10.8%)
- Parkinsonism, to include drooling, muscle rigidity, parkinsonism, and tremor (Placebo: 2.4%, Low dose: 4.9%, high dose: 7.8%)

7.5.2 Time Dependency for Adverse Events

Time dependency studies were not performed as there were no long term controlled data that was collected during the clinical development program.

7.5.3 Drug-Demographic Interactions

Due to less than 20% of all subjects being older than age 55, an analysis of adverse events in patients above this age range could not be fully assessed.

The sponsor did conduct an analysis of drug-gender, drug-race, and drug-region interactions. Although slight differences were noted within all these analyses, the numbers of patients involved in the two studies and a lack of clear, significant rates of adverse events in any demographic analyzed precludes this reviewer from making any drug-demographic interaction recommendations. The sponsor should be encouraged to continue to analyze accumulated clinical data for any drug-demographic interactions.

Tables for the sponsor-submitted drug-demographic interactions are provided in the appendix section of this review.

7.5.4 Drug-Disease Interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.5.5 Drug-Drug Interactions

There were no explorations conducted by the sponsor to examine drug-drug interactions in this clinical development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed as part of the clinical development program for bipolar depression.

7.6.2 Human Reproduction and Pregnancy Data

Human reproductive and pregnancy data is not available for lurasidone under this clinical development program as no cases of pregnancy were reported during the clinical trials.

Lurasidone is categorized as a category B drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

Since the bipolar depression clinical development program was conducted solely in adults with bipolar depression, there is no data to assess the effects of lurasidone on pediatric patients or effects on growth parameters.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No studies have been conducted to examine the drug abuse potential of lurasidone. In addition, there is no information current available to indicate lurasidone being a drug of abuse.

With regards to overdose, there has been one patient out of 2096 patients enrolled in pre-marketing trials who ingested 560mg of lurasidone. This patient recovered without any clinical sequelae and resumed treatment with lurasidone two months later. Spontaneous post-marketing reports with lurasidone identified five (5) patients who "overdosed" on lurasidone. One patient ingested 600mg and recovered. The amount taken in three of five of these reports was not known, with the last report stating that the patient took "200 tablets of various pills". Two of the five reports were associated with a fatal outcome.

The sponsor had previously conducted withdrawal and rebound studies in rats and monkeys prior to registration trials for schizophrenia. Results from these studies failed to provide any evidence that abrupt withdrawal of lurasidone treatment is associated with withdrawal phenomena or rebound. The reader is referred to read pharmacology and toxicology reviews for further details. In addition, there is no evidence to date from current clinical use and post-marketing safety reports that cessation of lurasidone treatment is associated with withdrawal phenomena.

7.7 Additional Submissions/Safety Issues

There are no additional safety issues of note.

8 POSTMARKET EXPERIENCE

Lurasidone is currently approved for the treatment of schizophrenia in the United States. As of the cutoff date of 12 April 2012, there have been over 600 post-marketing reports that indicate lurasidone as a suspect drug for the reported adverse event. Out of the 600 reports, 87 (14.5%) were serious adverse events, with 11 of these events being fatal. Of the fatal adverse events, six were unspecified deaths, 1 fatal suicide, one fatal myocardial infarction, one fatal infection, one fatal anemia, and one patient who committed homicide who was then shot by police.

Of the non-fatal serious adverse events that had more than 2 reports each, there were 8 reports of convulsions (6 convulsions, 2 grand mal seizures), 6 reports of suicidal ideation, 5 psychotic states, 4 reports each of confusional state and auditory hallucinations, and three reports each aggression, akathisia, aggression, intentional overdose, suicide attempt, insomnia, paranoia and swollen tongue. All of these serious adverse events are associated with antipsychotic use and with patients with schizophrenia. The proposed current labeling does not include a section for post-marketing adverse events however these adverse reactions are noted in both clinical trials experience and pre-market adverse events section of the label. Therefore this reviewer recommends that these adverse events do not need to be included in the post market adverse events section.

9 APPENDICES

9.1 Literature Review/References

The sponsor conducted a review of current literature. The updated review of literature did not identify any new safety or tolerability issues with the use of lurasidone.

9.2 Labeling Recommendations

Should lurasidone obtain approval, this reviewer strongly recommends that the clinical studies section of the label contain the subgroup efficacy analyses from the United States, Africa, Asia and Europe in order to fully inform the public and prescriber about the geographical variation of efficacy. Of note, the Agency has previously described geographical variation of efficacy results in the labeling for metoprolol succinate tablets, extended release. It is recommended that a relative risk with 95% confidence interval be used or use of a graph of week by week of efficacy results be adopted.

It is also recommended that the following sentence be added to the indications section of the label:

" The efficacy of lurasidone for the treatment of bipolar disorder has not been established."

9.3 Advisory Committee Meeting

No FDA advisory committee meeting was held for these two supplemental NDA applications.

9.4 Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 200-603

Submission Date(s): 31 Aug 2013

Applicant: Sunovion Pharmaceuticals

Product: Lurasidone HCl

Reviewer: Mark Ritter, M.D. RPh.

Date of Review: 31 May 2013

Covered Clinical Study (Name and/or Number): Studies D1050235 (S-011); D1050236 (S-010)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 4		
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): 4		
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: _____		

Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	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 ☐	No ☐ (Request explanation from applicant)

In study 236, three investigators disclosed financial obligations related to Sunovion-related activities prior to enrolling patients into the monotherapy bipolar depression trial. A summary of their disclosures is provided below.

From this reviewer's viewpoint, these financial disclosures did not impact the study results as the study was double-blinded with investigator's or staff not having any knowledge of which treatment group patients were assigned to.

9.5 Additional Tables

Drug-Gender Adverse Reactions
Monotherapy Study 235

Table 148 Number (%) of Subjects with Treatment-Emergent Adverse Events Reported in ≥ 2% with Lurasidone (Combined) and More Frequently than in the Placebo Group, by Gender – D1050236 Safety Population

System Organ Class / Preferred Term	D1050236 Monotherapy: Treatment Groups			
	Lurasidone 20-120 mg + Li/VPA		Placebo + Li/VPA	
	Males (N=137) n (%)	Females (N=194) n (%)	Males (N=78) n (%)	Females (N=90) n (%)
No. of Subjects with ≥ 1 TEAE	**85 (62.0%)**	**124 (63.9%)**	**39 (50.0%)**	**57 (63.3%)**
Gastrointestinal disorders	**24 (17.5%)**	**67 (34.5%)**	**11 (14.1%)**	**22 (24.4%)**
Diarrhoea	5 (3.6%)	8 (4.1%)	2 (2.6%)	1 (1.1%)
Dry mouth	4 (2.9%)	12 (6.2%)	2 (2.6%)	5 (5.6%)
Nausea	8 (5.8%)	38 (19.6%)	5 (6.4%)	8 (8.9%)
Vomiting	1 (0.7%)	13 (6.7%)	0	3 (3.3%)
Infections and infestations	**17 (12.4%)**	**30 (15.5%)**	**6 (7.7%)**	**13 (14.4%)**
Nasopharyngitis	6 (4.4%)	7 (3.6%)	1 (1.3%)	1 (1.1%)
Nervous system disorders	**40 (29.2%)**	**68 (35.1%)**	**15 (19.2%)**	**31 (34.4%)**
Akathisia	11 (8.0%)	20 (10.3%)	2 (2.6%)	2 (2.2%)
Parkinsonism	4 (2.9%)	5 (2.6%)	0	2 (2.2%)
Sedation	2 (1.5%)	15 (7.7%)	2 (2.6%)	1 (1.1%)
Somnolence	7 (5.1%)	11 (5.7%)	0	7 (7.8%)
Tremor	4 (2.9%)	8 (4.1%)	1 (1.3%)	1 (1.1%)
Psychiatric disorders	**25 (18.2%)**	**31 (16.0%)**	**12 (15.4%)**	**14 (15.6%)**
Anxiety	4 (2.9%)	10 (5.2%)	0	2 (2.2%)

Abbreviations: TEAE = treatment-emergent adverse event

Adjunctive Study 235

System Organ Class / Preferred Term	D1050235 Adjunctive Therapy: Treatment Groups			
	Lurasidone 20-120 mg + Li/VPA		Placebo + Li/VPA	
	Males (N=94) n (%)	Females (N=89) n (%)	Males (N=87) n (%)	Females (N=76) n (%)
No. of Subjects with ≥ 1 TEAE	**54 (57.4%)**	**63 (70.8%)**	**51 (58.6%)**	**43 (56.6%)**
Eye disorders	**6 (6.4%)**	**4 (4.5%)**	**1 (1.1%)**	**1 (1.3%)**
Vision blurred	3 (3.2%)	3 (3.4%)	0	0
Gastrointestinal disorders	**20 (21.3%)**	**33 (37.1%)**	**14 (16.1%)**	**21 (27.6%)**
Constipation	1 (1.1%)	3 (3.4%)	2 (2.3%)	1 (1.3%)
Nausea	11 (11.7%)	21 (23.6%)	4 (4.6%)	14 (18.4%)
Vomiting	3 (3.2%)	6 (6.7%)	1 (1.1%)	3 (3.9%)

System Organ Class / Preferred Term	D1050235 Adjunctive Therapy: Treatment Groups			
	Lurasidone 20-120 mg + Li/VPA		Placebo + Li/VPA	
General disorders and administration site conditions	**7 (7.4%)**	**5 (5.6%)**	**8 (9.2%)**	**8 (10.5%)**
Fatigue	3 (3.2%)	2 (2.2%)	2 (2.3%)	1 (1.3%)
Infections and infestations	**9 (9.6%)**	**12 (13.5%)**	**9 (10.3%)**	**11 (14.5%)**
Nasopharyngitis	2 (2.1%)	4 (4.5%)	2 (2.3%)	1 (1.3%)
Metabolism and nutrition disorders	**5 (5.3%)**	**5 (5.6%)**	**7 (8.0%)**	**3 (3.9%)**
Increased appetite	3 (3.2%)	3 (3.4%)	2 (2.3%)	1 (1.3%)
Musculoskeletal and connective tissue disorders	**7 (7.4%)**	**10 (11.2%)**	**7 (8.0%)**	**9 (11.8%)**
Muscle rigidity	2 (2.1%)	2 (2.2%)	0	0
Musculoskeletal stiffness	0	5 (5.6%)	1 (1.1%)	1 (1.3%)
Nervous system disorders	**32 (34.0%)**	**33 (37.1%)**	**23 (26.4%)**	**28 (36.8%)**
Akathisia	7 (7.4%)	7 (7.9%)	4 (4.6%)	3 (3.9%)
Parkinsonism	5 (5.3%)	3 (3.4%)	5 (5.7%)	2 (2.6%)
Sedation	2 (2.1%)	2 (2.2%)	1 (1.1%)	1 (1.3%)
Somnolence	10 (10.6%)	6 (6.7%)	0	7 (9.2%)
Tremor	8 (8.5%)	7 (7.9%)	4 (4.6%)	3 (3.9%)
Psychiatric disorders	**19 (20.2%)**	**18 (20.2%)**	**13 (14.9%)**	**11 (14.5%)**
Agitation	1 (1.1%)	3 (3.4%)	1 (1.1%)	1 (1.3%)
Insomnia	7 (7.4%)	6 (6.7%)	4 (4.6%)	5 (6.6%)
Restlessness	5 (5.3%)	2 (2.2%)	1 (1.1%)	1 (1.3%)
Renal and urinary disorders	**0**	**6 (6.7%)**	**0**	**0**
Pollakiuria	0	4 (4.5%)	0	0

Abbreviations: TEAE = treatment-emergent adverse event

Drug-Race Interactions

Monotherapy study 236

System Organ Class / Preferred Term	D1050236 Monotherapy: Treatment Groups					
	Combined Lurasidone			Placebo		
	White (N=218) n (%)	Black or African American (N=46) n (%)	Asian (N=48) n (%)	White (N=110) n (%)	Black or African American (N=23) n (%)	Asian (N=29) n (%)
No. of Subjects with ≥ 1 TEAE	**142 (65.1%)**	**26 (56.5%)**	**26 (54.2%)**	**66 (60.0%)**	**12 (52.2%)**	**15 (51.7%)**
Gastrointestinal disorders	**64 (29.4%)**	**15 (32.6%)**	**7 (14.6%)**	**24 (21.8%)**	**5 (21.7%)**	**3 (10.3%)**
Diarrhoea	10 (4.6%)	1 (2.2%)	0	3 (2.7%)	0	0
Dry mouth	11 (5.0%)	2 (4.3%)	2 (4.2%)	4 (3.6%)	1 (4.3%)	1 (3.4%)
Nausea	39 (17.9%)	5 (10.9%)	0	10 (9.1%)	2 (8.7%)	1 (3.4%)
Vomiting	8 (3.7%)	3 (6.5%)	2 (4.2%)	1 (0.9%)	1 (4.3%)	1 (3.4%)
Infections and infestations	**28 (12.8%)**	**8 (17.4%)**	**5 (10.4%)**	**15 (13.6%)**	**3 (10.3%)**	**1 (3.4%)**
Nasopharyngitis	10 (4.6%)	2 (4.3%)	1 (2.1%)	2 (1.8%)	0	0
Nervous system disorders	**79 (36.2%)**	**12 (26.1%)**	**10 (20.8%)**	**32 (29.1%)**	**5 (21.7%)**	**7 (24.1%)**
Akathisia	25 (11.5%)	3 (6.5%)	1 (2.1%)	3 (2.7%)	1 (4.3%)	0
Parkinsonism	7 (3.2%)	0	1 (2.1%)	1 (0.9%)	0	
Sedation	13 (6.0%)	3 (6.5%)	0	3 (2.7%)	0	0
Somnolence	15 (6.9%)	0	1 (2.1%)	6 (5.5%)	1 (4.3%)	0
Tremor	5 (2.3%)	1 (2.2%)	4 (8.3%)	1 (0.9%)	0	1 (3.4%)
Psychiatric disorders	**42 (19.3%)**	**4 (8.7%)**	**8 (16.7%)**	**18 (16.4%)**	**1 (4.3%)**	**6 (20.7%)**
Anxiety	10 (4.6%)	1 (2.2%)	2 (4.2%)	2 (1.8%)	0	0

Abbreviations: TEAE = treatment-emergent adverse event

Adjunctive Study 235

System Organ Class / Preferred Term	D1050235 Adjunctive Therapy: Treatment Groups			
	Lurasidone 20-120 mg + Li/VPA		Placebo + Li/VPA	
	White (N=109) n (%)	Asian (N=45) n (%)	White (N=103) n (%)	Asian (N=37) n (%)
No. of Subjects with ≥ 1 TEAE	**70 (64.2%)**	**29 (64.4%)**	**56 (54.4%)**	**21 (56.8%)**
Eye disorders	**5 (4.6%)**	**4 (8.9%)**	**1 (1.0%)**	**0**
Vision blurred	4 (3.7%)	2 (4.4%)	0	0
Gastrointestinal disorders	**37 (33.9%)**	**6 (13.3%)**	**23 (22.3%)**	**7 (18.9%)**
Constipation	4 (3.7%)	0	3 (2.9%)	0
Nausea	25 (22.9%)	2 (4.4%)	14 (13.6%)	2 (5.4%)
Vomiting	7 (6.4%)	1 (2.2%)	3 (2.9%)	1 (2.7%)
General disorders and administration site conditions	**8 (7.3%)**	**2 (4.4%)**	**11 (10.7%)**	**3 (8.1%)**
Fatigue	4 (3.7%)	0	2 (1.9%)	1 (2.7%)
Infections and infestations	**15 (13.8%)**	**2 (4.4%)**	**12 (11.7%)**	**4 (10.8%)**
Nasopharyngitis	4 (3.7%)	1 (2.2%)	2 (1.9%)	1 (2.7%)
Metabolism and nutrition disorders	**6 (5.5%)**	**1 (2.2%)**	**3 (2.9%)**	**4 (10.8%)**
Increased appetite	3 (2.8%)	0	1 (1.0%)	1 (2.7%)
Musculoskeletal and connective tissue disorders	**13 (11.9%)**	**4 (8.9%)**	**11 (10.7%)**	**1 (2.7%)**
Muscle rigidity	1 (0.9%)	3 (6.7%)	0	0
Musculoskeletal stiffness	5 (4.6%)	0	2 (1.9%)	0
Nervous system disorders	**39 (35.8%)**	**15 (33.3%)**	**33 (32.0%)**	**9 (24.3%)**
Akathisia	10 (9.2%)	3 (6.7%)	5 (4.9%)	0
Parkinsonism	4 (3.7%)	3 (6.7%)	3 (2.9%)	3 (8.1%)
Sedation	3 (2.8%)	0	1 (1.0%)	0
Somnolence	8 (7.3%)	3 (6.7%)	7 (6.8%)	0
Tremor	8 (7.3%)	6 (13.3%)	5 (4.9%)	2 (5.4%)
System Organ Class / Preferred Term	**D1050235 Adjunctive Therapy: Treatment Groups**			
	Lurasidone 20-120 mg + Li/VPA		**Placebo + Li/VPA**	
Psychiatric disorders	**22 (20.2%)**	**12 (26.7%)**	**13 (12.6%)**	**6 (16.2%)**
Agitation	2 (1.8%)	2 (4.4%)	2 (1.9%)	0
Insomnia	7 (6.4%)	6 (13.3%)	5 (4.9%)	3 (8.1%)
Restlessness	3 (2.8%)	2 (4.4%)	2 (1.9%)	0
Renal and urinary disorders	**4 (3.7%)**	**0**	**0**	**0**
Pollakiuria	2 (1.8%)	0	0	0

Abbreviations: TEAE = treatment-emergent adverse event

Drug-Geographic Region Interactions

Monotherapy study 236

System Organ Class / Preferred Term	D1050236 Monotherapy: Treatment Groups							
	Combined Lurasidone				Placebo			
	Asia (N=48) n (%)	Africa (N=38) n (%)	Europe (N=106) n (%)	North America (N=139) n (%)	Asia (N=28) n (%)	Africa (N=18) n (%)	Europe (N=59) n (%)	North America (N=63) n (%)
No. of Subjects with ≥ 1 TEAE	**26 (54.2%)**	**27 (71.1%)**	**48 (45.3%)**	**108 (77.7%)**	**14 (50.0%)**	**11 (61.1%)**	**27 (45.8%)**	**44 (69.8%)**
Gastrointestinal disorders	**7 (14.6%)**	**10 (26.3%)**	**17 (16.0%)**	**57 (41.0%)**	**3 (10.7%)**	**2 (11.1%)**	**8 (13.6%)**	**20 (31.7%)**
Diarrhoea	0	1 (2.6%)	0	12 (8.6%)	0	0	1 (1.7%)	2 (3.2%)
Dry mouth	2 (4.2%)	1 (2.6%)	1 (0.9%)	12 (8.6%)	1 (3.6%)	0	1 (1.7%)	5 (7.9%)
Nausea	0	6 (15.8%)	15 (14.2%)	25 (18.0%)	1 (3.6%)	2 (11.1%)	4 (6.8%)	6 (9.5%)
Vomiting	2 (4.2%)	0	2 (1.9%)	10 (7.2%)	1 (3.6%)	0	0	2 (3.2%)
Infections and infestations	**5 (10.4%)**	**5 (13.2%)**	**10 (9.4%)**	**27 (19.4%)**	**1 (3.6%)**	**0**	**7 (11.9%)**	**11 (17.5%)**
Nasopharyngitis	1 (2.1%)	0	5 (4.7%)	7 (5.0%)	0	0	2 (3.4%)	0
Nervous system disorders	**10 (20.8%)**	**15 (39.5%)**	**18 (17.0%)**	**65 (46.8%)**	**7 (25.0%)**	**4 (22.2%)**	**11 (18.6%)**	**24 (38.1%)**
Akathisia	1 (2.1%)	2 (5.3%)	2 (1.9%)	26 (18.7%)	0	0	1 (1.7%)	3 (4.8%)
Parkinsonism	1 (2.1%)	0	6 (5.7%)	2 (1.4%)	1 (3.6%)	0	1 (1.7%)	0
Sedation	0	8 (21.1%)	0	9 (6.5%)	0	2 (11.1%)	0	1 (1.6%)
Somnolence	1 (2.1%)	2 (5.3%)	5 (4.7%)	10 (7.2%)	0	0	0	7 (11.1%)
Tremor	4 (8.3%)	1 (2.6%)	0	7 (5.0%)	1 (3.6%)	0	0	1 (1.6%)
Psychiatric disorders	**18 (16.7%)**	**9 (23.7%)**	**7 (6.6%)**	**32 (23.0%)**	**6 (21.4%)**	**4 (22.2%)**	**4 (6.8%)**	**12 (19.0%)**
Anxiety	2 (4.2%)	3 (7.9%)	1 (0.9%)	8 (5.8%)	0	2 (11.1%)	0	0

Abbreviations: TEAE = treatment-emergent adverse event

Adjunctive Study 235

System Organ Class / Preferred Term	D1050235 Adjunctive Therapy: Treatment Groups					
	Lurasidone + Li/VPA			Placebo + Li/VPA		
	Asia (N=45) n (%)	Europe (N=68) n (%)	North America (N=60) n (%)	Asia (N=37) n (%)	Europe (N=64) n (%)	North America (N=54) n (%)
No. of Subjects with ≥1 TEAE	**29 (64.4%)**	**35 (51.5%)**	**47 (78.3%)**	**21 (56.8%)**	**23 (35.9%)**	**45 (83.3%)**
Eye disorders	**4 (8.9%)**	**4 (5.9%)**	**2 (3.3%)**	**0**	**0**	**2 (3.7%)**
Vision blurred	2 (4.4%)	4 (5.9%)	0	0	0	0
Gastrointestinal disorders	**6 (13.3%)**	**18 (26.5%)**	**26 (43.3%)**	**7 (18.9%)**	**10 (15.6%)**	**17 (31.5%)**
Constipation	0	2 (2.9%)	1 (1.7%)	0	0	3 (5.6%)
Nausea	2 (4.4%)	15 (22.1%)	14 (23.3%)	2 (5.4%)	7 (10.9%)	8 (14.8%)
Vomiting	1 (2.2%)	4 (5.9%)	3 (5.0%)	1 (2.7%)	1 (1.6%)	2 (3.7%)
General disorders and administration site conditions	**2 (4.4%)**	**2 (2.9%)**	**7 (11.7%)**	**3 (8.1%)**	**4 (6.3%)**	**9 (16.7%)**
Fatigue	0	1 (1.5%)	3 (5.0%)	1 (2.7%)	0	2 (3.7%)
Infections and infestations	**2 (4.4%)**	**4 (5.9%)**	**14 (23.3%)**	**4 (10.8%)**	**3 (4.7%)**	**13 (24.1%)**
Nasopharyngitis	1 (2.2%)	3 (4.4%)	2 (3.3%)	1 (2.7%)	1 (1.6%)	1 (1.9%)
Metabolism and nutrition disorders	**1 (2.2%)**	**2 (2.9%)**	**7 (11.7%)**	**4 (10.8%)**	**1 (1.6%)**	**5 (9.3%)**
Increased appetite	0	1 (1.5%)	5 (8.3%)	1 (2.7%)	1 (1.6%)	1 (1.9%)
Musculoskeletal and connective tissue disorders	**4 (8.9%)**	**3 (4.4%)**	**10 (16.7%)**	**1 (2.7%)**	**4 (6.3%)**	**11 (20.4%)**
Muscle rigidity	3 (6.7%)	0	1 (1.7%)	0	0	0
Musculoskeletal stiffness	0	0	5 (8.3%)	0	2 (3.1%)	0

System Organ Class / Preferred Term	D1050235 Adjunctive Therapy: Treatment Groups					
	Lurasidone + Li/VPA			Placebo + Li/VPA		
	Asia (N=45) n (%)	Europe (N=68) n (%)	North America (N=60) n (%)	Asia (N=37) n (%)	Europe (N=64) n (%)	North America (N=54) n (%)
Nervous system disorders	**15 (33.3%)**	**16 (23.5%)**	**32 (53.3%)**	**9 (24.3%)**	**14 (21.9%)**	**26 (48.1%)**
Akathisia	3 (6.7%)	2 (2.9%)	9 (15.0%)	0	1 (1.6%)	6 (11.1%)
Parkinsonism	3 (6.7%)	4 (5.9%)	1 (1.7%)	3 (8.1%)	1 (1.6%)	3 (5.6%)
Sedation	0	0	4 (6.7%)	0	0	2 (3.7%)
Somnolence	3 (6.7%)	5 (7.4%)	8 (13.3%)	0	2 (3.1%)	5 (9.3%)
Tremor	6 (13.3%)	1 (1.5%)	8 (13.3%)	2 (5.4%)	0	5 (9.3%)
Psychiatric disorders	**12 (26.7%)**	**7 (10.3%)**	**17 (28.3%)**	**6 (16.2%)**	**5 (7.8%)**	**12 (22.2%)**
Agitation	2 (4.4%)	0	2 (3.3%)	0	2 (3.1%)	0
Insomnia	6 (13.3%)	5 (7.4%)	2 (3.3%)	3 (8.1%)	2 (3.1%)	4 (7.4%)
Restlessness	2 (4.4%)	1 (1.5%)	4 (6.7%)	0	1 (1.6%)	1 (1.9%)
Renal and urinary disorders	**0**	**1 (1.5%)**	**5 (8.3%)**	**0**	**0**	**0**
Pollakiuria	0	0	4 (6.7%)	0	0	0

Abbreviations: TEAE = treatment-emergent adverse event

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/s/

MARK A RITTER
05/30/2013

ROBERT L LEVIN
05/30/2013
Refer to Cross-Discipline Team Leader review memo to follow.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

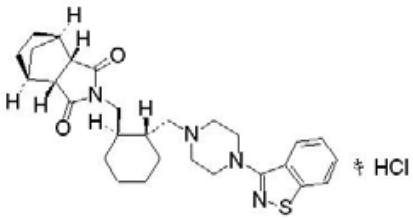
200-603/S010

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW OF SUPPLEMENT	**ORGANIZATION:**	**HFD-130**
	NDA NUMBER:	**200603**
	SUPPLEMENT NUMBER:	**S-010 and S-011**
	LETTER DATE	31-AUG-12
	STAMP DATE	31-AUG-12
	RECEIVED BY CHEMIST:	05-SEP-12

APPLICANT NAME AND ADDRESS: Sunovion Pharmaceuticals Inc.
One Bridge Plaza
Suite 510
Fort Lee, NJ 070

NAME OF DRUG: Latuda®
NONPROPRIETARY NAME: lurasidone hydrochloride
CHEMICAL NAME/STRUCTURE: (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R,*2*R*)- 2-[4- (1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7- methano-2*H*isoindole-1,3-dione hydrochloride



DOSAGE FORM(S): Tablet
STRENGTHS: 20 mg, 40 mg, and 80 mg
PHARMACOLOGICAL CATEGORY: Bipolar Disorder
HOW DISPENSED: **XX (Rx)** (OTC)
RECORDS/REPORTS CURRENT: **XX (YES)** (NO)
RELATED IND/NDA/DMF(S): N/A

EFFICACY SUPPLEMENT PROVIDES FOR: data to seek approval of an efficacy associated with short-term use of lurasidone hydrochloride in the treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy (S-010) and as adjunctive therapy to lithium or valproate (S-011).

COMMENTS: The applicant refers to NDA 200603 for Latuda® tablets, approved on 28-OCT-2010, which provides for the use of lurasidone in the treatment of patients with schizophrenia. In sNDA 200603/S-010 (Phase III multiple dose of 20-60 mg/day parallel study #DI050236), Sunovion requested approval for an efficacy associated with short-term (at least 6 weeks) use of lurasidone hydrochloride vs. placebo in the treatment of bipolar I disorder as monotherapy. In sNDA 200603/S-011 (Phase III multiple dose of 20-120 mg/day parellel study #DI050235), the applicant requested approval for an efficacy associated with short-term (at least 6 weeks) use of lurasidone hydrochloride vs. placebo in the treatment of bipolar I disorder as an adjunctive therapy to lithium or valproate.

Sunovion Pharmaceuticals Inc. claims a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR §25.31(b) as the expected introduction concentration (EIC) of lurasidone in the aquatic environment is below 1 parts per billion (0.093 ppb). To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

CONCLUSIONS AND RECOMMENDATIONS: Recommend **APPROVAL** from CMC perspective.

REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
Chhagan G. Tele, Ph.D.		Sept. 09, 2012

cc: Orig. NDA 200603/S-010 and S-011
HFD-130/PM/ASohn

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/s/

CHHAGAN G TELE
10/02/2012

RAMESH K SOOD
10/02/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	**200603** S-010 and S-011
Supporting document/s:	NA
Applicant's letter date:	31 August 2012
CDER stamp date:	31 August 2012
Product:	Latuda (lurasidone hydrochloride) tablets
Indication:	Bipolar depression as monotherapy (S-010) and as adjunctive therapy to lithium or valproate (S-011).
Applicant:	Sunovion Pharmaceuticals Inc. One Bridge Plaza, Suite 510 Fort Lee, NJ 070
Review Division:	Psychiatric Drug Products
Reviewer:	Sonia Tabacova, Ph.D.
Supervisor/Team Leader:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchell Mathis, MD
Project Manager:	Ann Sohn, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 200603 are owned by Sunovion Pharmaceuticals Inc. or are data for which Sunovion Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 200603 that Sunovion Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 200603.

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1 Executive Summary

1.1 Introduction

Lurasidone is an atypical antipsychotic with high affinities for dopamine D_2 and serotonin 5-HT_7, 5-HT_{2A}, 5-HT_{1A} receptors. Lurasidone acts predominantly as a potent antagonist of serotonin 5-HT_7 and dopamine D_{2L} receptors, a partial agonist of serotonin 5-HT_{1A} receptors, and to a lesser extent, an antagonist at noradrenaline α_1, α_2, α_{2A}, and α_{2C} receptors. Lurasidone hydrochloride (tablets for oral administration) was approved for the treatment of schizophrenia (NDA 200603, October 28, 2010) and is marketed in the United States under the trade name Latuda®. The current Supplemental New Drug Application to NDA 200603 aims to expand lurasidone indication to include treatment of patients with depressive episodes associated with bipolar disorder, and contains two supplemental New Drug Applications (sNDAs) for the use of lurasidone hydrochloride in the treatment of bipolar depression, as monotherapy (S-010) and as adjunct therapy to lithium or valproate (S-011).

1.2 Brief Discussion of Nonclinical Findings

Both sNDAs are supported by a complete battery of nonclinical studies previously submitted and cross-referenced from the original NDA 200603 (S-0000) and supplements (b) (4). These studies include pharmacology, ADME, acute and repeat-dose toxicity, reproductive and developmental toxicity, in vitro and in vivo genotoxicity and carcinogenicity studies. No new non-clinical studies were performed to support the current sNDAs, as previously agreed by the Division (Pre-IND 103427 meeting of 9/29/2008 and pre-NDA meeting of June 4, 2012).

Subsequent to the original NDA 200603, the sponsor completed 12 pharmacology studies that were "intended to replicate previous in vitro and in vivo pharmacological findings in support of a marketing application in Japan". These studies reconfirmed the sponsor's previous findings on the receptor-mediated activities of lurasidone and its metabolites and the pharmacodynamics of lurasidone in animal models, and did not alter the already known pharmacological characteristics of the compound.

In addition to these studies, the sponsor performed literature search to identify any relevant new information published between the original NDA and the current sNDA submission. The search did not provide any new information significant for the safety evaluation of lurasidone.

Overall, there are no new nonclinical data or concerns that affect *safety* evaluation of lurasidone for the treatment of depressive episodes associated with bipolar I disorder.

Since the dose range for lurasidone in the treatment of bipolar depression (20 to 120 mg/day) represents a lower dosing range than that previously shown to be safe and effective for schizophrenia (40 to 160 mg/day), no new safety issues are anticipated.

1.3 Recommendations

1.3.1 Approvability: Approvable

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: There are no new nonclinical data or concerns that require labeling changes.

2 Drug Information

2.1 Drug

CAS Registry Number: 139563-29-4 (hydrochloride)

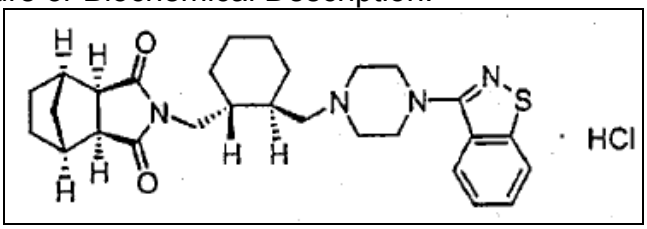
Generic Name: Lurasidone hydrochloride

Code Name: SM-13496

Chemical Name: *(3aR,4S,7R,7aS)-2-{(1R,2R)- 2-[4- (1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7- methano-2Hisoindole-1,3-dione hydro-chloride*

Molecular Formula/Molecular Weight: 529.15

Structure or Biochemical Description:



Pharmacologic Class: Antipsychotic (D2, 5HT1A, 5HT2A, 5HT7 receptor ligand)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 61 292; IND 103427; NDA 200603 Latuda® tablets for treatment of schizophrenia (approved on 10/28/2010)

2.3 Drug Formulation:

Tablet**:** 20 mg, 40 mg, and 80 mg

2.4 Comments on Novel Excipients

There are no changes to the chemistry, manufacturing, or control data related to lurasidone

2.5 Comments on Impurities/Degradants of Concern

A starting material and potential impurity of lurasidone drug substance, code-named (b) (4), has a structural alert. This compound was tested in the reverse bacterial mutation (Ames) test and results were negative. As discussed at the pre-NDA meeting (May 22, 2009), if the specification for this compound is below 0.15 %, no further testing is required in view of the negative Ames test. Since the sponsor has achieved control to the necessary level (below 0.15%) of this compound in the drug substance, no further nonclinical testing is required and none was performed.

2.6 Proposed Clinical Population and Dosing Regimen

Patients with depressive episodes associated with bipolar disorder as monotherapy or as an adjunct to lithium or valproate. Dose range: 20 to 120 mg/day [lower dosing range than that previously approved for schizophrenia (40 to 160 mg/day)].

2.7 Regulatory Background

Lurasidone hydrochloride (tablets for oral administration) was approved for the treatment of schizophrenia (NDA 200603, October 28, 2010) and is marketed by Sunovion in the United States under the trade name Latuda®.

3 Studies Submitted

The nonclinical studies supporting the current application are cross-referenced from the original NDA 200603 and were previously reviewed (see Pharmacology/Toxicology Review of NDA 200603 by S. Tabacova of 10/19/2010). Submitted with the present application are 12 pharmacology studies completed subsequently to the original NDA 200603 and listed in the following sponsor's table. These studies were "intended to replicate previous in vitro and in vivo pharmacological findings in support of a marketing application in Japan". These studies reconfirmed the sponsor's previous findings on the receptor-mediated activities of lurasidone and its metabolites and the effects of lurasidone on schizophrenia in animal models, and did not alter the already known pharmacological characteristics of the compound.

Nonclinical Pharmacology Studies Completed Subsequent to the Original NDA 200-603

Study Number	Study Title	NDA No./ Sequence No.	Date of Submission
AL-4654-G	Binding Activity and Affinity of SM- 13496 and Control Drugs for Human α_{1A}-Adrenergic, Histamine H_1 and Muscarinic M_1 Receptors	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-004	Effects of SM-13496 and reference drugs on methamphetamine-induced hyperactivity in rats	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-005	Effects of SM-13496 and reference drugs on apomorphine-induced climbing behavior in mice	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-006	Effects of SM-13496 and its metabolites on methamphetamine-induced hyperactivity in rats	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-007	Effects of SM-13496 on 5-MT-induced head twitch in mice	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-008	Effects of SM-13496 and reference drugs on catalepsy in rats	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-009	Effects of SM-13496 and its metabolites on tryptamine-induced forepaw clonic seizure in rats	200603/ (b) (4)	28 Jun 2011
DP1-SM-13496-010	Effects of SM-13496 and reference drugs on tryptamine-induced forepaw clonic seizure in rats	200603/ (b) (4)	28 Jun 2011
R-GE-SM-13496-001	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α_{1A} adrenergic receptor	200603/ (b) (4)	20 Dec 2011
R-GE-SM-13496-002	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α_{2C} adrenergic receptor	200603/ (b) (4)	20 Dec 2011
R-GE-SM-13496-003	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α_{1A} adrenergic receptor	200603/ (b) (4)	20 Dec 2011
R-GE-SM-13496-004	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α_{2C} adrenergic receptor	200603/ (b) (4)	20 Dec 2011

No other non-clinical studies were conducted to support the current sNDAs, as previously agreed by the Division (Pre-IND 103427 meeting of 9/29/2008 and pre-NDA meeting of June 4, 2012).

3.1 Studies Reviewed

Out of the submitted 12 studies, the following 4 studies were reviewed:

Study No.	Study Title
R-GE-SM-13496-001	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α1A adrenergic receptor
R-GE-SM-13496-002	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α2C adrenergic receptor
R-GE-SM-13496-003	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α1A adrenergic receptor
R-GE-SM-13496-004	Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α2C adrenergic receptor

The studies listed above assessed the in vitro effect of lurasidone and its pharmacologically active metabolites (ID-14283 and ID-14326) on human alpha-adrenergic receptors. These metabolites possess similar affinity as lurasidone for dopamine and serotonin receptors.

3.2 Studies Not Reviewed

Out of the submitted 12 studies, the following 8 studies are not reviewed as they were previously reviewed (S. Tabacova, NDA 200603 S-005, Pharmacology/Toxicology Review of 03/28/2012).

- Binding Activity and Affinity of SM-13496 and Control Drugs for Human alpha1A-Adrenergic, Histamine H1 and Muscarinic M1 Receptors (Study No: AL-4654-G)
- Effects of SM-13496 and Reference Drugs on Methamphetamine-Induced Hyperactivity in Rats (Study No: DP1-SM-13496-004)
- Effects of SM-13496 and Reference Drugs on Apomorphine-Induced Climbing Behavior in Mice (Study No: DP1-SM-13496-005)
- Effects of SM-13496 and Its Metabolites on Methamphetamine-Induced Hyperactivity in Rats (Study No: DP1-SM-13496-006)
- Effects of SM-13496 on 5-MT-Induced Head Twitch in Mice (Study No DP1-SM-13496-007)
- Effects on SM-13496 and Reference Drugs on Catalepsy in Rats (Study No DP1- SM-13496-008)
- Effects of SM-13496 and Its Metabolites on Tryptamine-Induced Forepaw Clonic Seizure in Rats (Study No. DP1-SM-13496-009)
- Effects of SM-13496 and Reference Drugs on Tryptamine-Induced Forepaw Clonic Seizure in Rats (Study No. DP1-SM-13496-010).

These studies reconfirmed the sponsor's previous findings on the receptor-mediated activities of lurasidone and its metabolites and the effects of lurasidone on schizophrenia in animal

models, and did not alter the already known pharmacological characteristics of the compound.

3.3 Previous Reviews Referenced

- NDA 200603, S-000, Letter Date 12/30/2009: S. Tabacova, Pharmacology/Toxicology Review dated 10/19/2010.
- NDA 200603, S-005, Letter Date 6/28/2011: S. Tabacova, Pharmacology/Toxicology Review dated 03/28/2012.

4 Pharmacology

4.1 Primary Pharmacology

Lurasidone acts predominantly as a potent antagonist of serotonin 5-HT_7, dopamine D_{2L} receptors, and as a partial agonist of serotonin 5-HT_{1A} receptors. The dopamine and serotonin receptor-mediated effects have been confirmed in vivo in a battery of previously reviewed rodent pharmacology studies.

4.2 Secondary Pharmacology

In Vitro Adrenergic (α)-Receptor Activity
The studies reviewed below assessed the in vitro effect of lurasidone and its pharmacologically active metabolites (ID-14283 and ID-14326 that possess similar affinity as lurasidone for dopamine and serotonin receptors) on human alpha-adrenergic receptors. These studies show that lurasidone and its active metabolites are antagonists of hα_{1A} and hα_{2C} adrenergic receptors. This antagonistic activity is weaker than that of risperidone. The active metabolites ID-14283 and ID-14326 possess similar affinity as lurasidone for human α-adrenergic receptors.

Study Title: **Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α1A adrenergic receptor**

Study Number: R-GE-SM-13496-001

Testing Facility: Genomic Science Laboratories, Drug Research Division,
Dainippon Sumitomo Pharma Co, Ltd. Osaka, Japan
Date of study initiation: Aug 9, 2010
Date of study completion: Aug 15, 2010

Key study findings: Evaluation of functional activity of Lurasidone (SM-13496), its pharmacologically active hydroxylated metabolites (ID-14283·HCl and ID-14326·HCl), and risperidone at the human α_{1A} (hα_{1A}) adrenergic receptor transiently expressed in Chinese hamster ovary-K1(CHO-K1) cells showed that all of the tested compounds inhibited the epinephrine-induced increase in intracellular calcium in hα1A-CHO-K1 cells with KB values of 20, 1.2, 2.4 and 0.28 nmol/L, for SM-13496, metabolites ID-14283·HCl, ID-14326·HCl, and risperidone respectively. These findings indicate that SM-13496, its hydroxylated metabolites as well as risperidone are antagonists of hα_{1A} adrenergic receptor.

Materials:

Test substances	Solvent	Reagents	Cells
Lurasidone (SM-13496), free form Molecular weight: 529.14 Lot No. : E-278 Purity: 99.0% Metabolite ID-14283•HCl Molecular weight: 545.14 Lot No. : RS070521 Purity: 100% Metabolite ID-14326•HCl Molecular weight: 545.14 Lot No. : RE7605 Purity: 99.97% Risperidone **(**SM-62621) Molecular weight: 410.48 Lot No. : RPRD-2-30-12 Purity: 98.07%	Dimethylsulfoxide (DMSO) Lot No. V6K0673	pTran3.1(+)_hADRA1A TransIT-LT1 Lot No. : KLN02203 Coelenterazine h Lot No. : 302524 (-)-Epinephrine Lot No. : 0001449137 Prazosin hydrochloride (prazosin) (positive control) Lot No. : EWJ5432	Chinese hamster ovary-K1 (CHO-K1 TRex^{TM}) expressing the mitochondrially targeted apoaequorin cells

Methods:

Luminescent calcium indicator aequorin assay to detect changes in intracellular calcium in CHO-K1 cells expressing the hα_{1A} adrenergic receptor

Deviations from the approved protocol

In this study, (-)-epinephrine (E) was mistakenly used instead of norepinephrine (NE). This mistake was discovered "after all experiments in this study were completed". As NE and E are both neurotransmitters that act on adrenergic receptors, this reviewer agrees with the sponsor that "test substances inhibition of E response could also be used to evaluate their antagonistic activity for the α_{1A} adrenergic receptor". Because the concentrations of E solutions had been mistakenly calculated based on the molecular weight of NE, the sponsor re-calculated the correct concentrations of E solutions using the molecular weight of E.

Results

(-)-Epinephrine (E) increased intracellular calcium in hα_{1A}-CHO-K1 cells in concentration-dependent fashion with an EC_{50} value of 1.0 ± 0.1 nmol/L (mean ± SE, n = 4). Lurasidone, its metabolites ID-14283·HCl and ID-14326·HCl, and risperidone inhibited the E-induced increase in intracellular calcium with K_B values of 20 ± 1, 1.2 ± 0.1, 2.4 ± 0.4, and 0.28 ± 0.07 nmol/L (n = 3 or 4), respectively. Prazosin, an α_{1A} adrenergic receptor antagonist used in this study as positive control, also inhibited E -induced increase in intracellular calcium with a K_B of 0.17 ± 0.03 nmol/L (n = 4). These findings indicate that SM-13496, ID-14283•HCl, and ID-14326•HCl as well as risperidone are antagonists of the hα_{1A} adrenergic receptor. The antagonistic activity of SM-13496, ID-14283·HCl and ID-14326·HCl at the hα_{1A} adrenergic receptor is weaker than that of risperidone (3 to 71 fold less activity).

Conclusion: Lurasidone and its pharmacologically active hydroxylated metabolites ID-14283•HCl and ID-14326•HCl are moderate to weak antagonists of the human α_{1A} adrenergic receptor, and their hα_{1A} adrenergic receptor-related effects are 3 to 71-fold weaker than that of risperidone.

Study Title: **Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α2c adrenergic receptor**
Study Number: R-GE-SM-13496-002

Testing Facility: Genomic Science Laboratories, Drug Research Division,
Dainippon Sumitomo Pharma Co, Ltd. Osaka, Japan
Date of study initiation: Aug 9, 2010
Date of study completion: Aug 15, 2010

Key study findings: Evaluation of functional activity of SM-13496, its pharmacologically active hydroxylated metabolites (ID-14283·HCl and ID-14326·HCl), and risperidone at the human α_{2C} ($h\alpha_{2C}$) adrenergic receptor transiently expressed in Chinese hamster ovary-K1 (CHO-K1) cells showed that all of the tested compounds inhibited the epinephrine-induced increase in intracellular calcium in $h\alpha_{2C}$-CHO-K1 cells with K_B values of 94, 66, 17, and 1.9 nmol/L, for SM-13496, metabolites ID-14283·HCl, ID-14326·HCl, and risperidone respectively. These findings indicate that SM-13496, ID-14283·HCl, and ID 14326·HCl are antagonists of the $h\alpha_{2C}$ adrenergic receptor and their antagonistic activity is weaker that that of risperidone.

Materials:

Test substances	**Solvent**	**Reagents**	**Cells**
Lurasidone (SM-13496), free form Molecular weight: 529.14 Lot No. : E-278 Purity: 99.0% Metabolite ID-14283•HCl Molecular weight: 545.14 Lot No. : RS070521 Purity: 100% Metabolite ID-14326•HCl Molecular weight: 545.14 Lot No. : RE7605 Purity: 99.97% Risperidone (SM-62621) Molecular weight: 410.48 Lot No. : RPRD-2-30-12 Purity: 98.07%	Dimethylsulfoxide (DMSO) Lot No. V6K0673	pTran3.1(+)_hADRA2C TransIT-LT1 Lot No. : KLN02203 Coelenterazine h Lot No. : 302524 (-)-Epinephrine Lot No. : 0001449137 Idazoxan hydrochloride (Idazoxan) (α2C adrenergic receptor antagonist used as positive control) Lot No. : 4B/46694	Gqi5-coupled CHO cells (CHO-K1/Gqi5) expressing the mitochondrially targeted apoaequorin cells

Methods: Luminescent calcium indicator aequorin assay to detect changes in intracellular calcium in CHO-K1 cells expressing the $h\alpha_{2C}$ adrenergic receptor

Deviations from the approved protocol

In this study, (-)-epinephrine (E) was mistakenly used instead of norepinephrine (NE) which was the compound to be tested. This mistake was discovered "after all experiments in this study were completed". As NE and E are both neurotransmitters that act on adrenergic receptors, this reviewer agrees with the sponsor that "test substances inhibition of E response could also be used to evaluate their antagonistic activity for the α_{1A} adrenergic receptor". Because the concentrations of E solutions had been mistakenly calculated based on the molecular weight of NE, the sponsor re-calculated the correct concentrations of E solutions using the molecular weight of E.

Results:
Epinephrine (E) increased intracellular calcium in hα2C-CHO-K1 cells in concentration-dependent fashion with an EC_{50} value of 30 ± 8 nmol/L (mean ± SE, n =5). SM-13496, ID-14283·HCl, ID-14326·HCl, and risperidone inhibited E (92.35 nmol/L)-induced increase in intracellular calcium with K_B values of 94 ± 24, 66 ± 13, 17 ± 3, and 1.9 ± 0.1 nmol/L (n = 3-5), respectively. Idazoxan, a α2C adrenergic receptor antagonist used in this study as positive control, also inhibited E (92.35 nmol/L)-induced increase in intracellular calcium with a K_B of 21 ± 4 nmol/L (n = 4). These findings indicate that SM-13496, ID-14283·HCl, and ID-14326·HCl have antagonistic activity for the hα2C adrenergic receptor. This antagonistic activity is weaker than that of risperidone.

Conclusion
Lurasidone and its pharmacologically active hydroxylated metabolites (ID-14283•HCl and ID-14326•HCl) act as antagonists for the hα2C adrenergic receptor. This antagonistic activity is weaker than that of risperidone.

Study Title: **Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α1A adrenergic receptor**
Study Number: R-GE-SM-13496-003

Testing Facility: Genomic Science Laboratories, Drug Research Division,
Dainippon Sumitomo Pharma Co, Ltd. Osaka, Japan
Date of study initiation: Oct. 9, 2010
Date of study completion: Oct. 20, 2010
Key study findings: Evaluation of the antagonistic actions of SM-13496, its pharmacologically active hydroxylated metabolites (ID-14283·HCl and ID-14326·HCl), and risperidone at the human α1A (hα1A) adrenergic receptor transiently expressed in Chinese hamster ovary-K1 (CHO-K1) cells showed that all of the tested compounds inhibited the norepinephrine-induced increase in intracellular calcium with K_B values 43, 3.6, 5.2, and 0.5 nmol/L, respectively. These findings indicate that SM-13496, ID-14283·HCl, and ID-14326·HCl as well as risperidone are antagonists of hα1A adrenergic receptor.
Materials:

Test substances	**Solvent**	**Reagents**	**Cells**
Lurasidone (SM-13496), free form Molecular weight: 529.14 Lot No. : E-278 Purity: 99.0% Metabolite ID-14283•HCl Molecular weight: 545.14 Lot No. : RS070521 Purity: 100% Metabolite ID-14326•HCl Molecular weight: 545.14 Lot No. : RE7605 Purity: 99.98% Risperidone (SM-62621) Molecular weight: 410.48 Lot No. : RPRD-2-30-12 Purity: 98.07%	Dimethylsulfoxide (DMSO) Lot No. V6K0673	pTran3.1(+)_hADRA1A TransIT-LT1 Lot No. : KLN02203 Coelenterazine h Lot No. : 302524 (-)-Norepinephrine Lot No. : 099K1022 Prazosin hydrochloride (prazosin) (positive control) Lot No. : EWJ5432	Chinese hamster ovary-K1 (CHO-K1 /TRex™) expressing the mitochondrially targeted apoaequorin cells

Methods:
Luminescent calcium indicator aequorin assay to detect changes in intracellular calcium in CHO-K1 cells expressing the hα1A adrenergic receptor
Deviations from the approved protocol: None

Results
Noradrenaline (NE) increased intracellular calcium in hα1A-CHO-K1 cells with an EC_{50} value of 6.4 ± 2.1 nmol/L (mean ± SE, n = 3). SM-13496, ID-14283·HC l, ID-14326·HCl, and risperidone inhibited NE -induced increase in intracellular calcium with K_B values of 43 ± 9, 3.6 ± 0.6, 5.2 ± 0.6, and 0.5 ± 0.08 nmol/L (n = 3), respectively. Prazosin (3 nmol/L), an α1A adrenergic receptor antagonist used in this study as positive control, also inhibited more than 50% of NE-induced increase in intracellular calcium.

Conclusion
Lurasidone and its pharmacologically active metabolites ID-14283·HCl and ID-14326·HCl act as moderate to weak antagonists for the hα1A adrenergic receptor, and their hα1A adrenergic receptor-related effects are weaker in comparison to risperidone. This study confirms the conclusion of the previously performed study entitled "Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α1A adrenergic receptor" (study# R-GE-SM-13496-001, reviewed herein) in which epinephrine was mistakenly used instead of norepinephrine to induce increase in intracellular calcium.

Study Title: **Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on norepinephrine response at the human α2c adrenergic receptor**
Study Number: R-GE-SM-13496-004
Testing Facility: Genomic Science Laboratories, Drug Research Division,
Dainippon Sumitomo Pharma Co, Ltd. Osaka, Japan
Date of study initiation: Oct. 9, 2010
Date of study completion: Oct. 15, 2010

Key study findings: Evaluation of functional activity of lurasidone (SM-13496), its pharmacologically active hydroxylated metabolites (ID-14283·HCl and ID-14326·HCl), and risperidone at the human α2C (hα2C) adrenergic receptor transiently expressed in Chinese hamster ovary-K1 (CHO-K1) cells showed that all of the tested compounds inhibited the norepinephrine-induced increase in intracellular calcium in hα2C-CHO-K1 cells with K_B values of 130, 90, 36, and 2.8 nmol/L, for SM-13496, metabolites ID-14283·HCl, ID-14326·HCl, and risperidone, respectively. These findings indicate that SM-13496, ID-14283·HCl, and ID 14326·HCl have antagonistic activity for the hα2C adrenergic receptor. This antagonistic activity is weaker than that of risperidone.

Materials:

Test substances	Solvent	Reagents	Cells
Lurasidone (SM-13496), free form Molecular weight: 529.14 Lot No. : E-278 Purity: 99.0% Metabolite ID-14283•HCl Molecular weight: 545.14 Lot No. : RS070521 Purity: 100% Metabolite ID-14326•HCl Molecular weight: 545.14 Lot No. : RE7605 Purity: 99.97% Risperidone (SM-62621) Molecular weight: 410.48 Lot No. : RPRD-2-30-12 Purity: 98.07%	Dimethylsulfoxide (DMSO) Lot No. V6K0673	pTran3.1(+)_hADRA2C TransIT-LT1 Lot No. : KLN02203 Coelenterazine h Lot No. : 302524 (-)-Norepinephrine Lot No. : 099K1022 Idazoxan hydrochloride (Idazoxan) (α2C adrenergic receptor antagonist used as positive control) Lot No. : 079K1138	Gqi5-coupled CHO cells (CHO-K1/Gqi5) expressing the mitochondrially targeted apoaequorin cells

Methods:
Luminescent calcium indicator aequorin assay to detect changes in intracellular calcium in CHO-K1 cells expressing the hα2C adrenergic receptor
Deviations from the approved protocol: There were no unforeseen circumstances that might have affected the reliability of the study and there were no deviations from the approved protocol.

Results: Norepinephrine (NE) increased intracellular calcium in hα2C-CHO-K1 cells in concentration-dependent manner with an EC_{50} value of 49 ± 15 nmol/L (mean ± SE, n = 3). SM-13496, ID-14283·HC l, ID-14326·HCl, and risperidone inhibited NE (100 nmol/L)-induced increase in intracellular calcium with K_B values of 130 ± 30, 90 ± 4, 36 ± 6, and 2.8 ± 0.4 nmol/L (n = 3), respectively.
Idazoxan, an α2C adrenergic receptor antagonist used in this study as positive control, also inhibited NE (100 nmol/L)-induced increase in intracellular calcium with a K_B of 35 ± 9 nmol/L (n = 3).

Conclusion: Lurasidone and its pharmacologically active metabolites (ID-14283 and ID-14326) have antagonistic activity for the hα2C adrenergic receptor. This antagonistic activity is weaker than that of risperidone. This study confirms the conclusion of the previously performed study entitled "Antagonistic actions of SM-13496, its hydroxylated metabolites, and risperidone on epinephrine response at the human α2c adrenergic receptor" (study# R-GE-SM-13496-002, reviewed herein) in which epinephrine was mistakenly used instead of norepinephrine to induce increase in intracellular calcium.

4.3 Safety Pharmacology

No new studies submitted

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new studies submitted

5.2 Toxicokinetics

No new studies submitted

6 General Toxicology

6.1 Single-Dose Toxicity

No new studies submitted

6.2 Repeat-Dose Toxicity

No new studies submitted

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

No new studies submitted

7.2 *In Vitro* Assays in Mammalian Cells

No new studies submitted

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

No new studies submitted

7.4 Other Genetic Toxicity Studies

Impurities

A lurasidone starting material and potential drug substance impuriry, (b) (4), has a structural alert. This issue was discussed at the pre-NDA meeting of 22 May 2009, as shown in the following excerpt from the meeting minutes:

> *"Question:* The lurasidone proposed starting material, (b) (4), has a structural alert. AMES test for this compound was negative demonstrating that it was a non-genotoxic compound. Thus, its levels would not need to be controlled below a certain threshold.
> Does FDA agree that the current in vitro and clinical data support the categorization of (b) (4) as a non-genotoxic agent?

Preliminary Comments: The current in vitro data (Ames test) are insufficient to support the qualification of (b) (4) as a non-genotoxic agent. A minimum screen for genotoxic potential should be conducted. An appropriate minimum screen includes a study to detect point mutations (i.e., Ames test) and a study to detect chromosomal aberrations in vitro (see Guidance Q3B (R2) Impurities in New Drug Products, ICH, 2006). Therefore, you need to perform a second genotoxicity test (chromosomal aberration test in vitro) to support the qualification of (b) (4).
Discussion at Meeting:
Based on further internal discussion, we wish to amend our comments made at the meeting regarding the further qualification of (b) (4). If the specification for this compound is 0.15 % (of drug substance) or greater, or if this compound cannot or will not be measured, then according to the ICH Q3A guidance, an *in vitro* chromosomal aberration assay will be required for qualification. If the specification for this compound is below 0.15 %, no further testing is required in view of the negative Ames test."(End citation)

Since the sponsor has achieved control to the necessary level (below 0.15%) of this compound in the drug substance, no further nonclinical testing is required and none was performed.

8 Carcinogenicity

No new studies submitted

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No new studies submitted

9.2 Embryonic Fetal Development

No new studies submitted

9.3 Prenatal and Postnatal Development

No new studies submitted

10 Special Toxicology Studies

No new studies submitted

11 Integrated Summary and Safety Evaluation

This application is supported by a complete battery of nonclinical studies previously reviewed and cross-referenced from the original NDA 200603 and supplements (b) (4). Except as noted below, no new non-clinical studies were conducted to support the current sNDAs, as previously agreed by the Division (Pre-IND 103427 meeting of 9/29/2008 and pre-NDA meeting of June 4, 2012).

Subsequent to the original NDA 200603, the sponsor performed 12 pharmacology studies that were "intended to replicate previous in vitro and in vivo pharmacological findings in support of a marketing application in Japan". The key findings of these studies confirm previous findings of the receptor-mediated activities of lurasidone and its metabolites as well as the pharmacodynamics of lurasidone in animal models, and did not alter the already known pharmacological characteristics of the compound. Four of these 12 studies have not been reviewed before and are a subject of this review. These 4 pharmacology studies assessed the in vitro effect of lurasidone and its active metabolites (ID-14283 and ID-14326) on human alpha-adrenergic receptors. These studies showed that lurasidone and its active metabolites are antagonists of human α_{1A} and α_{2C} adrenergic receptors, and this antagonistic activity is weaker than that of risperidone. The affinity of the active metabolites ID-14283 and ID-14326 for human α_{1A} and α_{2C} adrenergic receptors is higher than that of the parent compound, lurasidone.

Overall, there are no new nonclinical data or concerns that affect the *safety* evaluation of lurasidone for the treatment of depressive episodes associated with bipolar I disorder.

Since the dose range for lurasidone in the treatment of bipolar depression (20 to 120 mg/day) represents a lower dosing range than that previously shown to be safe and effective for schizophrenia (40 to 160 mg/day), no new safety issues are anticipated.

12 Appendix/Attachments

None

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/s/

SONIA A TABACOVA
05/10/2013

AISAR H ATRAKCHI
05/10/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	200603
Supplement #:	S10 (Monotherapy)
Drug Name:	Latuda (Lurasidone) tablets; 20-60 and 80-120 mg/day
Indication:	Depressive episodes associated with bipolar I disorder
Applicant:	Sunovion Pharmaceuticals Inc.
Dates:	Submitted: 08/31/2012
	PDUFA due date: 06/30/2013
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., Team Leader
	H. M. James Hung, Ph.D., Division Director
Medical Division:	**Division of Psychiatry Products**
Clinical Team:	Mark Ritter, M.D., Medical Reviewer
	Robert Levin, M.D., Team Leader
Project Manager:	Ann J. Sohn, Pharm.D.

Keywords: clinical studies, mixed models, multiple endpoints, sensitivity analysis

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1 EXECUTIVE SUMMARY

Lurasidone (trade name Latuda) is approved for the treatment of schizophrenia. The objective of Study D1050236 was to evaluate the efficacy and safety of monotherapy lurasidone in the treatment of depressive episodes in patients with bipolar I disorder. The trial was conducted in eight countries, with US sites providing about 40 percent of the Intent-to-Treat population. Subjects were randomized to either of two dose ranges of lurasidone (20-60 or 80-120 mg/day) or placebo. The primary outcome was the change from baseline in the Montgomery-Asberg Depression Rating Scale at week 6. The key secondary outcome was the change from baseline in the Clinical Global Impression-Bipolar Version-Severity of Illness score at week 6. The primary analyses were conducted using a Mixed Model Repeated Measures approach. The overall results of those analyses are statistically significant for both the primary as well as the key secondary outcome measure for both dose ranges. There is not sufficient evidence to conclude that the higher dose range produces more favorable efficacy results compared to the lower dose range. This reviewer confirmed the results obtained by the sponsor. Regional heterogeneity in efficacy outcomes, such as the smaller average treatment effect in the US and the finding of higher efficacy in the lower dose range also for the US subjects, could not be fully explained by the sponsor or this reviewer (for details see section 4.1.4).

The sponsor's claim that lurasidone in monotherapy treats depressive episodes in bipolar I disorder better than placebo is supported by the strength of the statistical evidence presented.

2 INTRODUCTION

2.1 Overview

Lurasidone has been approved for the treatment of patients with schizophrenia on October 28, 2010 (IND 61,292 and NDA 200,603). This review pertains to supplement 10 (S10) to the original NDA seeking approval of lurasidone in the treatment of patients with depressive episodes associated with bipolar I disorder. S10 (lurasidone as monotherapy) is supported by study D1050236, hereafter referred to as study 236.

Study 236 is a randomized, 6-week, double-blind, placebo-controlled, fixed-flexible dose, parallel-group trial of lurasidone for the treatment of Bipolar I Depression. It consists of three arms: lurasidone 20-60 mg/day (n=161), lurasidone 80-120 mg/day (n=162), and placebo (n=162). The study enrolled subjects at 55 sites: 4 sites in the Czech Republic, 1 site in France, 9 sites in India, 4 sites in Romania, 4 sites in Russia, 4 sites in South Africa, 5 sites in the Ukraine, and 24 sites in the United States. The proportion of ITT patients enrolled at US sites is 40.2 percent.

Table 1: Study Included in Analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
D1050236	*Phase 3, parallel, fixed-flexible dose*	*6 weeks*	*none*	*Lurasidone 20-60 mg: 161* *Lurasidone 80-120 mg: 162* *Placebo: 162*	*Subjects with bipolar I disorder, most recent episode depressed*

2.2 Data Sources

The following data sources were considered in this review:

a) Applicant's study report (\\Cdsesub1\evsprod\NDA200603\0076\m5\53-clin-stud-rep\535-rep-effic-safety-stud\bipolar-depression\5351-stud-rep-contr\d1050236)
b) Data sets (\\Cdsesub1\evsprod\NDA200603\0076\m5\datasets\d1050236\analysis\legacy\datasets)
c) Software code (\\Cdsesub1\evsprod\NDA200603\0076\m5\datasets\d1050236\analysis\legacy\programs)
d) Response to FDA information request (\\Cdsesub1\evsprod\NDA200603\0092)

3 STATISTICAL EVALUATION

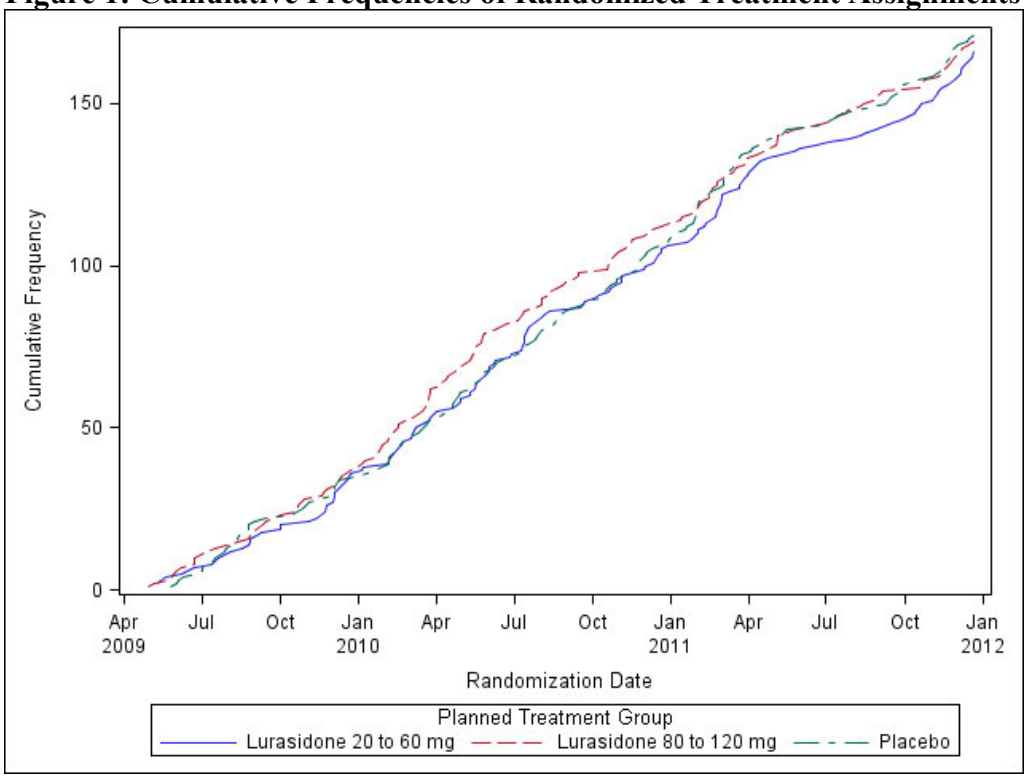
3.1 Data and Analysis Quality

This study was audited for GCP compliance. The sponsor used an independent internal auditing procedure. Of the 55 sites where subjects were randomized, 14 (25.5%) sites were audited by the sponsor's Research Quality Assurance department. Compliance was noted overall. Four out of 14 audits are documented in the appendix to the study report. The complete audit reports for those four sites were provided by the sponsor after an FDA request. Major items such as lack of PI involvement were identified by the auditor for two sites (104 [9 ITT subjects] and 150 [1 ITT subject]), but none impact the efficacy conclusions.

This study was monitored at all stages (see study report p. 58-59). This reviewer explored efficacy profiles for selected sites. Figure A3a) in the appendix displays the observed MADRS scores at the Russian site 191 which appear unusually homogeneous. Inspection reports by the Office of Scientific Investigation for this site and the Czech site 618 are not available yet.

The sponsor implemented a remote rater management (RRM) program for the primary outcome measure. In addition to the MADRS assessment by a qualified rater at the study site each subject was to complete an interactive depressive symptom interview on a computer. Data from this self-report computer-based interview were to be compared with data derived from the site rater interview on an ongoing basis by Concordant Rater Systems. "The RRM allowed the study team to monitor the primary outcome measure at treatment phase assessments in the study and give ongoing feedback and remediation to the rater in the study, when necessary" (study report p. 30). The rater's assigned scores were not altered by the review or any exchange with the central vendor.

Figure 1: Cumulative Frequencies of Randomized Treatment Assignments



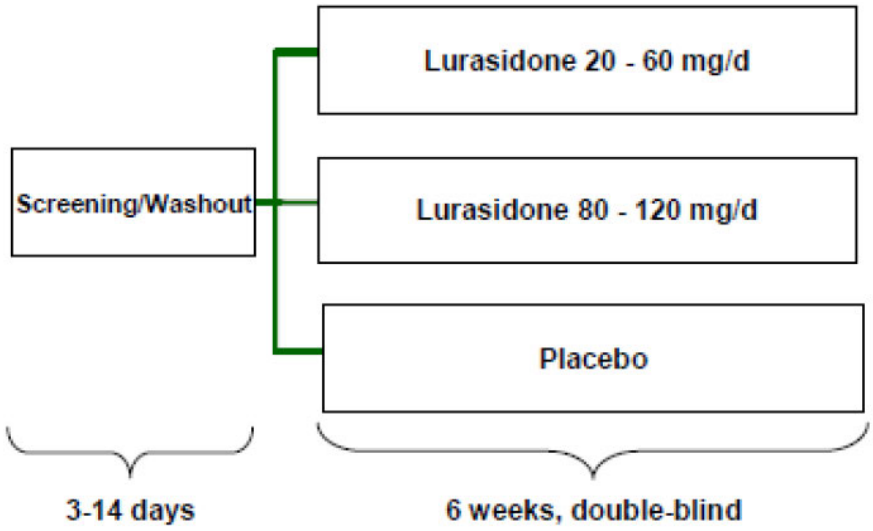
(Source: Computed by reviewer)

As a crude check on the randomization procedure this reviewer plotted the cumulative frequencies of patients in each treatment group against the randomization dates (Figure 1). The assignment process succeeded in forming groups that grew at similar rates. The repeated crossing of the curves in Figure 1 reflects the expected random variation in the rates at which subjects are assigned to a specific treatment group.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Figure 2: Study Design



(Source: SAP p. 13)

Study 236 is a randomized, 6-week, double-blind, placebo-controlled, fixed-flexible dose, parallel-group, multi-center phase 3 study of lurasidone for the treatment of bipolar I depression. The first subject was randomized on April 29, 2009 and the last subjected completed the study on February 1, 2012.

The main inclusion criteria are:

- Subject is 18 to 75 years of age, with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course (≥ 4 episodes of mood disturbance, but < 8 episodes in the previous 12 months) and without psychotic features.
- Subject has a lifetime history of at least one bipolar manic or mixed manic episode (based on information from reliable informant if available).
- Subject's current major depressive episode is ≥ 4 weeks and < 12 months in duration.
- Subject has a rater-administered and computerized MADRS total score ≥ 20 (at both Screening and Baseline visits).

Some noteworthy exclusion criteria are:

- Subject has a history of non-response to an adequate (6-week) study of three or more antidepressants.
- Subject demonstrates a decrease (improvement) of ≥ 25% in the MADRS total score between Screening and Baseline visits.

"The primary objective of this study was to evaluate the efficacy of lurasidone (20 to 60 mg/day and 80 to 120 mg/day, flexibly dosed) compared with placebo for the treatment of major depressive episodes associated with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course […], and without psychotic features" (study report p. 2).

The test product was administered in the following dosages: 20, 40, 60, 80, 100 or 120 mg/day. It was taken orally, once daily in the evening, with a meal or within 30 minutes after eating.

The primary efficacy endpoint is the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score after 6 weeks of treatment. The key secondary endpoint is the change from baseline to week 6 in the Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score.

Eligibility was determined in the Screening period of three to 14 days. Subjects were to be washed out from prior or concomitant medications, where applicable, prior to randomization. A computerized diagnostic instrument, the Bipolarity Index (BPI) and an interviewer-administered structured interview (Mini-International Neuropsychiatric Interview [MINI]) conducted by study site staff was used to confirm the DSM-IV-TR diagnosis of bipolar I disorder, most recent episode depressed. Subjects for whom diagnostic agreement between the Investigator and Concordant Rater Systems (evaluated computerized MINI interview) could not be reached were not eligible for continued study participation.

Subjects who met entry criteria were randomly assigned (1:1:1) via IVRS to lurasidone 20 to 60 mg/day (flexibly dosed), lurasidone 80 to 120 mg/day (flexibly dosed), or placebo treatment groups in a double-blind fashion (study report p. 3).

"Lurasidone dosing was to be fixed at 20 mg/day for Days 1 to 7 in the 20 to 60 mg/day treatment arm. Subjects randomized to the lurasidone 80 to 120 mg/day arm were to be treated with lurasidone 20 mg/day for Days 1 to 2, 40 mg/day for Days 3 to 4, 60 mg/day for Days 5 to 6, and 80 mg/day on Day 7. Lurasidone was to be flexibly dosed for Weeks 2 to 6" (study report p. 4).

A Data Safety and Monitoring Board (DSMB) reviewed blinded, unblinded, or partially unblinded data at regular intervals. The DSMB was empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility.

3.2.2 Statistical Methodologies

3.2.2.1 Primary Analysis

The primary efficacy analysis assessed the change from Baseline in MADRS total score at Week 6, employing an MMRM model with restricted maximum likelihood estimation under the assumption of an unstructured covariance matrix for within-subject correlation. The analysis evaluated the mean change from Baseline in MADRS total score over 6 weeks and how changes differed among the treatment groups. The model included factors for treatment, pooled center, visit (as a categorical variable), Baseline MADRS total score, and treatment-by-visit interaction. The Kenward-Rogers method was used to estimate the denominator degrees of freedom. The treatment and treatment by visit interaction terms allowed for comparisons of the treatment groups at each of the following time points: Weeks 1, 2, 3, 4, 5, and 6.

Additional analyses for the primary efficacy parameter were also performed to assess the consistency of the treatment effect across sites. A repeated measures model examined the change from Baseline in MADRS total score, with fixed effects for treatment, pooled center, visit, Baseline score, treatment by visit interaction, and treatment by pooled center interaction, assuming an unstructured covariance matrix. If there appeared to be a significant treatment by pooled center interaction effect (defined by sponsor as p-value < 0.10), estimates by pooled center were to be examined to determine the nature of the interaction.

The primary analysis was based on the ITT population. The analysis was also conducted for the PP population. The analysis was conducted by geographic region and North America versus Rest of World for the ITT population.

3.2.2.2 Supportive Analysis

As a supportive analysis, the change from Baseline in MADRS total score at Weeks 1 to 6 and LOCF Endpoint were evaluated using an analysis of covariance (ANCOVA) model with fixed effects for treatment, pooled center, and Baseline MADRS total score. This analysis was

conducted for the ITT and PP populations. The analysis was conducted at Baseline and LOCF Endpoint by geographic region and North America versus Rest of World for the ITT population.

Analysis of Key Secondary Endpoint

The key secondary efficacy analysis parameter was the change from Baseline in CGI-BP-S depression score at Week 6. It was evaluated using an MMRM model, utilizing the same procedures and reporting as indicated for the MADRS primary efficacy MMRM analysis. This analysis was also conducted by geographic region and North America versus Rest of World for the ITT population.

As supportive analysis the change from Baseline in CGI-BP-S depression score at Weeks 1 to 6 and LOCF Endpoint were evaluated using an ANCOVA, with effects for Baseline score, pooled center, and treatment. This analysis was also conducted at Baseline and LOCF Endpoint by geographic region and North America versus Rest of World for the ITT population (see study report p. 62-64).

Multiplicity

"The Hommel-based tree-gatekeeping procedure (described in Appendix 4 of the SAP) was applied to p-values from the mixed model for repeated measures (MMRM) analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints. The hypotheses associated with the primary and key secondary variables for efficacy claim were grouped into 2 hierarchical families:

1. Family F1: lurasidone 20-60 mg/day versus placebo (H_1) and lurasidone 80-120 mg/day versus placebo (H_2) based on change from Baseline in MADRS total score at Week 6 (E1);
2. Family F2: lurasidone 20-60 mg/day versus placebo (H_3) and lurasidone 80-120 mg/day versus placebo (H_4) based on change from Baseline in CGI-BP-S depression score at Week 6 (E2);

The gatekeeping procedure accounted for the logical restrictions in this problem by performing multiplicity adjustment in 2 steps:

1. Step 1: The lurasidone-placebo comparisons for E1 (hypotheses H_1 and H_2) were performed using a truncated version of the Hommel test.

2. Step 2: The lurasidone-placebo comparisons for E2 (hypotheses H_3 and H_4), corresponding to the doses that were significant at Step 1, were performed using a regular Hommel test. For example, H_4 was tested only if H_2 was rejected.

The value of the truncation parameter (Gamma1) used to determine the balance of power in Families 1 and 2 was set at Gamma1 = 0.0. The Hommel-based tree-gatekeeping procedure controlled the overall Type I error rate in the strong sense at the α level, meaning there is control on the probability to reject at least one true null hypothesis, regardless of which subset of null hypotheses happens to be true. There was no adjustment for multiplicity for the secondary efficacy analyses" (Study report p. 60).

For this study, the following power function was maximized by setting Gamma1 = 0: probability to reject at least one hypothesis in Family 1 and at least one hypothesis in Family 2 (SAP p. 29). For $\gamma_1 = 0$, the truncated Hommel test simplifies to the Bonferroni test and thus the truncated Hommel p-value is equal to the Bonferroni p-value (SAP p. 89).

3.2.2.3 Sensitivity Analysis

Random Effects Pattern Mixture Model

A random effects pattern mixture model (PMM) was applied as one of two sensitivity analyses to explore the robustness of the MMRM results for the primary and key secondary efficacy variables for the ITT population. The model includes fixed terms for treatment, time (as a continuous variable), dropout pattern, and two-way interaction terms (i.e., treatment-by-time, dropout pattern-by-treatment, dropout pattern-by-time), and a three-way interaction term (dropout pattern-by-treatment-by-time). The model also includes subject-specific random effects for intercept and time. The response variables are the observed values of the efficacy variables over time, including the baseline value. Subjects were classified into two separate patterns: dropouts and completers. The grouping in dropouts and completers is supported by the fact, that about 75% of subjects completed the study. A further sub-division of the dropouts could have led to sparseness of the data in particular subgroups.

Using a random effects PMM, one can examine (a) the degree to which the groups defined by the dropout patterns differ in terms of the outcome variable (i.e., main effect of the dropout pattern variable) and (b) the degree to which the dropout pattern moderates the influence of other model terms (i.e., interactions with the dropout pattern) (SAP p. 38).

Pattern Mixture Model with Placebo-based Multiple Imputation

A pattern-mixture model using a placebo-based multiple imputation method was performed as a second sensitivity analysis to explore the robustness of the MMRM results for the primary and key secondary efficacy variables for the ITT population. The assumption that efficacy profiles of dropouts after discontinuation are similar to those of placebo subjects is considered conservative because this methodology tends to minimize the difference between lurasidone and placebo groups.

The steps to implement this sensitivity analysis were as follows:

1. 1000 datasets were generated where missing data at intermediate visit(s) were imputed for each treatment group using non-missing data from all subjects within the treatment group by a Monte Carlo Markov Chain (MCMC) imputation model using the MCMC statement in the SAS PROC MI procedure. As a result, each dataset had only missing ending data, or a monotone missing data pattern.
2. For each dataset from step 1, missing ending data was imputed based on information from the placebo group. As a result, 1000 imputed complete datasets were generated.
3. Each imputed complete dataset was analyzed utilizing the MMRM model.
4. The estimates from the results of each MMRM model were combined using SAS MIANALYZE.

The results of the placebo-based multiple imputation analysis were then compared with the MMRM results for the primary and key secondary efficacy variables (SAP p. 40-41).

Dropout Profiles

In an additional analysis, subjects were grouped by the visit at which they had their last MADRS total score (or CGI-BP-S score). This resulted in seven categories for subjects discontinuing: Week 1 dropouts, Week 2 dropouts … Week 6 dropouts, and Completers. The change from Baseline in MADRS total score and CGI-BP-S score was summarized by dropout category, treatment, and visit in several seven-line plots (study report p. 68). The resulting plots are included as Figure A10 in the appendix.

Pooling Strategy

All centers with seven or fewer subjects were pooled. Small centers were pooled by size within country or geographic region if necessary (see Table 2).

Table 2: Pooled Centers

Pooled Center ID	Center ID(Number of Subjects)	Country	Number of Subjects
901	069(5), 099(2), 663(4)	USA	11
902	070(8), 078(5)	USA	13
903	085(1), 107(8), 109(3)	USA	12
904	086(4), 089(2), 095(8)	USA	14
905	105(18), 113(4)	USA	22
906	150(1), 157(8)	India	9
907	152(7), 158(3)	India	10
908	156(21), 164(1)	India	22
909	189(1), 190(4), 192(4)	Russia	9
910	274(9), 275(4), 277(2), 278(1)	Romania	16
911	413(4), 416(24)	South Africa	28
912	414(3), 415(26)	South Africa	29

(Source: SAP p. 25-26)

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 818 subjects were screened to participate in this study, of which 505 were randomized. A total of 374 subjects (74%) completed the 6-week DB phase of the study. The proportion of subjects completing was similar among the three treatment groups (Lur 20-60 mg: 74%, Lur 80-120 mg: 73 %, and Placebo: 75%). Overall, 39 subjects (8%) discontinued from the 6-week phase of the study for insufficient clinical response or worsening of existing condition. This proportion was 9% in the Lur 20-60 mg group, 4% in the Lur 80-120 mg group, and 11% in the placebo group. Twenty-three subjects (5%) withdrew from the study for an adverse event not associated with worsening of an existing condition, with similar proportions among the three treatment groups. Table 3 below provides an overview of the subject disposition.

Table 3: Subject Disposition

		Treatment Group				
	Statistic	**Lurasidone 20-60 mg**	**Lurasidone 80-120 mg**	**Combined Lurasidone**	**Placebo**	**Total**
Number of Screened Subjects	n	-	-	-	-	818
Number of Screening Failures	n	-	-	-	-	313 (38%)
Number of Subjects Randomized	n	166	169	335	170	505 (62%)
Completed the Double-Blind Phase	n (%)	123 (74)	124 (73)	247 (74)	127 (75)	374 (74)
Discontinued from the Double-Blind Phase	n (%)	43 (26)	45 (27)	88 (26)	43 (25)	131 (26)
Insufficient Clinical Response	n (%)	12 (7)	5 (3)	17 (5)	13 (8)	30 (6)
Adverse Event	n (%)	11 (7)	10 (6)	21 (6)	11 (6)	32 (6)
Discontinued for Worsening of Existing Condition on Adverse Event Page	n (%)	3 (2)	1 (<1)	4 (1)	5 (3)	9 (2)
Discontinued Due to an Event other than Worsening of Existing Condition on Adverse Event Page	n (%)	8 (5)	9 (5)	17 (5)	6 (4)	23 (5)
Lost to Follow-up	n (%)	7 (4)	7 (4)	14 (4)	5 (3)	19 (4)
Protocol Violation	n (%)	7 (4)	4 (2)	11 (3)	6 (4)	17 (3)
Withdrew Consent	n (%)	3 (2)	10 (6)	13 (4)	2 (1)	15 (3)
Administrative	n (%)	3 (2)	9 (5)	12 (4)	6 (4)	18 (4)
Subjects Discontinued Due to Insufficient Clinical Response or Worsening of Existing Condition	n (%)	15 (9)	6 (4)	21 (6)	18 (11)	39 (8)
Continuing into Extension Study	n (%)	109 (89)	102 (82)	211 (85)	107 (84)	318 (85)

Note: For screening failures and subjects randomized, percentages were based on the number of subjects screened. For subjects continuing into the extension study, percentages were based on the number of subjects that completed the double-blind phase. All other percentages were based on the number of randomized subjects.

Note: For "Number of Screened Subjects" and "Number of Screening Failures," subjects screened multiple times were counted more than once.

Note: Subjects "Discontinued Due to an Event other than Worsening of Existing Condition on Adverse Event Page" were those subjects with adverse events with action taken reported as study medication permanently discontinued that were not associated with a worsening of bipolar I disorder.

Note: "Subjects Discontinued Due to Insufficient Clinical Response or Worsening of Existing Condition" were those subjects recording Insufficient Clinical Response on the termination page or subjects with an adverse event leading to discontinuation with a preferred term associated with worsening of bipolar I disorder.

Note: Subject 23610312 enrolled in the study a second time (as 23611218 in placebo treatment group) and results from the second enrollment were excluded from the summary above and from all efficacy and safety analyses. Subject 23611226 (in placebo treatment group) previously participated in other lurasidone studies (as 23510306 in Study D1050235 and 25610305 in Study D1050256) and was excluded from all Per Protocol analyses.

(Source: Study report p. 80-81)

Analysis populations

The primary population for efficacy analysis was the Intent-to-Treat (ITT) population, which was defined as all subjects who were randomized, received at least one dose of study medication, and had at least one Baseline and one post-Baseline efficacy measurement for the MADRS or CGI-BP-S.

The Per Protocol (PP) Population included all ITT subjects without protocol deviations. The Safety population included all randomized subjects who received at least one dose of study medication.

Of the 505 subjects randomized six never received study medication leaving 499 patients for the Safety Population. The additional requirement for a Baseline and at least one post-Baseline efficacy measurement narrowed the ITT Population to 485 subjects. A total of 102 subjects in the

ITT population had one or more protocol deviations yielding a total PP Population of 383 subjects. Table 4 summarizes the number of subjects in the three analysis populations by treatment group.

Table 4: Analysis Populations (All Randomized Subjects)

		Treatment Group				
	Statistic	**Lurasidone 20-60 mg (N = 166)**	**Lurasidone 80-120 mg (N = 169)**	**Combined Lurasidone (N = 335)**	**Placebo (N = 170)**	**Total (N = 505)**
Number of Subjects in the Safety Population	n (%)	164 (99)	167 (99)	331 (99)	168 (99)	499 (99)
Number of Subjects in the Intent-to-Treat Population	n (%)	161 (97)	162 (96)	323 (96)	162 (95)	485 (96)
Number of Subjects in the Per Protocol Population	n (%)	126 (76)	135 (80)	261 (78)	122 (72)	383 (76)

Note: All subjects who were randomized and received at least one dose of study medication were in the Safety population.
Note: All subjects who were randomized, received at least one dose of study medication, and had a Baseline and at least one post-Baseline efficacy measurement (MADRS or CGI-BP-S) were in the ITT population.
Note: All subjects who were in the ITT population and had no protocol deviations were included in the Per Protocol population.
Note: Subject 23610312 enrolled in the study a second time (as 23611218 in placebo treatment group) and results from the second enrollment were excluded from the summary above and from all efficacy and safety analyses. Subject 23611226 (in placebo treatment group) previously participated in other lurasidone studies (as 23510306 in Study D1050235 and 25610305 in Study D1050256) and was excluded from all Per Protocol analyses.
Abbreviations: CGI-BP-S = Clinical Global Impressions Scale – Bipolar Version – Severity of Illness; ITT = Intent-to-Treat; MADRS = Montgomery-Asberg Depression Rating Scale.

(Source: Study report p. 86)

Of the 499 subjects in the Safety population, 215 (43%) were male and 284 (57%) were female. The age of the participants ranged from 18 to 74 years, with a mean age of 41.6 years. The majority of subjects were White (66%), followed by Asian (15%), and Black or African American (14%). This reviewer agrees with the sponsor's statement that no meaningful differences were observed among treatment groups for any of the demographic variables (Study report p. 91).

The highest proportion of subjects treated were in North America (40%), followed by Europe (33%), Asia (15%) and Africa (11%). Table 5 gives an overview of the demographics and baseline efficacy assessments.

Table 5: Demographics (Safety Population) and Selected Efficacy Parameter Baseline Scores (ITT Population)

		Treatment Group				
	Statistic	Lurasidone 20-60 mg (N=164)	Lurasidone 80-120 mg (N=167)	Combined Lurasidone (N=331)	Placebo (N=168)	Total (N=499)
Gender	n	164	167	331	168	499
Male	n (%)	71 (43)	66 (40)	137 (41)	78 (46)	215 (43)
Female	n (%)	93 (57)	101 (60)	194 (59)	90 (54)	284 (57)
Age (years)	n	164	167	331	168	499
	Mean (SD)	41.4 (12.40)	42.2 (12.27)	41.8 (12.32)	41.0 (12.48)	41.6 (12.37)
	Median	41.0	42.0	42.0	42.0	42.0
	Min, Max	18, 69	19, 74	18, 74	20, 73	18, 74
20 and Under	n (%)	4 (2)	4 (2)	8 (2)	4 (2)	12 (2)
21 to 30	n (%)	39 (24)	30 (18)	69 (21)	37 (22)	106 (21)
31 to 40	n (%)	33 (20)	44 (26)	77 (23)	37 (22)	114 (23)
41 to 50	n (%)	45 (27)	41 (25)	86 (26)	47 (28)	133 (27)
51 to 60	n (%)	33 (20)	39 (23)	72 (22)	31 (18)	103 (21)
61 to 70	n (%)	10 (6)	7 (4)	17 (5)	10 (6)	27 (5)
Over 70	n (%)	0	2 (1)	2 (<1)	2 (1)	4 (<1)
<55 years	n (%)	137 (84)	136 (81)	273 (82)	140 (83)	413 (83)
≥55 Years	n (%)	27 (16)	31 (19)	58 (18)	28 (17)	86 (17)
<65 years	n (%)	160 (98)	164 (98)	324 (98)	165 (98)	489 (98)
≥65 Years	n (%)	4 (2)	3 (2)	7 (2)	3 (2)	10 (2)
Race	n	164	167	331	168	499
White	n (%)	108 (66)	110 (66)	218 (66)	110 (65)	328 (66)
Black or African American	n (%)	21 (13)	25 (15)	46 (14)	23 (14)	69 (14)
Asian	n (%)	24 (15)	24 (14)	48 (15)	29 (17)	77 (15)
American Indian or Alaska Native	n (%)	2 (1)	1 (<1)	3 (<1)	0	3 (<1)
Native Hawaiian or Other Pacific Islander	n (%)	1 (<1)	0	1 (<1)	0	1 (<1)
Other	n (%)	8 (5)	7 (4)	15 (5)	6 (4)	21 (4)
Ethnicity	n	164	167	331	168	499
Hispanic or Latino	n (%)	8 (5)	6 (4)	14 (4)	9 (5)	23 (5)
Not Hispanic or Latino	n (%)	156 (95)	161 (96)	317 (96)	159 (95)	476 (95)
Geographic Region	n	164	167	331	168	499
North America	n (%)	67 (41)	72 (43)	139 (42)	63 (38)	202 (40)
Rest of World	n (%)	97 (59)	95 (57)	192 (58)	105 (63)	297 (60)
Africa	n (%)	20 (12)	18 (11)	38 (11)	18 (11)	56 (11)
Asia	n (%)	24 (15)	24 (14)	48 (15)	28 (17)	76 (15)
Europe	n (%)	53 (32)	53 (32)	106 (32)	59 (35)	165 (33)
Country	n	164	167	331	168	499
Czech Republic	n (%)	17 (10)	19 (11)	36 (11)	19 (11)	55 (11)
France	n (%)	4 (2)	4 (2)	8 (2)	5 (3)	13 (3)
India	n (%)	24 (15)	24 (14)	48 (15)	28 (17)	76 (15)
Romania	n (%)	4 (2)	3 (2)	7 (2)	9 (5)	16 (3)
Russia	n (%)	11 (7)	10 (6)	21 (6)	10 (6)	31 (6)
South Africa	n (%)	20 (12)	18 (11)	38 (11)	18 (11)	56 (11)

		Treatment Group				
	Statistic	Lurasidone 20-60 mg (N=164)	Lurasidone 80-120 mg (N=167)	Combined Lurasidone (N=331)	Placebo (N=168)	Total (N=499)
Ukraine	n (%)	17 (10)	17 (10)	34 (10)	16 (10)	50 (10)
United States		67 (41)	72 (43)	139 (42)	63 (38)	202 (40)
Baseline MADRS Total Score	n	161	162	323	162	485
	Mean (SD)	30.3 (5.02)	30.6 (4.93)	30.5 (4.97)	30.5 (4.95)	30.5 (4.96)
	Median	30.0	30.0	30.0	30.0	30.0
	Min, Max	20, 50	20, 45	20, 50	20, 48	20, 50
Baseline CGI-BP-S Depression Score	n	161	162	323	162	485
	Mean (SD)	4.52 (0.623)	4.55 (0.641)	4.54 (0.631)	4.48 (0.613)	4.52 (0.625)
	Median	4.00	4.00	4.00	4.00	4.00
	Min, Max	3, 6	4, 6	3, 6	3, 6	3, 6
Baseline SDS Total Score	n	115	123	238	118	356
	Mean (SD)	19.7 (4.75)	19.8 (5.58)	19.7 (5.18)	19.8 (4.99)	19.8 (5.11)
	Median	20.0	21.0	20.0	21.0	20.0
	Min, Max	5, 30	2, 30	2, 30	0, 30	0, 30

Note: Higher observed MADRS total score, CGI-BP-S depression score, and SDS total score indicate greater severity of illness.
Note: Baseline was the last measurement on or before the date of first dose of study medication.
Abbreviations: CGI-BP-S = Clinical Global Impressions Scale – Bipolar Version – Severity of Illness; MADRS = Montgomery-Asberg Depression Rating Scale; SDS = Sheehan Disability Scale.

(Source: Study report p. 88-90)

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Primary Analysis for Primary Endpoint

Recall, that this study recruited subjects with bipolar I disorder, most recent episode depressed. The primary efficacy analysis parameter was the change from Baseline MADRS total score at week 6, evaluated by an MMRM model assuming an unstructured covariance matrix. The model results show a decrease in MADRS total score for both the lurasidone and the placebo group, indicating an improvement in depressive symptoms. The mean decrease (LS mean ± SE) in the MADRS total score from Baseline to Week 6 is -15.4 ± 0.83 for both the lurasidone 20-60 mg and for the lurasidone 80-120 mg group, the mean decrease for the placebo group is -10.7 ± 0.83. The treatment difference at week 6 (lurasidone minus placebo) of -4.6 (95% CI: -6.9, -2.3) is statistically significant after adjustment for multiplicity for both lurasidone treatment groups (adjusted $p < 0.001$). The treatment differences are statistically significant starting at week 2 in both lurasidone groups. Table 6 provides the detailed MMRM model results.

Table 6: Change from Baseline in Montgomery-Asberg Depression Rating Scale Total Score – Repeated Measures (ITT Population)

Parameter	Estimate	SE	95% CI	p-value
Number of Subjects	485	--	--	--
Lurasidone 20-60 mg	161	--	--	--
Lurasidone 80-120 mg	162	--	--	--

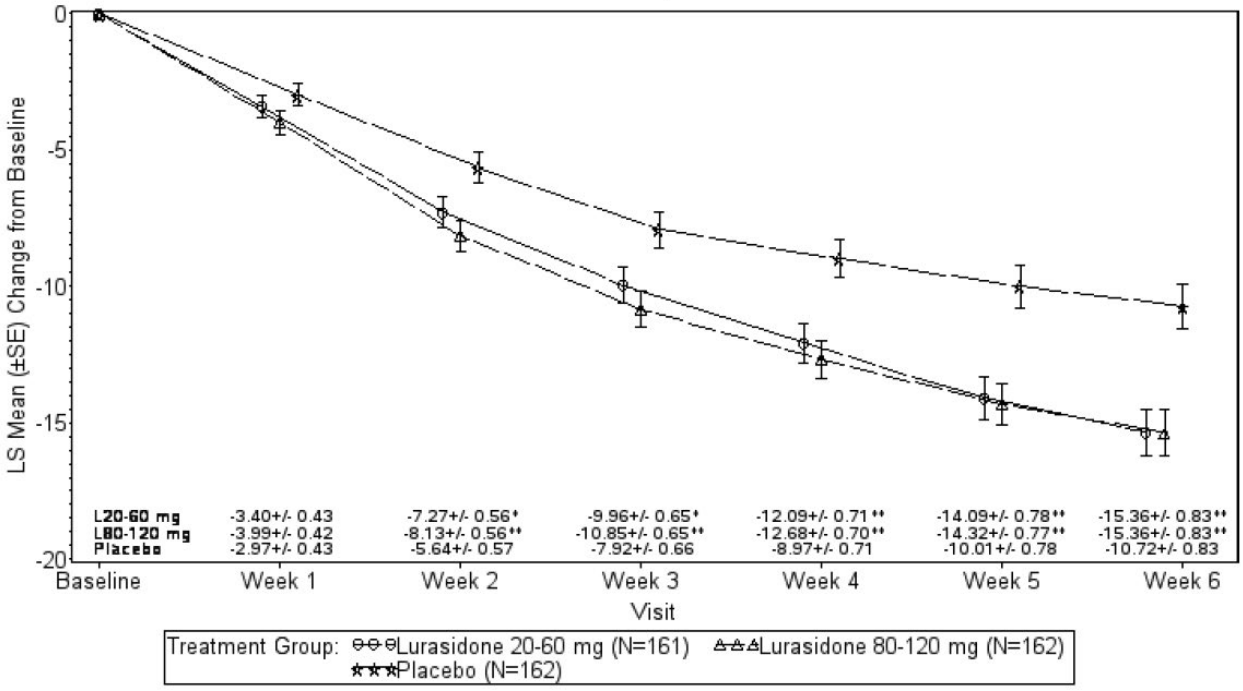
Placebo	162	--	--	--
Repeated Measures Model:				
Pooled Center	--	--	--	<0.001
Visit	--	--	--	<0.001
Baseline Score	--	--	--	<0.001
Treatment	--	--	--	<0.001
Treatment*Visit	--	--	--	0.041
Model Estimates:	--	--	--	--
Change from Baseline:	--	--	--	--
Lurasidone 20-60 mg	--	--	--	--
Week 1	-3.4	0.43	(-4.2, -2.6)	--
Week 2	-7.3	0.56	(-8.4, -6.2)	--
Week 3	-10.0	0.65	(-11.2, -8.7)	--
Week 4	-12.1	0.71	(-13.5,-10.7)	--
Week 5	-14.1	0.78	(-15.6,-12.6)	--
Week 6	-15.4	0.83	(-17.0,-13.7)	--
Change from Baseline:				
Lurasidone 80-120 mg				
Week 1	-4.0	0.42	(-4.8, -3.2)	--
Week 2	-8.1	0.56	(-9.2, -7.0)	--
Week 3	-10.8	0.65	(-12.1, -9.6)	--
Week 4	-12.7	0.70	(-14.1,-11.3)	--
Week 5	-14.3	0.77	(-15.8,-12.8)	--
Week 6	-15.4	0.83	(-17.0,-13.7)	--
Change from Baseline:				
Placebo				
Week 1	-3.0	0.43	(-3.8, -2.1)	--
Week 2	-5.6	0.57	(-6.7, -4.5)	--
Week 3	-7.9	0.66	(-9.2, -6.6)	--
Week 4	-9.0	0.71	(-10.4, -7.6)	--
Week 5	-10.0	0.78	(-11.5, -8.5)	--
Week 6	-10.7	0.83	(-12.4, -9.1)	--
Contrast: Lurasidone 20-60 mg versus Placebo				

Parameter	Estimate	SE	95% CI	p-value
Change from Baseline:				
Week 1	-0.4	0.59	(-1.6, 0.7)	0.463
Week 2	-1.6	0.79	(-3.2, -0.1)	0.040
Week 3	-2.0	0.92	(-3.8, -0.2)	0.027
Week 4	-3.1	1.00	(-5.1, -1.2)	0.002
Week 5	-4.1	1.09	(-6.2, -1.9)	<0.001
Week 6	-4.6	1.17	(-6.9, -2.3)	<0.001, <0.001[a]
Contrast: Lurasidone 80-120 mg versus Placebo				
Change from Baseline:				
Week 1	-1.0	0.59	(-2.2, 0.1)	0.085
Week 2	-2.5	0.79	(-4.1, -0.9)	0.002
Week 3	-2.9	0.92	(-4.7, -1.1)	0.001
Week 4	-3.7	1.00	(-5.7, -1.7)	<0.001
Week 5	-4.3	1.09	(-6.5, -2.2)	<0.001
Week 6	-4.6	1.17	(-6.9, -2.3)	<0.001, <0.001[a]
Tests of Dose-Response at Week 6:				
Linear Trend Test of 0, 20-60, 80-120 mg	--	--	--	<0.001
Lurasidone 80-120 mg versus 20-60 mg	-0.0	1.17	(-2.3, 2.3)	0.998
Treatment*Pooled Center Interaction	--	--	--	0.649

Note: Estimates, SE, CI, and p-values were based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. Adjusted p-values[a] were obtained with Hommel-based tree-gatekeeping procedures.
Note: Treatment*Pooled Center Interaction p-value was based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.
Note: Higher observed MADRS total scores indicate greater severity of depression.
Abbreviations: CI = confidence interval; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error.
(Source: Study report p. 93-95; the results were confirmed by this reviewer)

Note that the test titled "Linear Trend test" in Table 6) is actually only a contrast between the placebo and lurasidone 80-120 mg groups. Also note that no numerical difference was observed between the lurasidone 20-60 mg and the lurasidone 80-120 mg dose groups with respect to the primary outcome. Both groups achieved a change from BL in MADRS total score at week 6 of -15.4. Figure 3 depicts the LS mean changes by week for the three treatment groups.

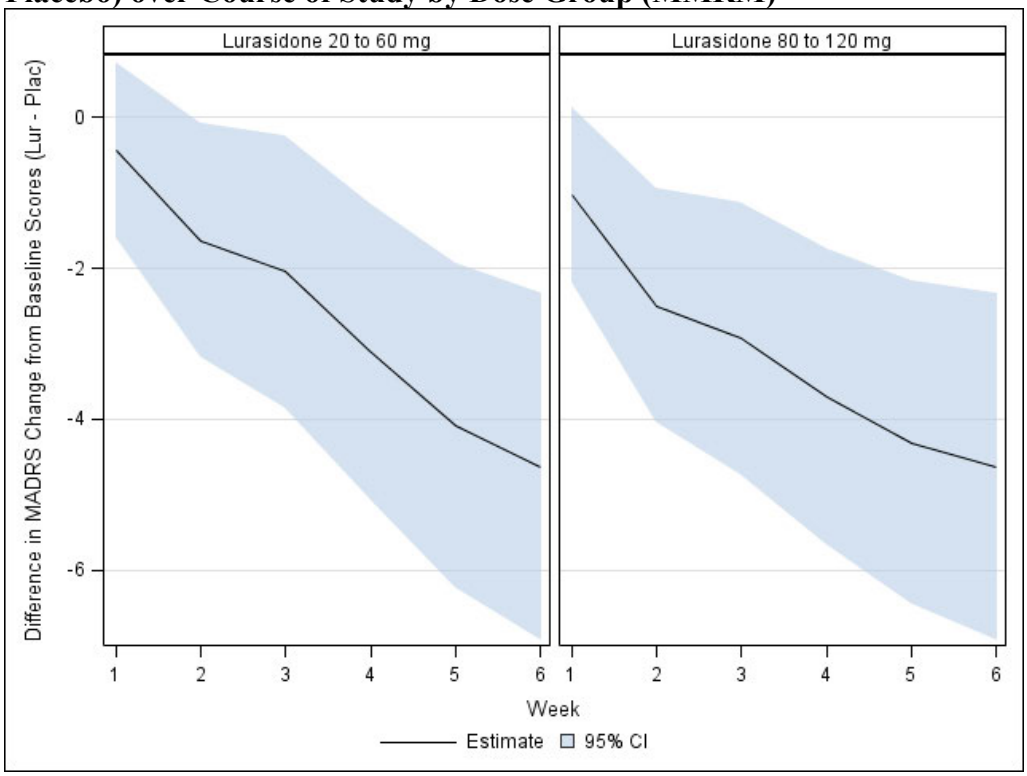
Figure 3: Change from Baseline (LS Mean ± SE) in Montgomery-Asberg Depression Rating Scale Total Score in Subjects Treated with Lurasidone or Placebo – Repeated Measures (ITT Population)



Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: L = lurasidone; LS = least square; N = number of subjects summarized; SE = standard error.
(Source: Study report p. 96)

Figure 4 displays the treatment difference (lurasidone minus placebo) for both dose groups over the course of the 6-week study. Those estimates were computed using the primary MMRM model. The trajectories of both curves are very similar.

Figure 4: LS Mean Difference in MADRS Change from Baseline Scores (Lurasidone minus Placebo) over Course of Study by Dose Group (MMRM)



(Source: Computed by reviewer using primary MMRM model)

3.2.4.2 Sponsor's Primary Analysis for Key Secondary Endpoint

The decrease (LS mean ± SE) in the CGI-BP-S depression score from baseline to week 6 is -1.83 ± 0.102 for the lurasidone 20-60 mg group, -1.71 ± 0.101 for the lurasidone 80-120 mg group, and -1.14 ± 0.102 for the placebo group. There is a significant treatment difference at week 6 (lurasidone minus placebo) for both lurasidone treatment groups. This difference is -0.69 (95% CI: -0.97, -0.41) for the lurasidone 20-60 mg group and -0.57 (95% CI: -0.85, -0.29) for the lurasidone 80-120 mg group. After adjustment for multiplicity using a Hommel-based tree-gatekeeping procedure both differences are statistically significant with $p < 0.001$. A more granular presentation of the MMRM model results for the key secondary endpoint is given in Table 7 below.

Table 7: Change from Baseline in Clinical Global Impression Bipolar Version –Severity Scale – Repeated Measures (ITT Population)

Parameter	Estimate	SE	95% CI	p-value
Number of Subjects	485	--	--	--
Lurasidone 20-60 mg	161	--	--	--
Lurasidone 80-120 mg	162	--	--	--
Placebo	162	--	--	--
Repeated Measures Model:				
Pooled Center	--	--	--	<0.001
Visit	--	--	--	<0.001
Baseline Score	--	--	--	<0.001
Treatment	--	--	--	<0.001
Treatment*Visit	--	--	--	0.004
Model Estimates:				
Change from Baseline:				
Lurasidone 20-60 mg				
Week 1	-0.26	0.043	(-0.35, -0.18)	--
Week 2	-0.71	0.067	(-0.84, -0.58)	--
Week 3	-1.04	0.078	(-1.20, -0.89)	--
Week 4	-1.32	0.085	(-1.48, -1.15)	--
Week 5	-1.53	0.094	(-1.72, -1.35)	--
Week 6	-1.83	0.102	(-2.03, -1.63)	--
Change from Baseline:				
Lurasidone 80-120 mg				
Week 1	-0.30	0.043	(-0.38, -0.21)	--
Week 2	-0.77	0.067	(-0.90, -0.64)	--
Week 3	-1.06	0.077	(-1.21, -0.91)	--
Week 4	-1.28	0.084	(-1.45, -1.12)	--
Week 5	-1.55	0.093	(-1.74, -1.37)	--
Week 6	-1.71	0.101	(-1.91, -1.51)	--
Change from Baseline:				
Placebo				
Week 1	-0.17	0.043	(-0.26, -0.09)	--

Parameter	Estimate	SE	95% CI	p-value
Week 2	-0.46	0.067	(-0.59, -0.33)	--
Week 3	-0.71	0.078	(-0.86, -0.55)	--
Week 4	-0.80	0.085	(-0.97, -0.64)	--
Week 5	-0.98	0.094	(-1.16, -0.79)	--
Week 6	-1.14	0.102	(-1.34, -0.94)	--
Contrast: Lurasidone 20-60 mg versus Placebo				
Change from Baseline:				
Week 1	-0.09	0.060	(-0.21, 0.03)	0.141
Week 2	-0.25	0.094	(-0.43, -0.06)	0.009
Week 3	-0.34	0.110	(-0.55, -0.12)	0.002
Week 4	-0.51	0.119	(-0.75, -0.28)	<0.001
Week 5	-0.56	0.133	(-0.82, -0.30)	<0.001
Week 6	-0.69	0.143	(-0.97, -0.41)	<0.001, <0.001[a]
Contrast: Lurasidone 80-120 mg versus Placebo				
Change from Baseline:				
Week 1	-0.12	0.060	(-0.24, -0.01)	0.041
Week 2	-0.31	0.094	(-0.50, -0.13)	<0.001
Week 3	-0.35	0.109	(-0.56, -0.14)	0.001
Week 4	-0.48	0.119	(-0.71, -0.24)	<0.001
Week 5	-0.58	0.132	(-0.84, -0.32)	<0.001
Week 6	-0.57	0.143	(-0.85, -0.29)	<0.001, <0.001[a]
Tests of Dose-Response at Week 6:				
Linear Trend Test of 0, 20-60, 80-120 mg	--	--	--	<0.001
Lurasidone 80-120 mg vs. 20-60 mg	0.12	0.143	(-0.16, 0.40)	0.403
Treatment*Pooled Center Interaction	--	--	--	0.573

Note: Estimates, SE, CI, and p-values were based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. Adjusted p-values[a] were obtained with Hommel-based tree-gatekeeping procedures.

Note: Contrasts were from differences of the change from Baseline treatment estimates for each lurasidone treatment group versus placebo.

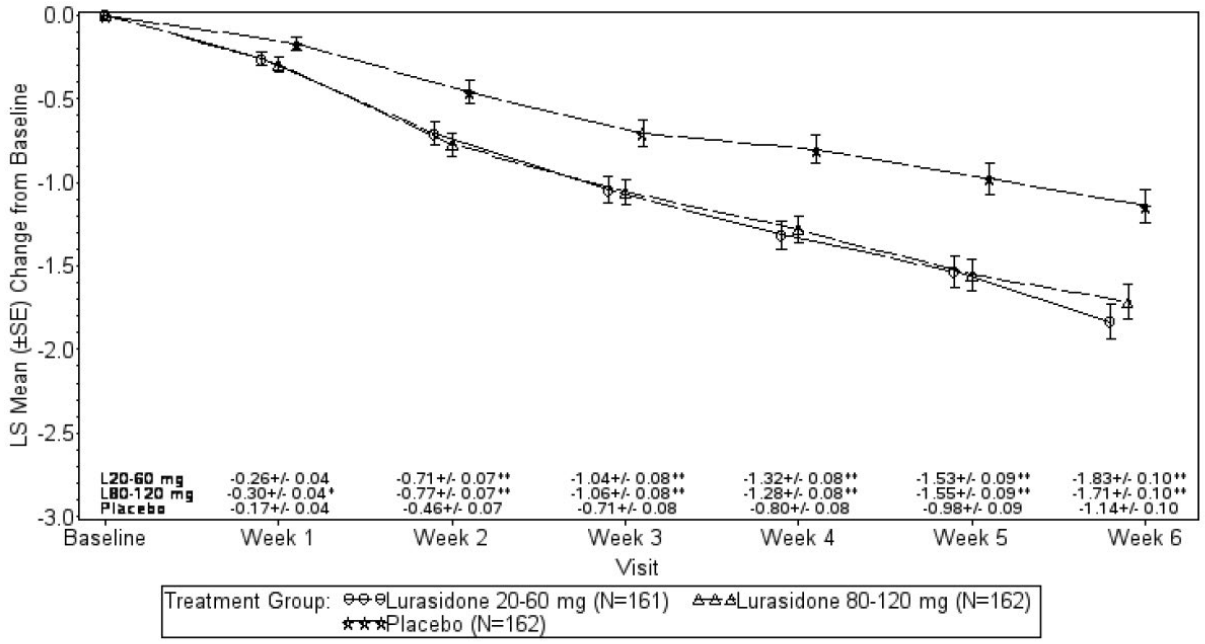
Note: Treatment*Pooled Center Interaction p-value was based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.

Note: Higher observed CGI-BP-S total scores indicate greater severity of depression.
Abbreviations: CGI-BP-S Clinical Global Impression Bipolar version – Severity Scale; CI = confidence interval; SE = standard error.
(Source: Study report p. 119-121; the results were confirmed by this reviewer)

Again, there is no clear differentiation in terms of efficacy as measured by CGI-BP-S between the two dose groups. The estimate of difference in the change from baseline CGI-BP-S scores between the two dose groups with 0.12 is small. Also, the "linear trend test" displayed in the table is again just the contrast between the higher lurasidone dose and placebo.

The trajectories of the CGI-BP-S scores over the 6-week study period are shown in Figure 5.

Figure 5: Change from Baseline (LS Mean ± SE) in Clinical Global Impression Bipolar Version – Severity Scale (CGI-BP-S) in Subjects Treated with Lurasidone or Placebo (ITT Population)



Note: Display represents model estimate of change from Baseline ± SE.
Note: * $p \leq 0.05$; ** $p \leq 0.01$ for contrast with placebo.
Abbreviations: CGI-BP-S Clinical Global Impression Bipolar version – Severity Scale; L = lurasidone; LS = least square; N = number of subjects summarized; SE = standard error.
(Source: Study report p. 122)

This reviewer verified the primary analyses results obtained by the sponsor for the primary and key secondary endpoints.

3.2.4.3 Sponsor's Supportive Analysis for Primary Endpoint

A summary of the sponsor's analyses with regards to the observed change from Baseline to Week 6 in MADRS total score (ANCOVA) for the ITT population is presented in Table 8 below.

Observed Change MADRS (ANCOVA)

Table 8: Montgomery-Asberg Depression Rating Scale Total Score – Observed and Change from Baseline (ITT population)

		Treatment Group					
		Lurasidone 20-60 mg (N = 161)		Lurasidone 80-120 mg (N = 162)		Placebo (N = 162)	
Visit	Statistic	Observed	Change	Observed	Change	Observed	Change
Baseline	n	161	--	162	--	162	--
	Mean (SD)	30.3 (5.02)	--	30.6 (4.93)	--	30.5 (4.95)	--
	Median	30.0	--	30.0	--	30.0	--
	Min, Max	20, 50	--	20, 45	--	20, 48	--
	LS Mean (SE)	30.4 (0.34)	--	30.7 (0.34)	--	30.7 (0.34)	--
	Tmt Diff (SE)	-0.2 (0.47)	--	0.1 (0.47)	--		--
	95% CI (Tmt Diff)	(-1.2, 0.7)	--	(-0.9, 1.0)	--		--
	p-value[1]	0.618	--	0.887	--		--
Week 6	n	125	--	123	--	127	--
	Baseline Mean (SD)	30.0 (4.55)	--	30.3 (5.03)	--	30.3 (5.07)	--
	Mean (SD)	14.4 (9.78)	-15.6 (9.75)	14.1 (8.84)	-16.3 (9.07)	18.5 (9.71)	-11.7 (9.21)
	Within-group Effect Size	--	1.60	--	1.79	--	1.27
	Median	13.0	-16.0	13.0	-18.0	18.0	-11.0
	Min, Max	0, 46	-36, 10	0, 41	-38, 13	0, 42	-31, 6
	LS Mean (SE)	--	-16.3 (0.80)	--	-16.4 (0.80)	--	-12.1 (0.79)
	95% CI (LS Mean)	--	(-17.8, -14.7)	--	(-17.9, -14.8)	--	(-13.7, -10.5)
	p-value[2]	--	<0.001	--	<0.001	--	<0.001
	Tmt Diff (SE)	--	-4.2 (1.08)	--	-4.3 (1.09)	--	--
	95% CI (Tmt Diff)	--	(-6.3, -2.1)	--	(-6.4, -2.1)	--	--
	Between-group Effect Size	--	0.49	--	0.49	--	--
	p-value[3]	--	<0.001	--	<0.001	--	--

(Source: Study report p. 98-99; the results were confirmed by this reviewer)

LOCF Endpoint MADRS (ANCOVA)

Table 9 displays the supportive ANCOVA analysis results when LOCF is applied to replace missing MADRS scores at week 6.

Table 9: Montgomery-Asberg Depression Rating Scale Total Score – LOCF Change from Baseline (ITT population)

		Treatment Group					
		Lurasidone 20-60 mg (N = 161)		Lurasidone 80-120 mg (N = 162)		Placebo (N = 162)	
Visit	**Statistic**	**Observed**	**Change**	**Observed**	**Change**	**Observed**	**Change**
LOCF Endpoint	n	161	--	162	--	162	--
	Baseline Mean (SD)	30.3 (5.02)	--	30.6 (4.93)	--	30.5 (4.95)	--
	Mean (SD)	16.5 (11.27)	-13.8 (11.10)	16.4 (10.23)	-14.2 (9.99)	21.1 (10.56)	-9.3 (9.90)
	Within-group Effect Size	--	1.25	--	1.42	--	0.94
	Median	15.0	-15.0	15.0	-16.0	22.0	-8.0
	Min, Max	0, 46	-36, 14	0, 45	-38, 13	0, 45	-31, 13
	LS Mean (SE)	--	-13.9 (0.80)	--	-13.9 (0.78)	--	-9.5 (0.79)
	95% CI (LS Mean)	--	(-15.5, -12.3)	--	(-15.4, -12.3)	--	(-11.0, -7.9)
	p-value[2]	--	<0.001	--	<0.001	--	<0.001
	Tmt Diff (SE)	--	-4.5 (1.10)	--	-4.4 (1.10)	--	--
	95% CI (Tmt Diff)	--	(-6.6, -2.3)	--	(-6.6, -2.3)	--	--
	Between-group Effect Size	--	0.45	--	0.45	--	--
	p-value[3]	--	<0.001	--	<0.001	--	--
Tests of Dose-Response at Week 6:							
Linear Trend Test of 0, 20-60, 80-120 mg			p-value[a]		<0.001	--	--
Lurasidone 80-120 mg versus 20-60 mg			Tmt Diff (SE)		-0.1 (1.09)	--	--
			95% CI (Tmt Diff)		(-2.2, 2.1)	--	--
			p-value[a]		0.950	--	--
Tests of Dose-Response at LOCF Endpoint:							
Linear Trend Test of 0, 20-60, 80-120 mg			p-value[a]		<0.001	--	--
Lurasidone 80-120 mg versus 20-60 mg			Tmt Diff (SE)		0.0 (1.10)	--	--
			95% CI (Tmt Diff)		(-2.1, 2.2)	--	--
			p-value[a]		0.974	--	--

Note: Baseline was the last measurement on or before the date of first dose of study medication. LOCF Endpoint was the last post-Baseline measurement through the Week 6 visit day if entering the extension study or within 7 days after treatment discontinuation if not entering the extension study. At post-Baseline visits and LOCF Endpoint, observed values were based on those subjects with both a Baseline and post-Baseline measurement.

Note: At Baseline, p-values[1] versus placebo, LS means, and CIs are from an ANOVA with treatment and pooled center as fixed factors. At change from Baseline, within-group p-values[2] are from a one-sample *t* test of the LS mean; p-values[3] versus placebo, p-value[a] comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and Baseline value as a covariate.

Note: Within-group effect size is the absolute value of the mean divided by the SD. Between-group effect size is the absolute value of the LS mean difference from placebo divided by the model estimate of the pooled SD (the SE of the LS Mean difference divided by the square root of the sum of inverse treatment group sizes).

Note: Higher observed MADRS total scores indicate greater severity of depression.

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; max = maximum; min = minimum; SD = standard deviation; SE = standard error; tmt diff = treatment difference.

(Source: Study report p. 100-101; the results were confirmed by this reviewer)

The sponsor's ANCOVA results for the change from baseline in MADRS score were confirmed by the reviewer's own ANCOVA analyses. The results are consistent with the results of the primary MMRM model.

3.2.4.4 Sponsor's Supportive Analysis for Key Secondary Endpoint

Observed Change CGI-BP-S (ANCOVA)

A summary of the observed change from Baseline to Week 6 in CGI-BP-S total score for the ITT population is provided in Table 10 below.

Table 10: Clinical Global Impression Bipolar Version – Severity Scale – Observed and Change from Baseline (ITT population)

		Treatment Group					
		Lurasidone 20-60 mg (N = 161)		Lurasidone 80-120 mg (N = 162)		Placebo (N = 162)	
Visit	Statistic	Observed	Change	Observed	Change	Observed	Change
Baseline	n	161	--	162	--	162	--
	Mean (SD)	4.52 (0.623)	--	4.55 (0.641)	--	4.48 (0.613)	--
	Median	4.00	--	4.00	--	4.00	--
	Min, Max	3, 6	--	4, 6	--	3, 6	--
	LS Mean (SE)	4.58 (0.041)	--	4.59 (0.041)	--	4.53 (0.041)	--
	Tmt Diff (SE)	0.05 (0.057)	--	0.07 (0.057)	--		--
	95% CI (Tmt Diff)	(-0.06, 0.17)	--	(-0.04, 0.18)	--		--
	p-value[1]	0.343	--	0.235	--		--
Week 6	n	125	--	123	--	127	--
	Baseline Mean (SD)	4.50 (0.604)	--	4.54 (0.657)	--	4.44 (0.586)	--
	Mean (SD)	2.68 (1.154)	-1.82 (1.201)	2.74 (1.122)	-1.80 (1.214)	3.21 (1.199)	-1.23 (1.170)
	Within-group Effect Size	--	1.51		1.48		1.05
	Median	3.00	-2.00	3.00	-2.00	3.00	-1.00
	Min, Max	1, 6	-4, 1	1, 6	-5, 1	1, 6	-4, 1
	LS Mean (SE)	--	-1.88 (0.100)	--	-1.80 (0.102)	--	-1.32 (0.100)
	95% CI (LS Mean)	--	(-2.08, -1.68)	--	(-2.00, -1.60)	--	(-1.51, -1.12)
	p-value[2]	--	<0.001	--	<0.001	--	<0.001
	Tmt Diff (SE)	--	-0.56 (0.137)	--	-0.48 (0.138)	--	--
	95% CI (Tmt Diff)	--	(-0.83, -0.29)	--	(-0.75, -0.21)	--	--
	Between-group Effect Size	--	0.52	--	0.44	--	--
	p-value[3]	--	<0.001	--	<0.001	--	--

(Source: Study report p. 124; the results were confirmed by this reviewer)

LOCF Endpoint CGI-BP-S

Table 11: Clinical Global Impression Bipolar Version – Severity Scale – LOCF Change from Baseline (ITT population)

		Treatment Group					
		Lurasidone 20-60 mg (N = 161)		Lurasidone 80-120 mg (N = 162)		Placebo (N = 162)	
Visit	Statistic	Observed	Change	Observed	Change	Observed	Change
LOCF Endpoint	n	161	--	162	--	162	--
	Baseline Mean (SD)	4.52 (0.623)	--	4.55 (0.641)	--	4.48 (0.613)	--
	Mean (SD)	2.88 (1.274)	-1.65 (1.301)	2.96 (1.215)	-1.59 (1.274)	3.53 (1.281)	-0.95 (1.205)
	Within-group Effect Size	--	1.27	--	1.25	--	0.79
	Median	3.00	-2.00	3.00	-2.00	4.00	-1.00
	Min, Max	1, 6	-4, 1	1, 6	-5, 1	1, 7	-4, 2
	LS Mean (SE)	--	-1.66 (0.096)	--	-1.55 (0.094)	--	-0.98 (0.095)
	95% CI (LS Mean)	--	(-1.84, -1.47)	--	(-1.73, -1.36)	--	(-1.17, -0.79)
	p-value[2]	--	<0.001	--	<0.001	--	<0.001
	Tmt Diff (SE)	--	-0.68 (0.132)	--	-0.57 (0.132)	--	--
	95% CI (Tmt Diff)	--	(-0.93, -0.42)	--	(-0.83, -0.31)	--	--
	Between-group Effect Size	--	0.57	--	0.48	--	--
	p-value[3]	--	<0.001	--	<0.001	--	--
Tests of Dose-Response at Week 6:							
Linear Trend Test of 0, 20-60, 80-120 mg			p-value[a]		<0.001	--	--
Lurasidone 80-120 mg versus 20-60 mg			Tmt Diff (SE)		0.08 (0.137)	--	--
			95% CI (Tmt Diff)		(-0.19, 0.35)	--	--
			p-value[a]		0.547	--	--
Tests of Dose-Response at LOCF Endpoint:							
Linear Trend Test of 0, 20-60, 80-120 mg			p-value[a]		<0.001	--	--
Lurasidone 80-120 mg versus 20-60 mg			Tmt Diff (SE)		0.11 (0.132)	--	--
			95% CI (Tmt Diff)		(-0.15, 0.37)	--	--
			p-value[a]		0.410	--	--

Note: Baseline was the last measurement on or before the date of first dose of study medication. LOCF endpoint was the last post-Baseline measurement through the Week 6 visit day if entering the extension study or within 7 days after treatment discontinuation if not entering the extension study. At post-Baseline visits and LOCF Endpoint, observed values were based on those subjects with both a Baseline and post-Baseline measurement.

Note: At Baseline, p-values[1] versus placebo, LS means, and CIs are from an ANOVA with treatment and pooled center as fixed factors. At change from Baseline, within-group p-values[2] are from a one-sample *t* test of the LS mean; p-values[3] versus placebo, p-value[a] comparing lurasidone groups, LS means, and CIs are from an ANCOVA with treatment and pooled center as fixed factors and Baseline value as a covariate.

Note: Within-group effect size is the absolute value of the mean divided by the SD. Between-group effect size is the absolute value of the LS mean difference from placebo divided by the model estimate of the pooled SD (the SE of the LS Mean difference divided by the square root of the sum of inverse treatment group sizes).

Note: Higher observed CGI-BP-S total scores indicate greater severity of depression.

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CGI-BP-S Clinical Global Impression Bipolar version – Severity Scale; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error; tmt diff = treatment difference.

(Source: Study report p. 125; the results were confirmed by this reviewer)

The ANCOVA results are consistent with the MMRM results. The results of the observed change as well as the LOCF ANCOVA's for the CGI-BP-S depression score were confirmed by this reviewer's own analyses.

3.2.4.5 Multiplicity Adjustment

The Hommel-based tree-gatekeeping procedure was applied to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple endpoints. Primary and key secondary efficacy adjusted p-values from the MMRM analysis are provided in Table 12.

Table 12: Primary and Key Secondary Efficacy Adjusted p-values - Repeated Measures (ITT population)

Efficacy Measure	Statistic	Treatment Group	
		Lurasidone 20-60 mg (N=161)	Lurasidone 80-120 mg (N=162)
1. MADRS Total Score Change from Baseline at Week 6	Unadjusted p-value	<0.001	<0.001
	Adjusted p-value	<0.001	<0.001
2. CGI-BP-S Depression Score Change from Baseline at Week 6	Unadjusted p-value	<0.001	<0.001
	Adjusted p-value	<0.001	<0.001

(Source: Study report p. 134)

The unadjusted p-values are so small that the adjustment does not impact statistical significance at $\alpha = 0.05$.

3.2.4.6 Sponsor's Sensitivity Analysis

The sponsor conducted a sensitive analysis using a random effects mixture model with two patterns (PPM), completers and dropouts, to support the missing at random assumption underlying the primary and key secondary efficacy MMRM analysis. The sponsor found, that there were small numerical differences between the completers and the dropouts in the model estimates of the intercept and slopes for time, treatment group, and interaction of treatment and time; however, the PPM model for the MADRS total score as well as the PPM model for the CGI-BP-S Depression score showed very similar numerical estimates to the overall models (see Tables 13 and 14 below), indicating the dropout status did not alter the overall results with respect to the treatment comparisons.

Table 13: Sensitivity Analysis – Random Effects Pattern Mixture Model with Two Patterns (Completers and Dropouts) – MADRS (ITT Population)

	Statistic	Intercept	Time	Lurasidone 20-60 mg	Lurasidone 80-120 mg	Time* Lurasidone 20-60 mg	Time* Lurasidone 80-120 mg
Montgomery-Asberg Depression Rating Scale (MADRS)							
REM	Model Estimate (SE)	29.4 (0.43)	-0.3 (0.02)	-0.1 (0.61)	-0.4 (0.61)	-0.1 (0.03)	-0.1 (0.03)
	95% CI	(28.6, 30.2)	(-0.3, -0.2)	(-1.3, 1.1)	(-1.6, 0.8)	(-0.2, -0.1)	(-0.2, -0.1)
	p-value	<0.001**	<0.001**	0.869	0.521	<0.001**	<0.001**
PMM Overall	Model Estimate (SE)	29.3 (0.43)	-0.2 (0.02)	0.0 (0.61)	-0.3 (0.61)	-0.1 (0.03)	-0.1 (0.03)
	95% CI	(28.4,30.1)	(-0.3,-0.2)	(-1.2,1.2)	(-1.5,0.9)	(-0.2,-0.1)	(-0.2,-0.1)
	p-value	<0.001**	<0.001**	0.992	0.613	<0.001**	<0.001**
PMM Completers	Model Estimate (SE)	29.0 (0.48)	-0.3 (0.02)	0.1 (0.68)	-0.3 (0.68)	-0.1 (0.03)	-0.1 (0.03)
	95% CI	(28.0, 29.9)	(-0.3, -0.2)	(-1.3, 1.4)	(-1.7, 1.0)	(-0.2, -0.0)	(-0.2, -0.0)
	p-value	<0.001**	<0.001**	0.921	0.623	0.002**	<0.001**
PMM Dropouts	Model Estimate (SE)	30.3 (0.97)	-0.0 (0.06)	-0.2 (1.34)	-0.2 (1.34)	-0.3 (0.09)	-0.3 (0.09)
	95% CI	(28.4, 32.2)	(-0.2, 0.1)	(-2.8, 2.4)	(-2.8, 2.4)	(-0.5, -0.1)	(-0.4, -0.1)
	p-value	<0.001**	0.455	0.885	0.869	<0.001**	0.002**

* p<=0.05; ** p<=0.01.
Note: REM = Random effects model without dropout pattern; PMM Overall = Overall random effects pattern mixture model using a weighted average of the parameter estimates for each dropout pattern (completers and dropouts);
PMM Completers = Random effects pattern mixture model for completers only;
PMM Dropouts = Random effects pattern mixture model for dropouts only.
Note: Time = Actual day of assessment; 95% CI = 95% confidence interval.

(Source: Study report Table 14.2.3.3)

Table 14: Sensitivity Analysis – Random Effects Pattern Mixture Model with Two Patterns (Completers and Dropouts) – CGI-BP-S Depression Score (ITT Population)

	Statistic	Intercept	Time	Lurasidone 20-60 mg	Lurasidone 80-120 mg	Time* Lurasidone 20-60 mg	Time* Lurasidone 80-120 mg
Clinical Global Impressions Scale - Bipolar Version - Severity of Illness (CGI-BP-S) Depression Score							
REM	Model Estimate (SE)	4.47 (0.050)	-0.03 (0.003)	0.02 (0.071)	0.00 (0.071)	-0.02 (0.004)	-0.02 (0.004)
	95% CI	(4.37, 4.56)	(-0.03, -0.02)	(-0.11, 0.16)	(-0.14, 0.14)	(-0.02, -0.01)	(-0.02, -0.01)
	p-value	<0.001**	<0.001**	0.728	0.985	<0.001**	<0.001**
PMM Overall	Model Estimate (SE)	4.45 (0.051)	-0.02 (0.003)	0.04 (0.072)	0.01 (0.072)	-0.02 (0.004)	-0.02 (0.004)
	95% CI	(4.35,4.55)	(-0.03,-0.02)	(-0.10,0.18)	(-0.13,0.15)	(-0.03,-0.01)	(-0.03,-0.01)
	p-value	<0.001**	<0.001**	0.554	0.873	<0.001**	<0.001**
PMM Completers	Model Estimate (SE)	4.41 (0.056)	-0.03 (0.003)	0.08 (0.080)	0.04 (0.080)	-0.01 (0.004)	-0.01 (0.004)
	95% CI	(4.30, 4.52)	(-0.04, -0.02)	(-0.07, 0.24)	(-0.12, 0.19)	(-0.02, -0.01)	(-0.02, -0.01)
	p-value	<0.001**	<0.001**	0.303	0.644	<0.001**	<0.001**
PMM Dropouts	Model Estimate (SE)	4.57 (0.116)	-0.00 (0.008)	-0.09 (0.159)	-0.07 (0.159)	-0.05 (0.011)	-0.03 (0.011)
	95% CI	(4.35, 4.80)	(-0.02, 0.01)	(-0.40, 0.23)	(-0.38, 0.24)	(-0.07, -0.03)	(-0.06, -0.01)
	p-value	<0.001**	0.894	0.587	0.651	<0.001**	0.001**

* p<=0.05; ** p<=0.01.
Note: REM = Random effects model without dropout pattern; PMM Overall = Overall random effects pattern mixture model using a weighted average of the parameter estimates for each dropout pattern (completers and dropouts);
PMM Completers = Random effects pattern mixture model for completers only;
PMM Dropouts = Random effects pattern mixture model for dropouts only.
Note: Time = Actual day of assessment; 95% CI = 95% confidence interval.

(Source: Study report Table 14.2.3.3)

The sponsor states that the results of the second sensitivity analysis (placebo-based multiple imputation) were in line with the MMRM results for the primary and key secondary efficacy variables. The sponsor concluded and this reviewer agrees that the MMRM results are robust

(see study report p. 134-135). Results for the placebo-based multiple imputation models for MADRS and CGI-BP-S are displayed in Tables 15 and 16.

Table 15: Sensitivity Analysis – Pattern Mixture Model with Placebo-based Multiple Imputation for Comparison with the Primary Analysis for MADRS Score at Week 6 (ITT population)

	Statistic	Lurasidone 20-60 mg	Lurasidone 80-120 mg	Placebo
Montgomery-Asberg Depression Rating Scale (MADRS)				
PMM with Placebo-based Multiple Imputation Result at Week 6	LS Mean (SE)	-15.3 (0.85)	-15.2 (0.84)	-11.6 (0.87)
	95% CI	(-17.0, -13.6)	(-16.9, -13.6)	(-13.3, -9.9)
	Difference from Placebo			
	LS Mean Difference (SE)	-3.7 (1.17)	-3.6 (1.17)	
	LS Mean Difference 95% CI	(-6.0, -1.4)	(-5.9, -1.3)	
	p-value	0.002**	0.002**	
MMRM Result at Week 6	LS Mean (SE)	-15.4 (0.83)	-15.4 (0.83)	-10.7 (0.83)
	95% CI	(-17.0, -13.7)	(-17.0, -13.7)	(-12.4, -9.1)
	Difference from Placebo			
	LS Mean Difference (SE)	-4.6 (1.17)	-4.6 (1.17)	
	LS Mean Difference 95% CI	(-6.9, -2.3)	(-6.9, -2.3)	
	p-value	<0.001**	<0.001**	

* p<=0.05; ** p<=0.01.
Note: PMM with placebo-based multiple imputation = Pattern mixture model with placebo-based multiple imputation with 1000 imputations using a monotone regression imputation method.
Note: MMRM = mixed model for repeated measures, where estimates, standard errors (SE), confidence intervals (CI), least squares mean difference from placebo estimates, and p-values are based on a repeated measures linear regression model of the change from baseline score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

(Source: Study report Table 14.2.3.4)

Table 16: Sensitivity Analysis – Pattern Mixture Model with Placebo-based Multiple Imputation for Comparison with the Primary Analysis for CGI-BP-S at Week 6 (ITT population)

	Statistic	Lurasidone 20-60 mg	Lurasidone 80-120 mg	Placebo
Clinical Global Impressions Scale - Bipolar Version - Severity of Illness (CGI-BP-S) Depression Score				
PMM with Placebo-based Multiple Imputation Result at Week 6	LS Mean (SE)	-1.80 (0.107)	-1.70 (0.106)	-1.24 (0.108)
	95% CI	(-2.01, -1.59)	(-1.90, -1.49)	(-1.45, -1.03)
	Difference from Placebo			
	LS Mean Difference (SE)	-0.55 (0.148)	-0.45 (0.148)	
	LS Mean Difference 95% CI	(-0.85, -0.26)	(-0.74, -0.16)	
	p-value	<0.001**	0.002**	
MMRM Result at Week 6	LS Mean (SE)	-1.83 (0.102)	-1.71 (0.101)	-1.14 (0.102)
	95% CI	(-2.03, -1.63)	(-1.91, -1.51)	(-1.34, -0.94)
	Difference from Placebo			
	LS Mean Difference (SE)	-0.69 (0.143)	-0.57 (0.143)	
	LS Mean Difference 95% CI	(-0.97, -0.41)	(-0.85, -0.29)	
	p-value	<0.001**	<0.001**	

* p<=0.05; ** p<=0.01.
Note: PMM with placebo-based multiple imputation = Pattern mixture model with placebo-based multiple imputation with 1000 imputations using a monotone regression imputation method.
Note: MMRM = mixed model for repeated measures, where estimates, standard errors (SE), confidence intervals (CI), least squares mean difference from placebo estimates, and p-values are based on a repeated measures linear regression model of the change from baseline score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

(Source: Study report Table 14.2.3.4)

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for the assessment of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

"Subgroup analyses were conducted on change from Baseline results for MADRS total score and CGI-BP-S depression score at LOCF Endpoint to examine the effects of geographic region, gender, race (e.g., White, Black, Asian, and Other), ethnicity (Hispanic and Non-Hispanic), age (categorized as "<55" and "≥55"), and bipolar I diagnosis subtype (rapid cycling and non-rapid cycling). Geographic regions included North America (USA), Europe (Czech Republic, France, Germany, Poland, Romania, Russia, and Ukraine), Africa (S. Africa), and Asia (India). Separate ANCOVA models including independent terms for treatment, pooled center, Baseline score, subgroup, and treatment-by-subgroup interaction were performed for each set of subgroups. For the by-geographic region analyses, pooled center was nested within region. All subgroup analyses were based on the ITT population" (Study report p. 67).

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender

The analysis of change from Baseline to LOCF Endpoint in MADRS total and CGI-BP-S score (LS mean ± SE) by gender revealed that within treatment groups, the decrease in MADRS total score was similar for males and females (see Tables 17 and 18 below).

Table 17: MADRS Total Score Change by Gender

Gender (n)	MADRS total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
Males (209)	-9.3 ± 1.18	-14.5 ± 1.23	-12.4 ± 1.29
	75	70	64
Females (276)	-9.6 ± 1.11	-13.5 ± 1.07	-14.9 ± 1.04
	87	91	98

(Source: Study report p. 107-108)

There was no treatment by gender interaction (p = 0.292) according to the ANCOVA model (study report p. 108).

Table 18: CGI-BP-S Total Score Change by Gender

Gender (n)	CGI-BP-S total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
Males (209)	-1.03 ± 0.14	-1.67 ± 0.15	-1.38 ± 0.16
	75	70	64
Females (276)	-0.94 ± 0.13	-1.64 ± 0.13	-1.66 ± 0.13
	87	91	98

(Source: Study report p. 132)

4.1.2 Race

Table 19: MADRS Total Score Change by Race

Race (n)	MADRS total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
White (320)	-11.3 ± 2.00 107	-15.9 ± 1.99 107	-16.0 ± 2.00 106
Black or African American (67)	-13.7 ± 3.03 21	-19.3 ± 2.93 21	-15.8 ± 2.86 25
Asian (74)	-2.0 ± 8.72 28	-1.3 ± 9.11 23	-3.0 ± 9.11 23
Other (24)	-14.6 ± 4.70 6	-15.5 ± 3.80 10	-17.1 ± 4.25 8

(Source: Study report p. 108)

The efficacy picture appears to be different for Asian participants compared to all other races considered by the sponsor regardless of treatment assignment. The mean decrease in MADRS total score is in the low one digit range (with a large standard error though) whereas the mean decrease for the other races is in the two digit range. However, according to the ANCOVA model, there is no treatment by race interaction (p = 0.889).

Table 20: CGI-BP-S Total Score Change by Race

Race (n)	CGI-BP-S total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
White (320)	-1.14 ± 0.24 107	-1.83 ± 0.24 107	-1.77 ± 0.24 106
Black or African American (67)	-1.26 ± 0.36 21	-2.04 ± 0.35 21	-1.39 ± 0.34 25
Asian (74)	-0.06 ± 1.05 28	-0.65 ± 1.09 23	-0.75 ± 1.09 23
Other (24)	-1.29 ± 0.56 6	-1.62 ± 0.46 10	-1.69 ± 0.51 8

(Source: Study report p. 133)

The inconsistency with respect to Asian (Indian) patients is also seen when considering the CGI-BP-S score. Again, a smaller decrease in the scores is observed compared to the other races regardless of treatment.

4.1.3 Age

Table 21: MADRS Total Score Change by Age

Age (n)	MADRS total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
< 55 years (402)	-10.2 ± 0.88	-13.9 ± 0.88	-14.0 ± 0.89
	135	135	132
≥ 55 years (83)	-5.8 ± 1.98	-14.1 ± 1.99	-13.4 ± 1.94
	27	26	30

(Source: Study report p. 108)

There was no treatment by age interaction (p = 0.262) according to the Ancova model.

Table 22: CGI-BP-S Total Score Change by Age (threshold 55 years)

Age (n)	CGI-BP-S total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
< 55 years (402)	-1.03 ± 0.11	-1.68 ± 0.11	-1.56 ± 0.11
	135	135	132
≥ 55 years (83)	-0.72 ± 0.24	-1.55 ± 0.24	-1.51 ± 0.23
	27	26	30

(Source: Study report p. 133)

The results are fairly consistent across age groups. The decreases in MADRS as well as CGI-BP-S total scores are somewhat smaller for the Placebo patients 55 years of age or older.

Table 23: MADRS Total Score Change by Age (threshold 65 years)

Age (n)	MADRS total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
< 65 years (476)	-9.4 ± 0.81	-14.0 ± 0.81	-13.8 ± 0.79
	159	158	159
≥ 65 years (9)	-11.2 ± 6.01	-9.1 ± 5.94	-19.9 ± 5.91
	3	3	3

(Source: computed by reviewer)

This reviewer divided the ITT population in two different age groups: one with subjects less than 65 and the other one with subjects 65 years of age or older. The results are shown in table 23. Unfortunately, there are only 9 subjects in the 65 years of age or older category. This low number does not lend itself to reliable conclusions.

4.1.4 Geographic Region

The ITT population is made up of patients from eight countries with the US providing about 40% of the patients.

Table 24: ITT Population by Country

Country	Frequency	Percent of ITT population
Czech Republic	55	11.3
France	13	2.7
India	73	15.1
Romania	15	3.1
Russia	31	6.4
South Africa	54	11.1
Ukraine	49	10.1
USA	195	40.2

(Source: computed by reviewer)

MADRS by geographic region: MMRM Analysis

A subgroup analysis by geographic region (US vs. Non-US) was performed by the sponsor using the primary MMRM model. The results are given in Table 25. There are two noteworthy observations:

1) The estimated treatment difference is smaller in the US compared to the Non-US.

2) The lower dose range shows a greater numeric decrease in the MADRS total score compared to the higher dose range for US patients.

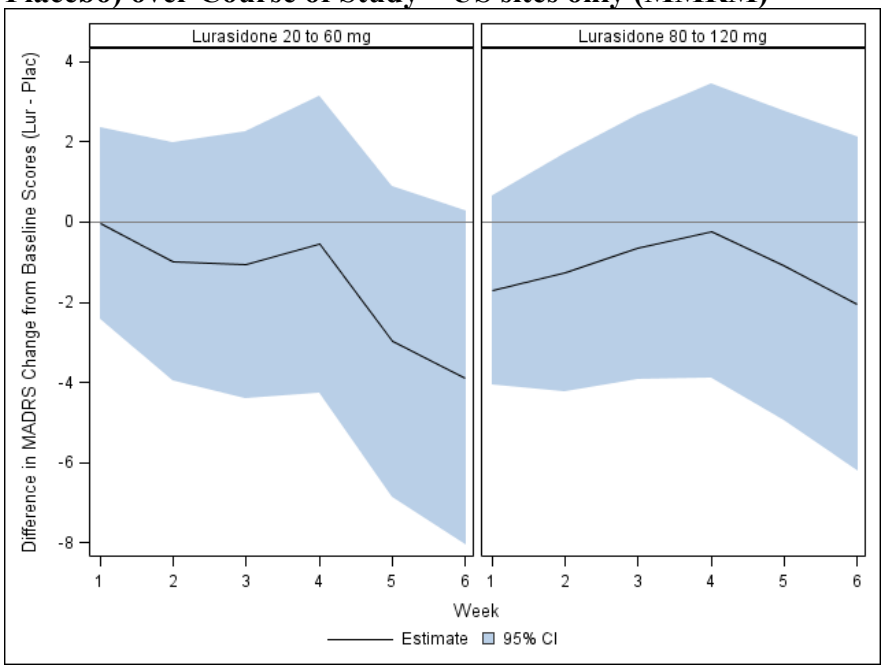
Table 25: MADRS Total Score Change from Baseline at Week 6 by Region (MMRM analysis)

Geographic Region	MADRS total score change from baseline (LS mean ± SE)			Treatment difference to Placebo (LS mean diff ± SE)	
	Placebo	L20-60 mg	L80-120 mg	L20-60 mg	L80-120 mg
North America	-13.2 ± 1.53	-17.1 ± 1.46	-15.3 ± 1.45	-3.9 ± 2.11	-2.1 ± 2.11
Rest of the World	-8.9 ± 0.96	-14.0 ± 1.00	-15.4 ± 0.99	-5.2 ± 1.38	-6.6 ± 1.37

(Source: Study report p. 103)

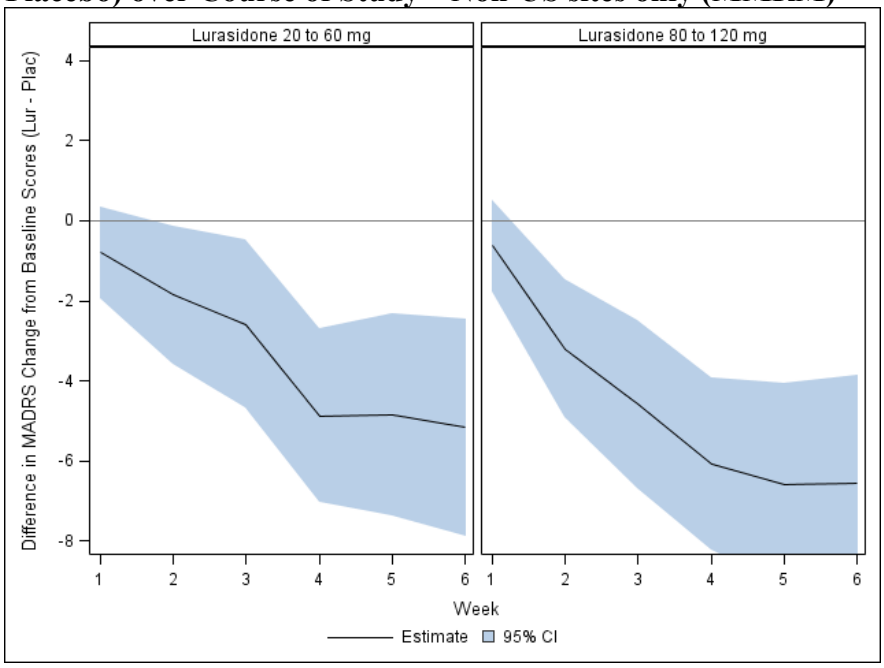
The treatment differences over the course of the six week study as assessed by the MADRS are displayed below - once for the US patients and once for the Non-US patients (Figures 6 and 7).
A relatively flat trajectory is observed until week 4 and followed by an increase in difference during weeks 5 and 6 for the US patients. The opposite appears to be the case for the Non-US patients: the difference between placebo and lurasidone treated patients increases until week 4 but remains flat afterwards.

Figure 6: LS Mean Difference in MADRS Change from Baseline Scores (Lurasidone minus Placebo) over Course of Study – US sites only (MMRM)



(Source: computed by reviewer; Model: MMRM fit only for patients at US sites)

Figure 7: LS Mean Difference in MADRS Change from Baseline Scores (Lurasidone minus Placebo) over Course of Study – Non-US sites only (MMRM)



(Source: computed by reviewer; Model: MMRM fit only for patients at Non-US sites)

Table 26: MADRS Total Score Treatment Difference at Week 6: Active minus Placebo by Region (MMRM Analysis)

Geographic Region	Treatment difference to Placebo (LS mean diff ± SE)	
	L20-60 mg	**L80-120 mg**
North America	-3.9 ± 2.11	-2.1 ± 2.11
Africa	0.4 ± 2.26	-0.8 ± 2.33
Asia	-3.6 ± 3.49	-2.8 ± 3.40
Europe	-7.8 ± 1.82	-10.1 ± 1.82

(Source: Study report p. 103)

When considering the sponsor defined regions (North America, Africa, Asia, and Europe) we see that Europe shows the greatest treatment differences of all four regions (Table 26). Europe is also the only region besides Africa, which provided just 11% of the total ITT patients, where the higher dose range appears to provide a greater efficacy compared to the lower dose range.

CGI-BP-S by geographic region: MMRM Analysis

The following section explores geographic differences (US vs. Non-US, by sponsor defined regions and by country) in the results of the key secondary endpoint CGI-BP-S.

Table 27: CGI-BP-S Total Score Change from Baseline by Region (MMRM analysis)

Geographic Region	CGI-BP-S total score change from baseline (LS mean ± SE)			Treatment difference to Placebo (LS mean diff ± SE)	
	Placebo	**L20-60 mg**	**L80-120 mg**	**L20-60 mg**	**L80-120 mg**
North America	-1.35 ± 0.18	-2.01 ± 0.17	-1.72 ± 0.17	-0.66 ± 0.25	-0.36 ± 0.25
Rest of the World	-0.99 ± 0.12	-1.68 ± 0.13	-1.72 ± 0.13	-0.70 ± 0.18	-0.73 ± 0.18

(Source: Study report p. 128)

The lower dose range appears to offer greater efficacy as assessed by the CGI-BP-S total score for US patients but appears tied with the higher dose range for Non-US patients (Table 27).

Table 28: CGI-BP-S Treatment Difference at Week 6: Active minus Placebo by Region (MMRM Analysis)

Geographic Region	Treatment difference to Placebo (LS mean diff ± SE)	
	L20-60 mg	**L80-120 mg**
North America	-0.66 ± 0.25	-0.36 ± 0.25
Africa	0.01 ± 0.33	-0.00 ± 0.35
Asia	-0.51 ± 0.41	-0.19 ± 0.40
Europe	-0.99 ± 0.23	-1.15 ± 0.23

(Source: Study report p. 128)

The results of the MMRM analysis by region displayed in Table 28 confirm for the CGI-BP-S score what was already observed earlier for the MADRS score: the treatment differences in favor of lurasidone are larger in Europe compared to all other regions.

Supportive Analysis: LOCF Endpoint by geographic region

Table 29: MADRS Total Score Change by Region

Geographic Region (n)	MADRS total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
North America (195)	-11.3 ± 1.32 58	-15.0 ± 1.22 67	-12.8 ± 1.19 70
Africa (54)	-12.3 ± 2.29 18	-10.9 ± 2.25 19	-12.6 ± 2.36 17
Asia (73)	-9.0 ± 1.92 27	-12.4 ± 2.11 23	-14.1 ± 2.04 23
Europe (163)	-6.7 ± 1.32 59	-14.2 ± 1.39 52	-15.6 ± 1.38 52

(Source: Study report p. 107)

The LOCF analysis is consistent with the MMRM results. The difference between treatments is estimated to be greatest in Europe. The ANCOVA model for the MADRS total score change detected a statistically significant treatment by geographic region interaction (p = 0.043).

Table 30: CGI-BP-S Total Score Change by Region

Geographic Region (n)	CGI-BP-S total score change from baseline to LOCF Endpoint LS mean ± SE n		
	Placebo	L20-60 mg	L80-120 mg
North America (195)	-1.20 ± 0.16 58	-1.80 ± 0.15 67	-1.45 ± 0.14 70
Africa (54)	-1.45 ± 0.28 18	-1.43 ± 0.27 19	-1.49 ± 0.28 17
Asia (73)	-0.87 ± 0.23 27	-1.46 ± 0.25 23	-1.57 ± 0.25 23
Europe (163)	-0.65 ± 0.16 52	-1.65 ± 0.17 57	-1.71 ± 0.16 52

(Source: Study report p. 132)

Reviewer's exploratory analysis of US - Non-US differences

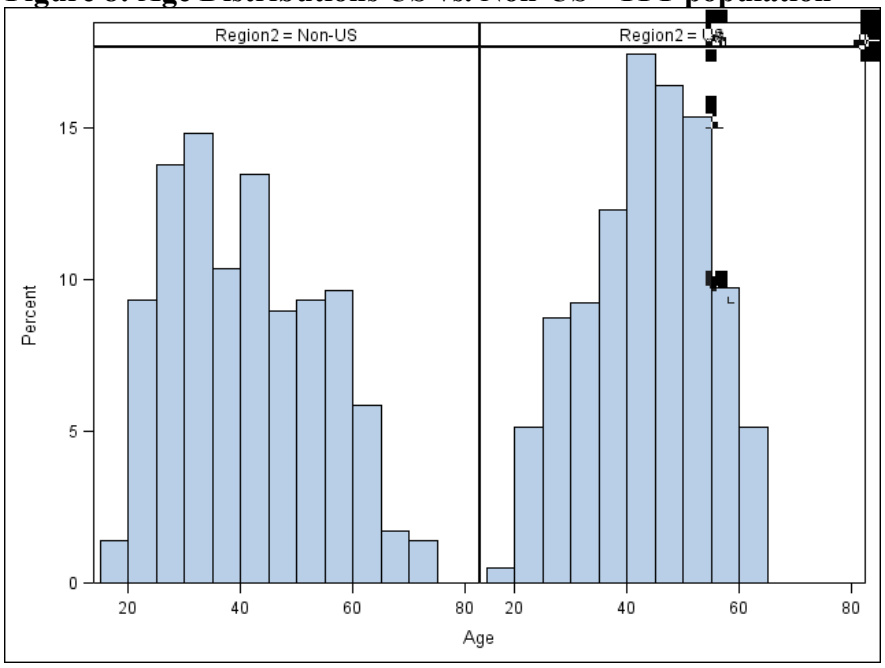
Recall that there are 195 patients enrolled at US sites and 290 at Non-US sites. The following factors could have played a role in producing the observed regional differences:

Gender: US (62.6% female); Non-US (53.1% female)

Age: US (mean 43 years, median 44); Non-US (mean 41 years, median 40)

Weight: US (mean 85 kg, median 85); Non-US (mean 72 kg, median 70)

Figure 8: Age Distributions US vs. Non-US – ITT population



(Source: computed by reviewer)

The US has a higher proportion of participants in their 40th and 50th and a somewhat lower proportion of participants in their 20th, early 30th when compared to the age distribution of the Non-US participants (Figure 8).

Race: 73 (98.7%) Asians are enrolled in Non-US centers (in India). It was already noted that Asians did not see much improvement with respect to efficacy. This could be a potential reason why the overall the results (US vs. Non-US) are not that far apart as in the Adjunctive Therapy Study (D1050235).

An exploratory MMRM analysis for change from baseline in MADRS total score was conducted by this reviewer where the variable "pooled site" was replaced with the binary variable "region" (US, Non-US) and a "region by treatment" term was added (Model 0 in table below). Changes in the p-value of this interaction term when potential explanatory variables are added are viewed as indicative of the value of the added predictor to explain some of the regional heterogeneity. The following variables were added one at a time: Model 1: gender; Model 2: weight; Model 3: age. The results are displayed in Table 31. The treatment by region interaction term is not statistically significant in Model 0. This does not change when adding gender, weight or age. None of those variables themselves are significant. In conclusion, the data did not support this reviewer's candidates for explaining the regional differences in the MADRS change from baseline scores between the US and the Rest of the World.

Table 31: Type 3 test p-values for Exploratory MMRM Models for MADRS Change from Baseline

	Exploratory Model			
Effect	**0**	**1**	**2**	**3**
Age				0.0741
Weight			0.7717	
Visit Number	<0.0001	<0.0001	<0.0001	<0.0001
Region (US vs. Non-US)	<0.0001	<0.0001	<0.0001	<0.0001
Treatment*Region (US vs. Non-US)	0.4786	0.4768	0.4731	0.4307
Gender		0.7577		
Total Score Baseline	<0.0001	<0.0001	<0.0001	<0.0001
Treatment	0.0001	0.0001	0.0001	0.0001
Treatment*Visit Number	0.0421	0.0421	0.0423	0.0421

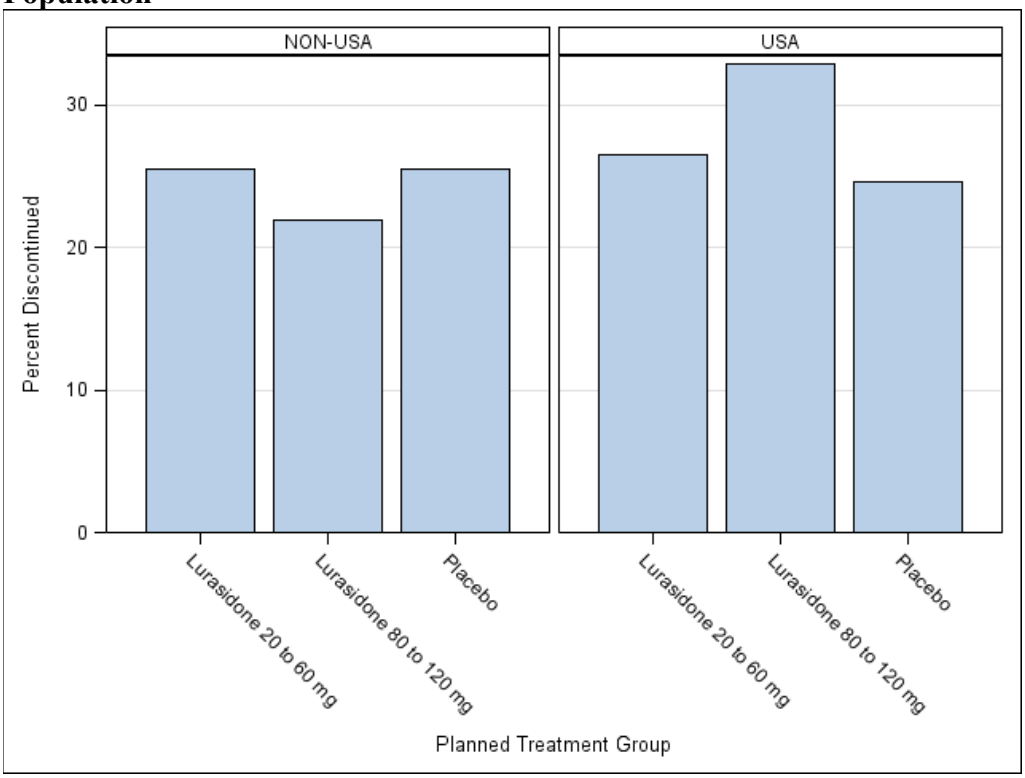
(Source: Computed by reviewer)

The sponsor per FDA request explored potential reasons why the lower dose range of 20-60 mg/day appears numerically more effective than the higher dose range of 80-120 mg/day for US patients. The following factors were explored: baseline demographic and clinical characteristics,

subject disposition, dosage parameters and lurasidone exposure (see response to information request p. 15-20). The only factors identified as having a potential impact are differences in discontinuation rates US (33%) vs. Non-US (22%) in the 80-120 mg/day dose groups and differences in discontinuation rates due to insufficient clinical response in the 20-60 mg/day dose groups (US: 0 vs. Non-US: 12).

The next section expands on the differences in discontinuations between the US and the Non-US patients. Figure 9 shows that the percentage of discontinuations was somewhat lower in the lurasidone 80-120 mg group (21.9%) compared to the lower dose and placebo groups for Non-US patients. The opposite is observed in the US, where the percentage of discontinued patients is the highest in the lurasidone 80-120 mg group (32.9%) compared to the lower dose and placebo groups.

Figure 9: Percent Discontinued Non-US vs. US by Treatment Group – Randomized Population



(Source: Computed by reviewer)

Considering the discontinuation reasons by treatment and within region this reviewer confirms the finding that zero US patients on lurasidone 20-60 mg discontinued due to insufficient clinical

response. This compares to 12 discontinuations for the Non-US patient group in the lower dose group (16.4 % out of all discontinued Non-US patients and 48.0% of discontinued Non-US patients on lower dose). However, there are also 12 discontinuations due to insufficient clinical response in the Non-US placebo group and only 1 in the US placebo group.

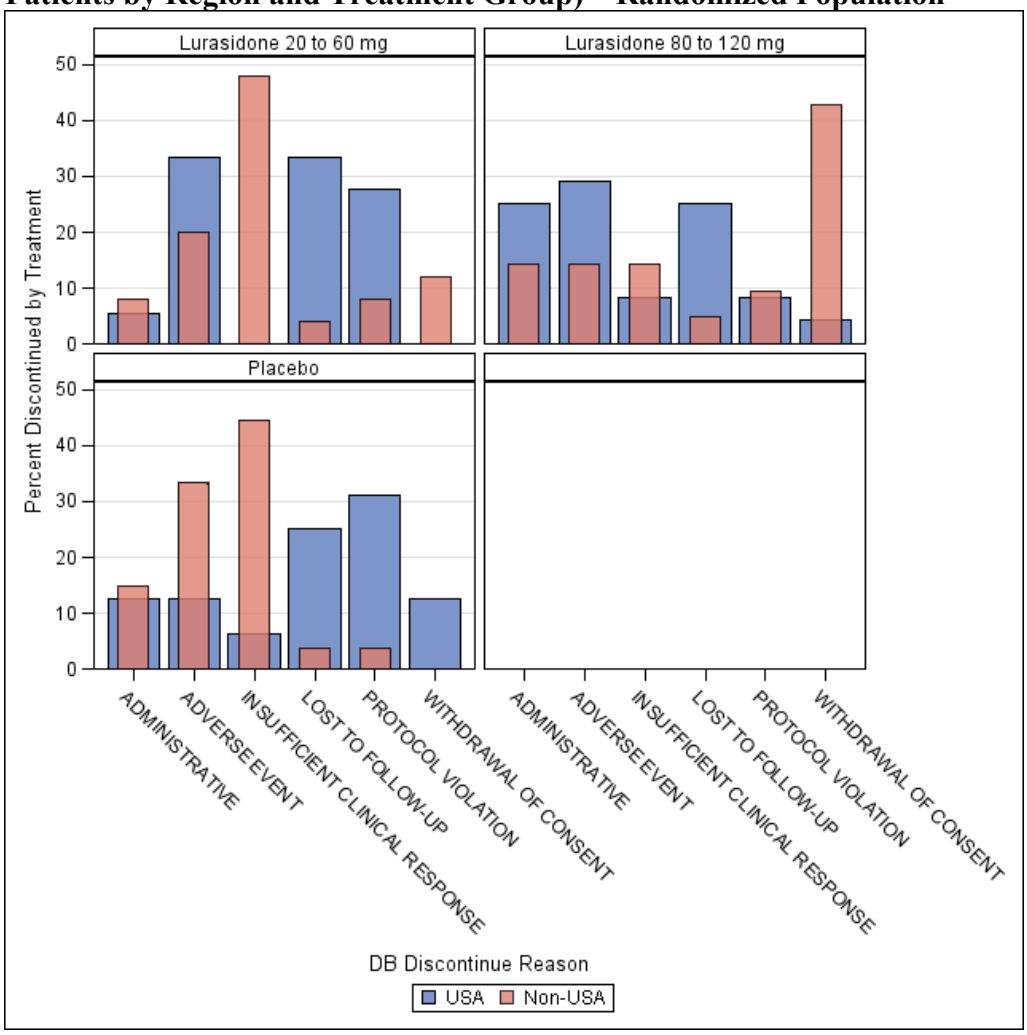
Table 32: Discontinuation Reasons Non-US vs. US – Randomized Population

DB Discontinuation Reason	**US** (206) n_{disc} = 58			**NON-US** (300) n_{disc} = 73		
	Lurasidone 20 - 60 mg n (%)	Lurasidone 80 - 120 mg n (%)	Placebo n (%)	Lurasidone 20 - 60 mg n (%)	Lurasidone 80 - 120 mg n (%)	Placebo n (%)
Administrative	1 (5.6)	6 (25.0)	2 (12.5)	2 (8.0)	3 (14.3)	4 (14.8)
Adverse Event	6 (33.3)	7 (29.2)	2 (12.5)	5 (20.0)	3 (14.3)	9 (33.3)
Insufficient Clinical Response	0 (0.0)	2 (8.3)	1 (6.3)	12 (48.0)	3 (14.3)	12 (44.4)
Lost to Follow-Up	6 (33.3)	6 (25.0)	4 (25.0)	1 (4.0)	1 (4.8)	1 (3.7)
Protocol Violation	5 (27.8)	2 (8.3)	5 (31.3)	2(8.0)	2 (9.5)	1 (3.7)
Withdrawal of Consent	0 (0.0)	1 (4.2)	2 (12.5)	3 (12.0)	9 (42.9)	0 (0.0)
Total	18 (31.0)	24 (41.4)	16 (27.6)	25 (34.3)	21 (28.8)	27 (37.0)

(Source: Computed by reviewer)

The percentages of discontinued patients within a treatment arm nested in region are displayed graphically in Figure 10 for an easier comparison.

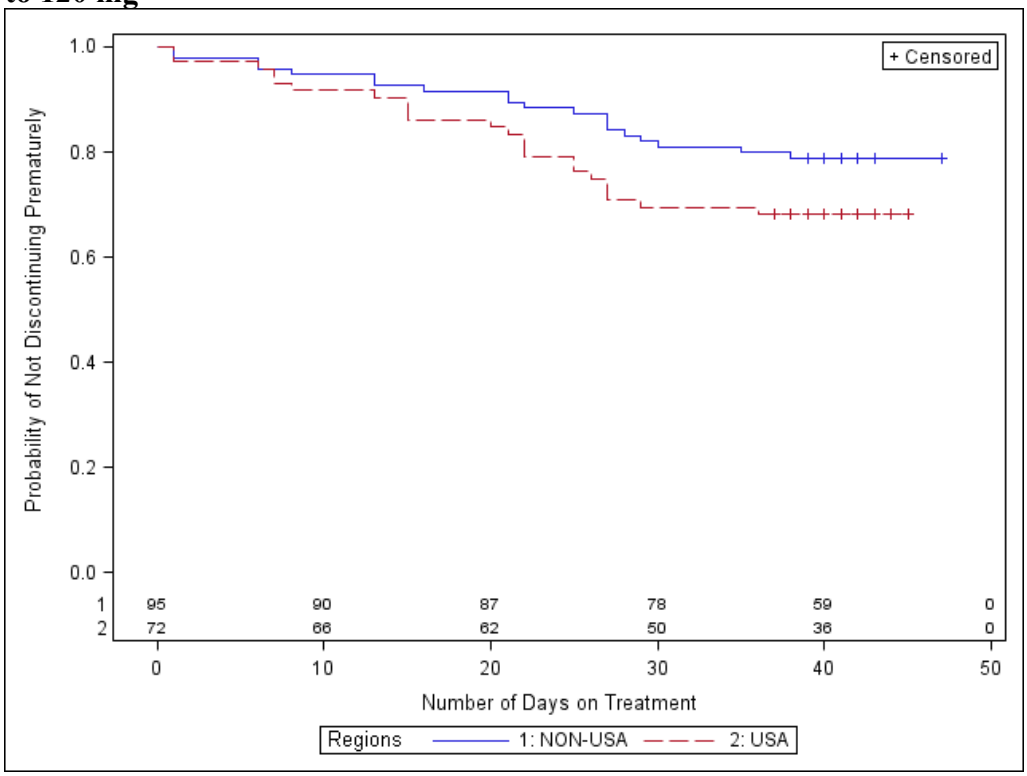
Figure 10: Discontinuation Reasons Non-US vs. US (Percentages out of the Discontinued Patients by Region and Treatment Group) – Randomized Population



(Source: Computed by reviewer)

We have seen already that there is an 11 percentage point difference in the number of discontinuations between US and Non-US patients groups on the higher dose of lurasidone. The Kaplan Meier curves in Figure 11 let us know that this difference manifests itself between weeks 2 and 4 of the DB treatment phase.

Figure 11: Kaplan-Meier Plots for Time to Discontinuation US vs. Non-US – Lurasidone 80 to 120 mg



(Source: Computed by reviewer)

Kaplan-Meier plots for the lurasidone 20-60 mg and the Placebo groups reveal no marked differences between US and Non-US patients with respect to time to discontinuation.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Although there is a trend in favor of lurasidone in US patients the effect for both dose ranges is smaller compared to the Rest of the World. Also, US patients randomized to the lower dose range of 20-60 mg/day experienced a numerically greater effect compared to US patients on the higher dose of 80-120 mg/day. Complete explanations for those findings remain elusive.

5.2 Collective Evidence

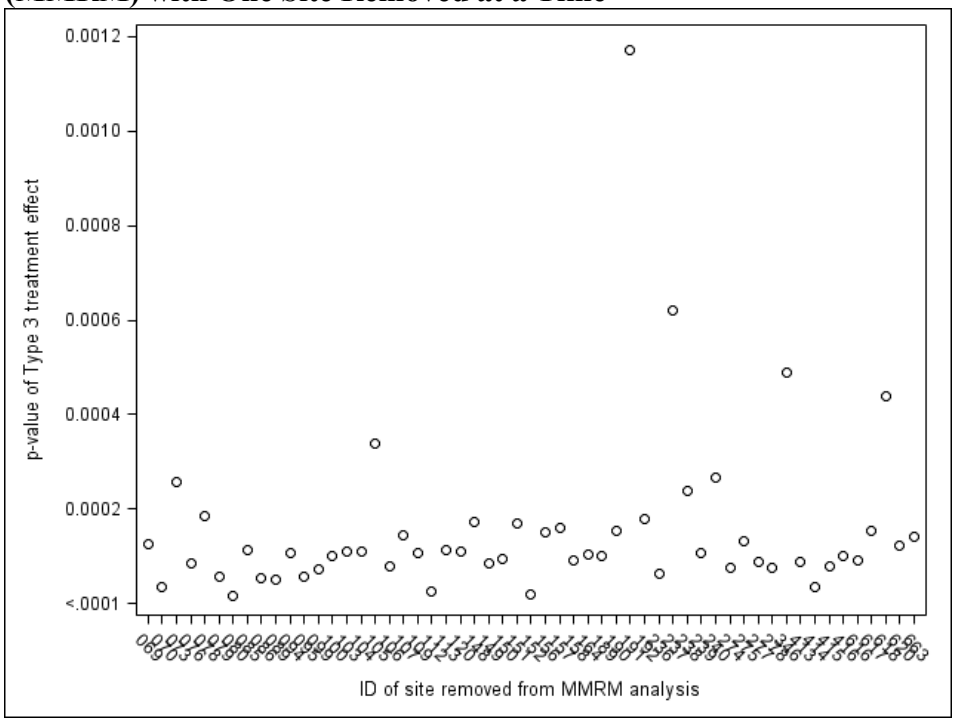
Statistically significant results were obtained for the primary and key secondary outcome measures in Study 236 overall.

5.3 Conclusions and Recommendations

The statistical results provide adequate evidence to support the claim that lurasidone in monotherapy is more efficacious than placebo in treating patients with depressive episodes associated with bipolar I disorder.

6 APPENDICES

Figure A1: Type 3 test p-value of the Treatment Coefficient in the Primary Analysis Model (MMRM) with One Site Removed at a Time



(Source: computed by reviewer)

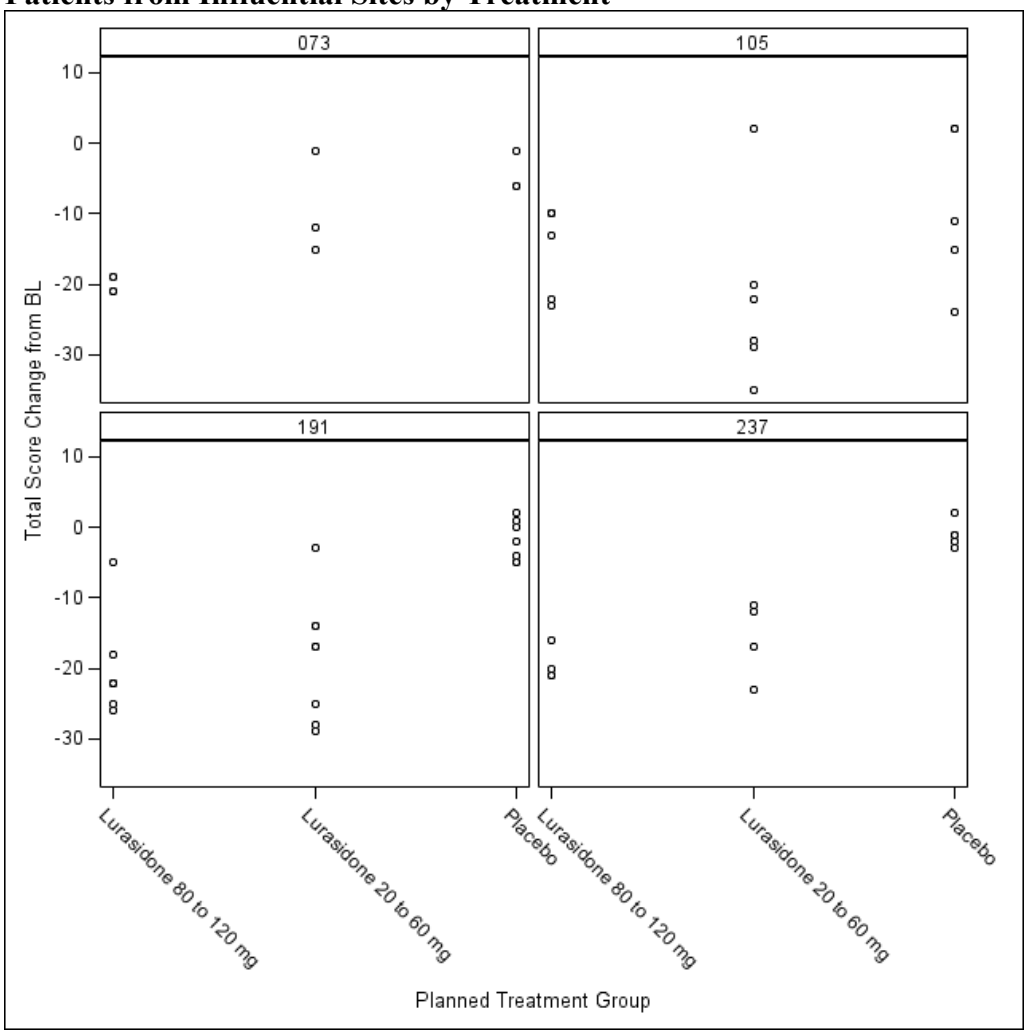
The removal of the Russian site 191 has the strongest impact on the overall significance of the treatment effect coefficient. However, removal of data from a single site from the analysis would not impact the statistical significance of the treatment coefficient.

Table A1. Top 8 Influential Sites on Overall Significance in Descending Order (MMRM for Change from Baseline in MADRS score)

Region	Country	Site	P-value of treatment effect with site removed
Europe	RUSSIA	191	0.0012
Europe	UKRAINE	237	0.0006
Europe	FRANCE	346	0.0005
Europe	CZECH	618	0.0004
North America	USA	105	0.0003
Europe	UKRAINE	240	0.0003
North America	USA	073	0.0003
Europe	UKRAINE	238	0.0002

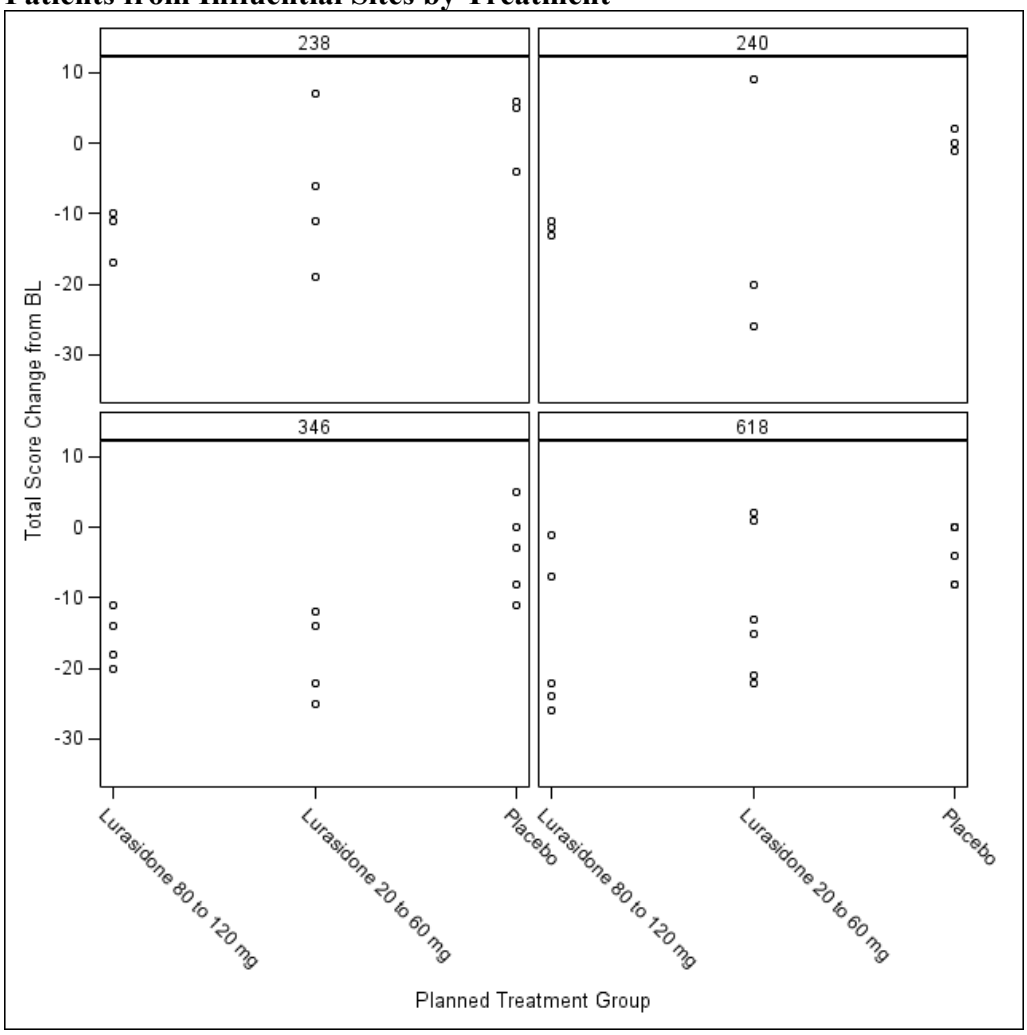
(Source: computed by reviewer)

Figure A2a: MADRS Total Score Change from Baseline to Week 6 or Last Observed for Patients from Influential Sites by Treatment



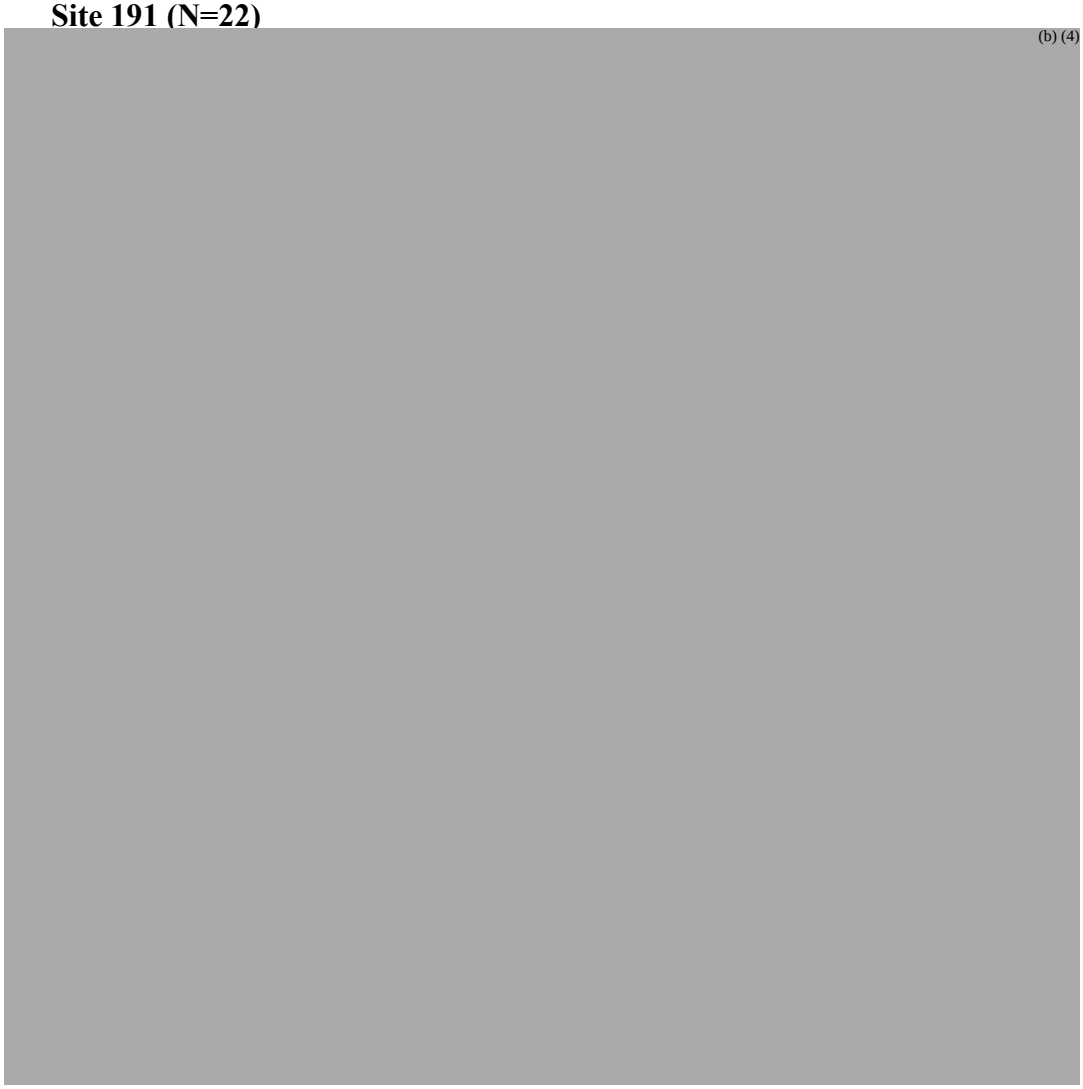
(Source: computed by reviewer)

Figure A2b: MADRS Total Score Change from Baseline to Week 6 or Last Observed for Patients from Influential Sites by Treatment



(Source: computed by reviewer)

Figure A3a: Observed MADRS Total Score over Course of Study by Patient at Russian Site 191 (N=22)



Note the unusually homogeneous trajectories of the MADRS total scores over the course of the study at site 191, especially in the lurasidone 80 to 120 mg group.

Figure A3b

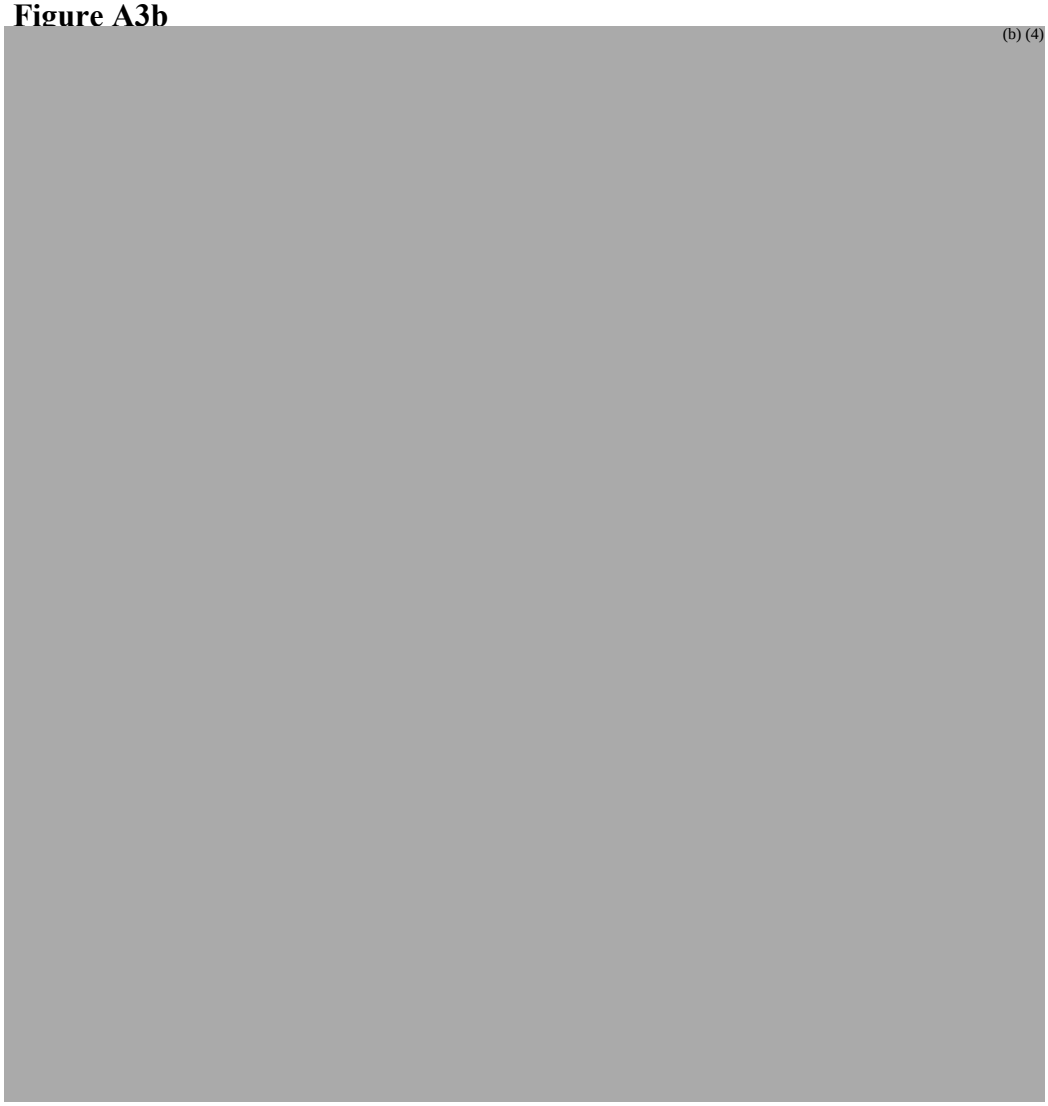


Figure A3c

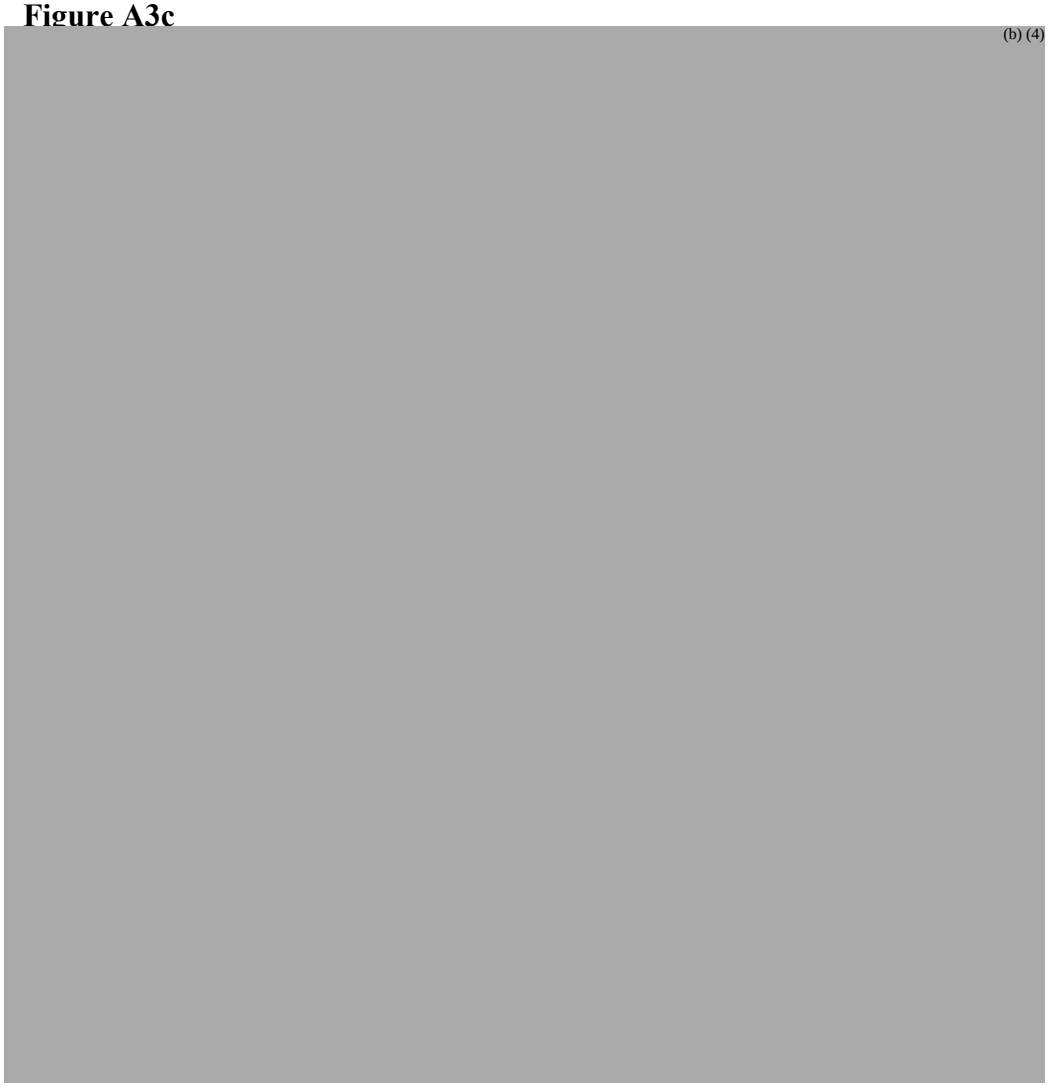


Figure A3d

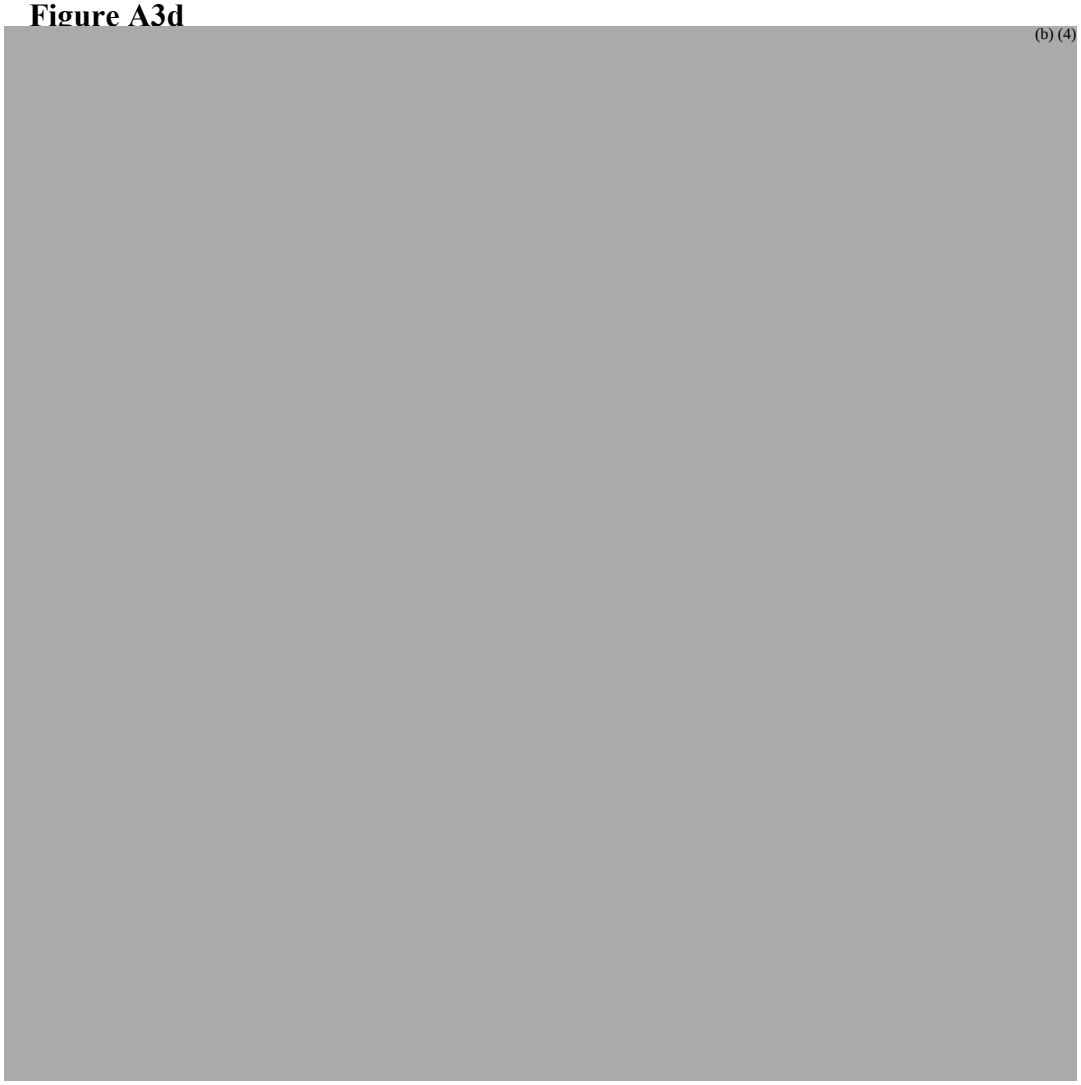
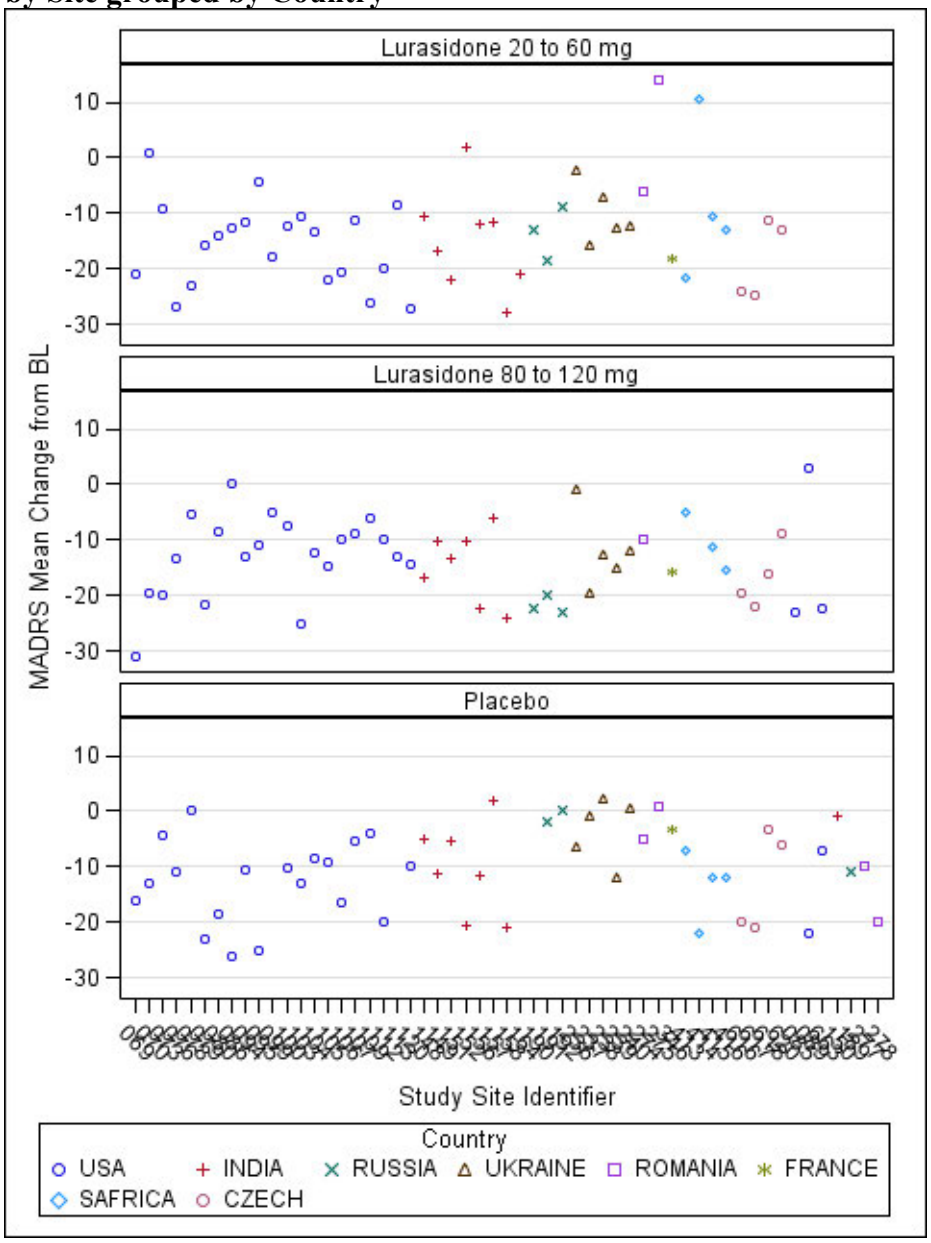


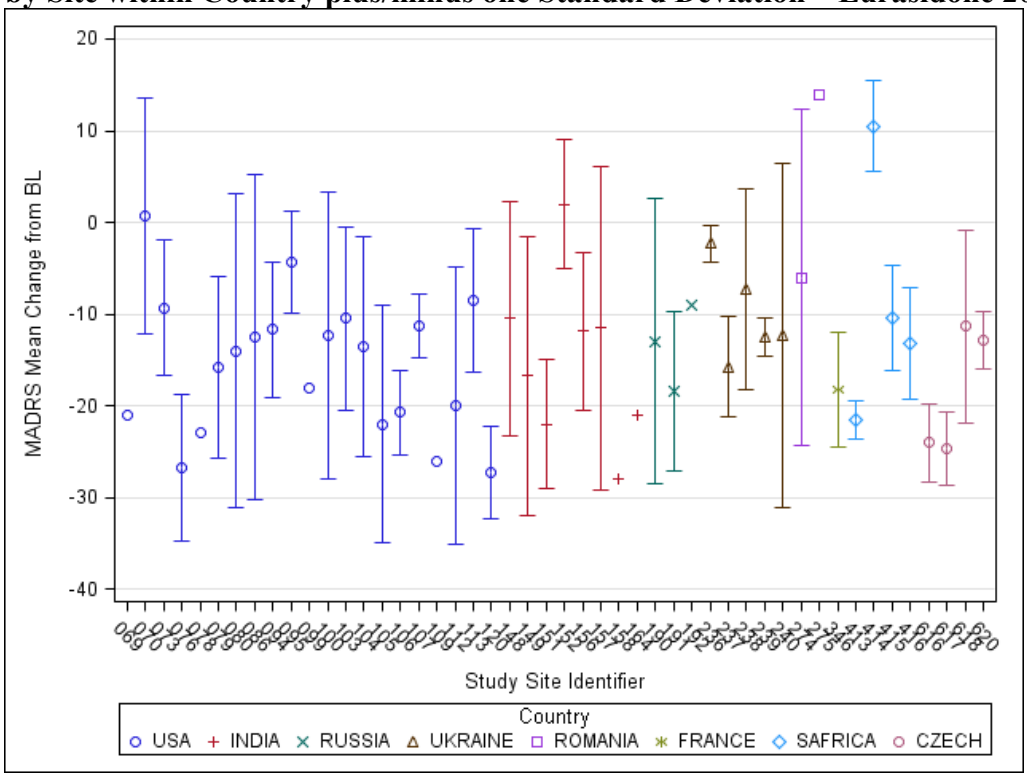
Figure A4: Mean MADRS Total Score Change from Baseline at Week 6 or Last Observed by Site grouped by Country



(Source: computed by reviewer)

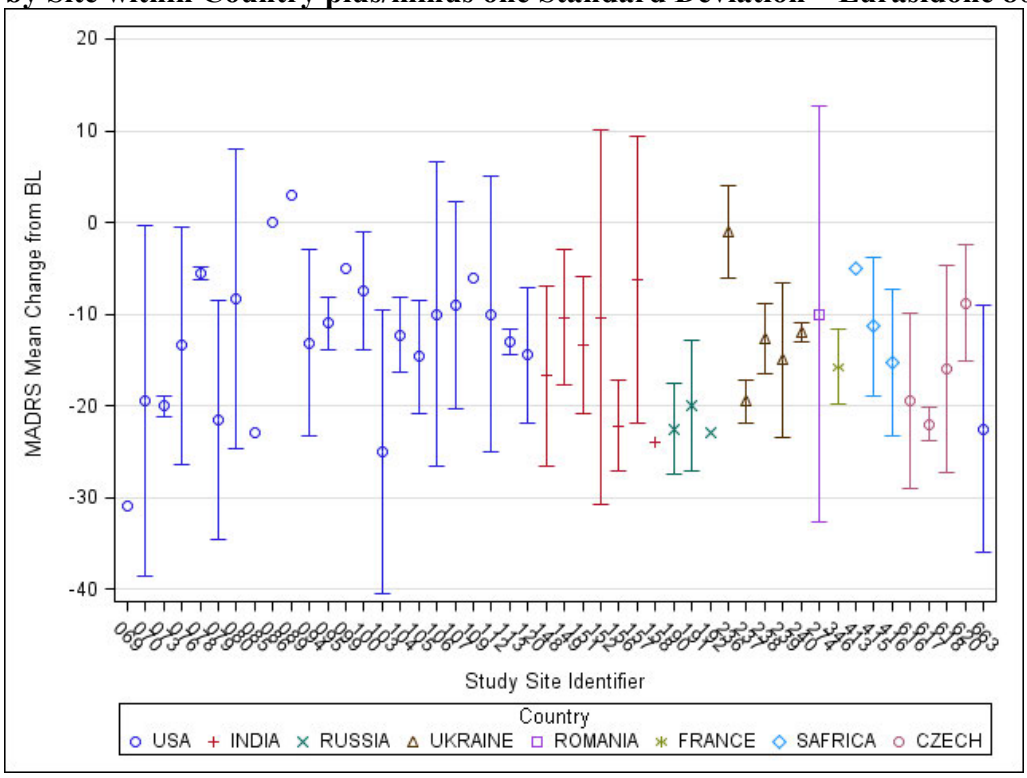
Word of caution: Sample sizes vary across treatment groups per site and between sites (minimum number of subjects for one treatment group within site: 1, maximum 9; mean of 3.3 and median of 3).

Figure A5a: Mean MADRS Total Score Change from Baseline at Week 6 or Last Observed by Site within Country plus/minus one Standard Deviation – Lurasidone 20-60mg patients



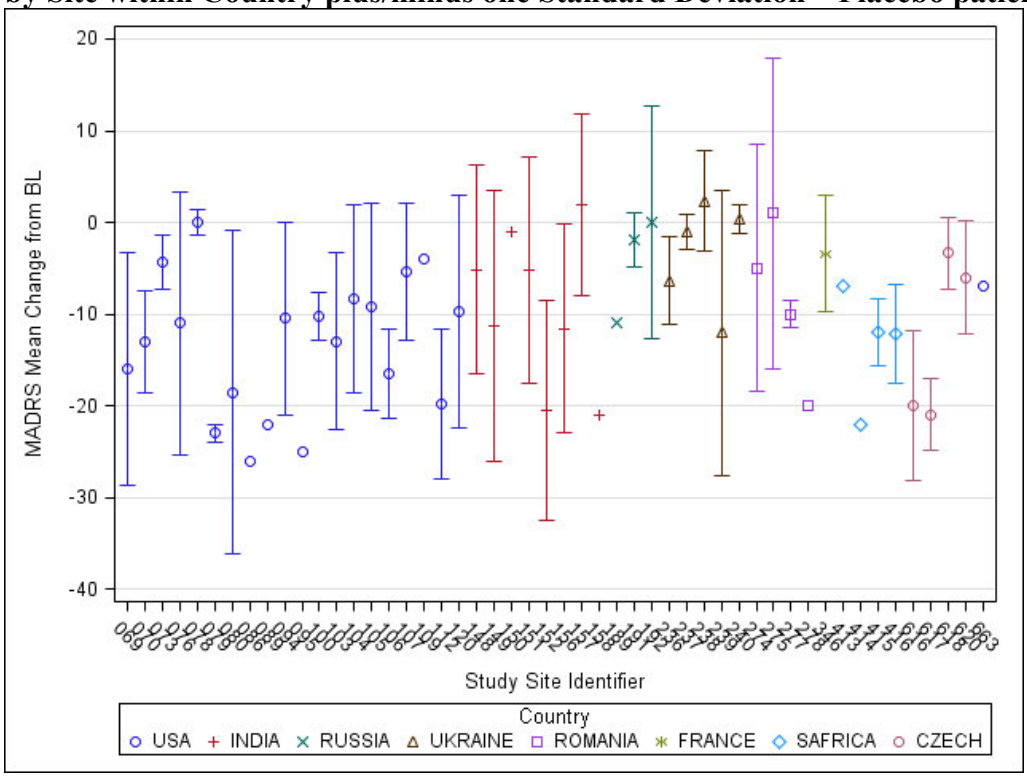
(Source: computed by reviewer)

Figure A5b: Mean MADRS Total Score Change from Baseline at Week 6 or Last Observed by Site within Country plus/minus one Standard Deviation – Lurasidone 80-120mg patients



(Source: computed by reviewer)

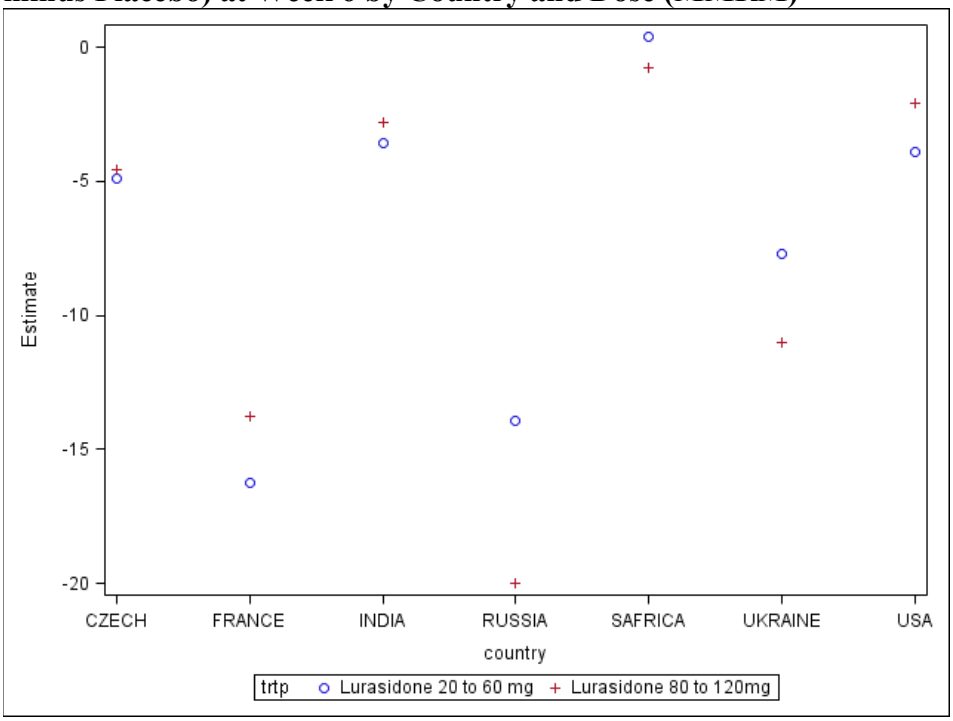
Figure A5c: Mean MADRS Total Score Change from Baseline at Week 6 or Last Observed by Site within Country plus/minus one Standard Deviation – Placebo patients



(Source: computed by reviewer)

This reviewer took the forming of subgroups a step further by the fitting the primary MMRM model separately to each country. Figure A6 displays the differences in the MADRS change from baseline scores between placebo and lurasidone (two dose ranges) at week 6 by country. There is clear heterogeneity in the estimated treatment differences with Russian and French patients exhibiting the greatest differences and South African and US patients the least. Also, there are only three countries (Russia, Ukraine and South Africa) where the higher dose range appears to offer increased efficacy (at least numerically) compared to the lower dose range.

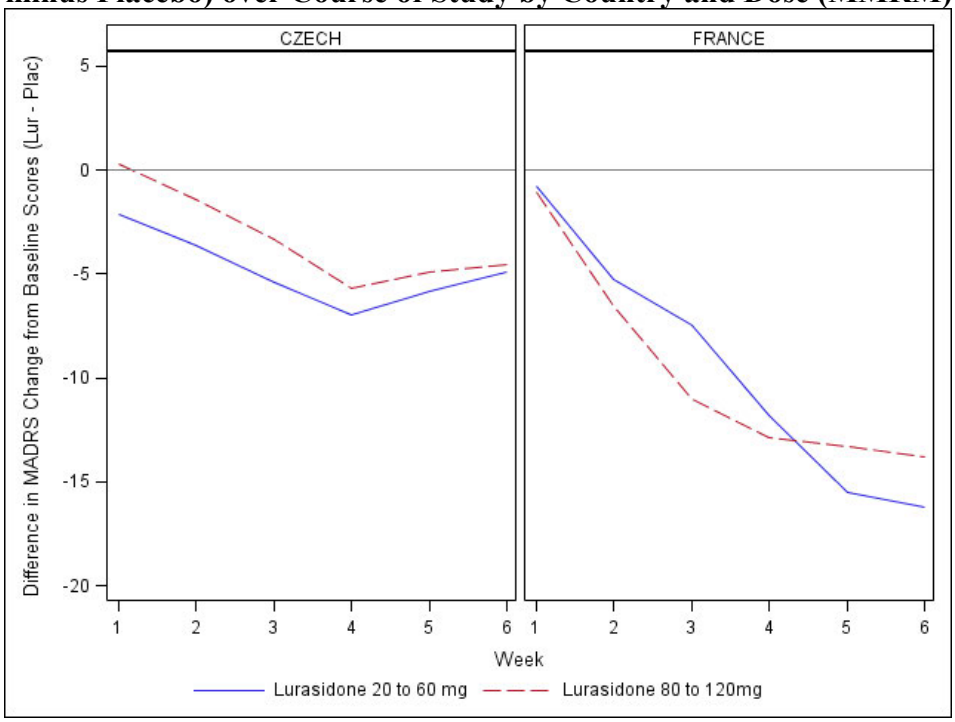
Figure A6: LS Mean Difference in MADRS Change from Baseline Scores (Lurasidone minus Placebo) at Week 6 by Country and Dose (MMRM)

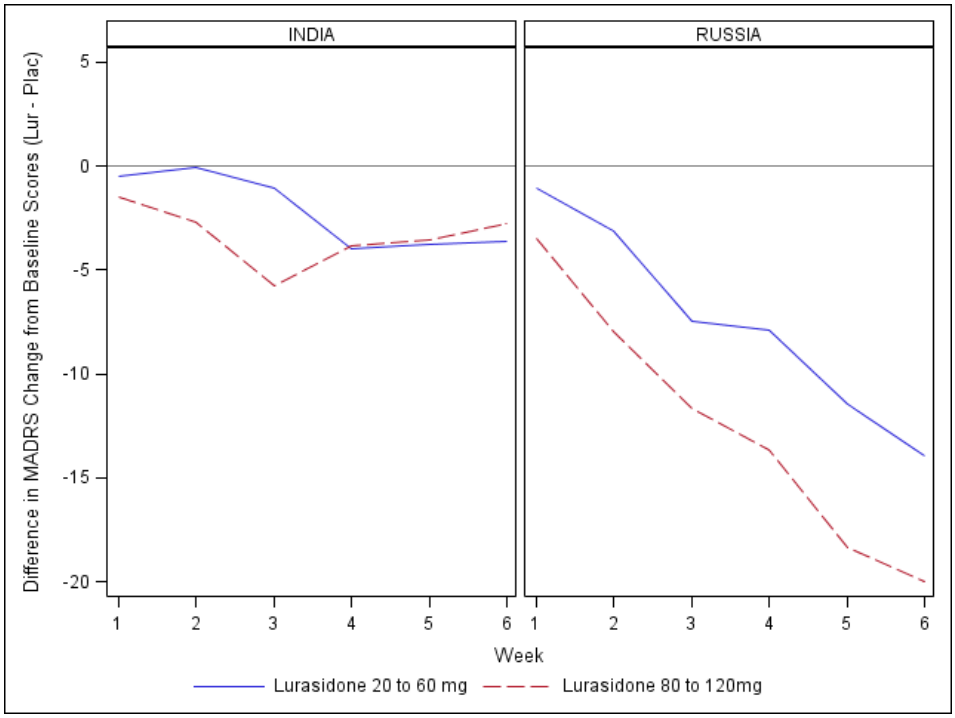


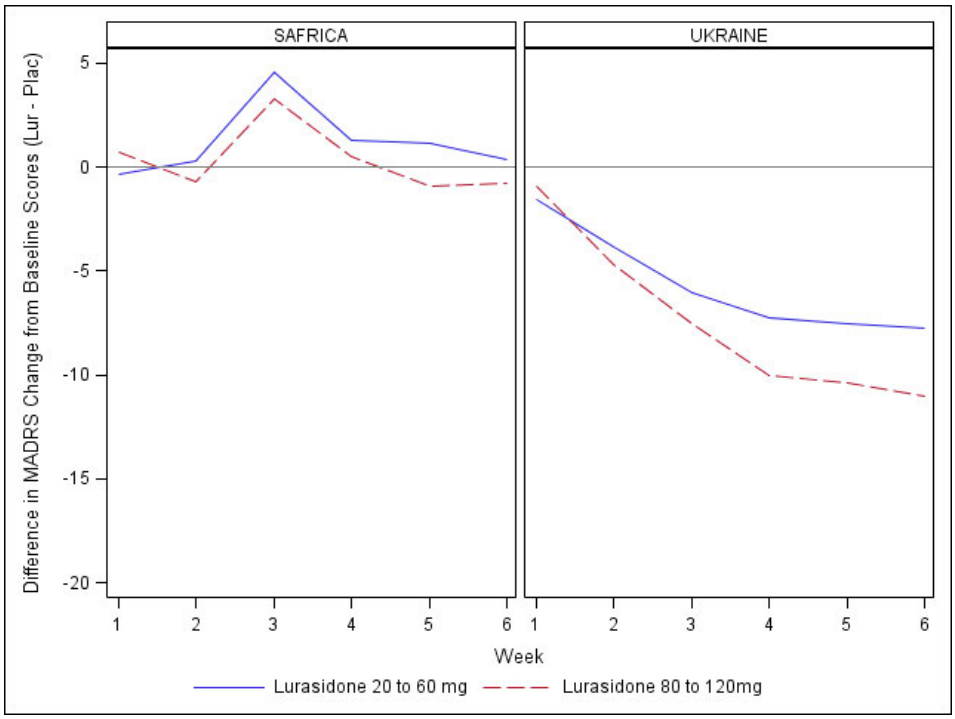
(Source: computed by reviewer; note: primary MMRM model failed for Romanian subjects)

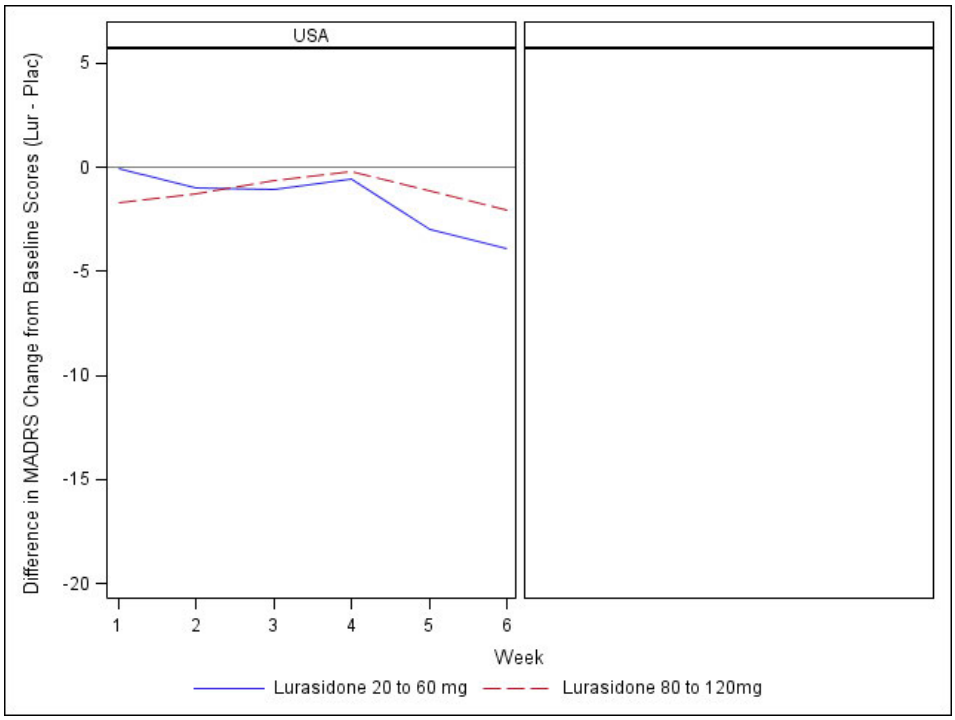
Figure A7 provides the estimated treatment differences (lurasidone minus placebo) in the MADRS total score over the course of the 6-week study by country.

Figure A7: LS Mean Difference in MADRS Change from Baseline Scores (Lurasidone minus Placebo) over Course of Study by Country and Dose (MMRM)





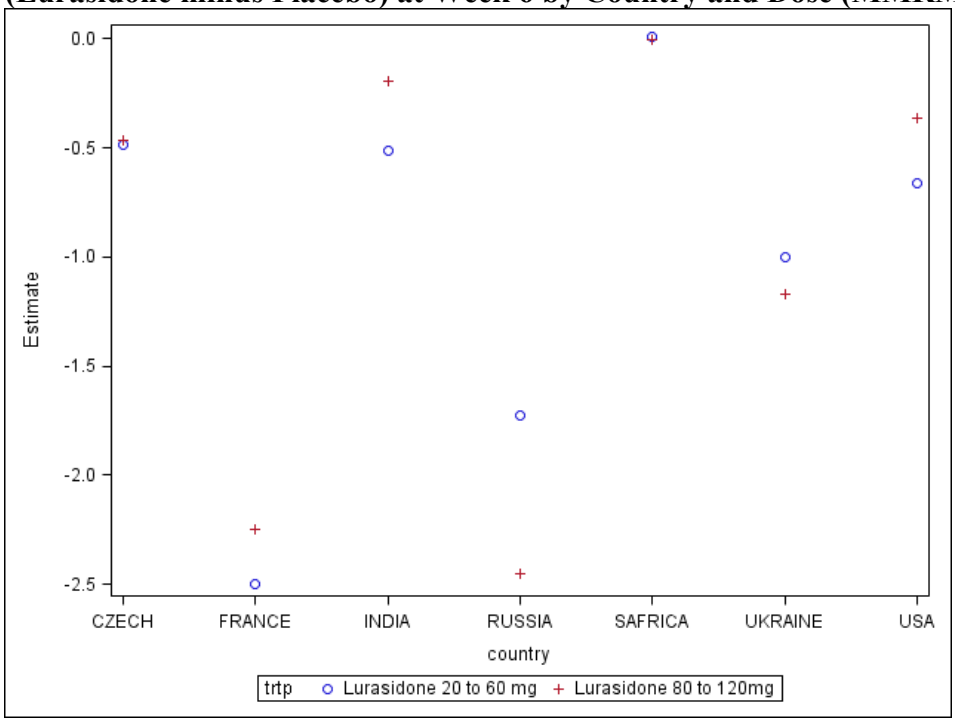




(Source: Computed by reviewer, note: primary MMRM model failed for Romanian subjects)

Figure A8 below displays the results of the MMRM model when analyzing the CGI-BP-S change score at week 6 one country at a time by dose.

Figure A8: LS Mean Difference in CGI-BP-S Total Score Change from Baseline Scores (Lurasidone minus Placebo) at Week 6 by Country and Dose (MMRM)

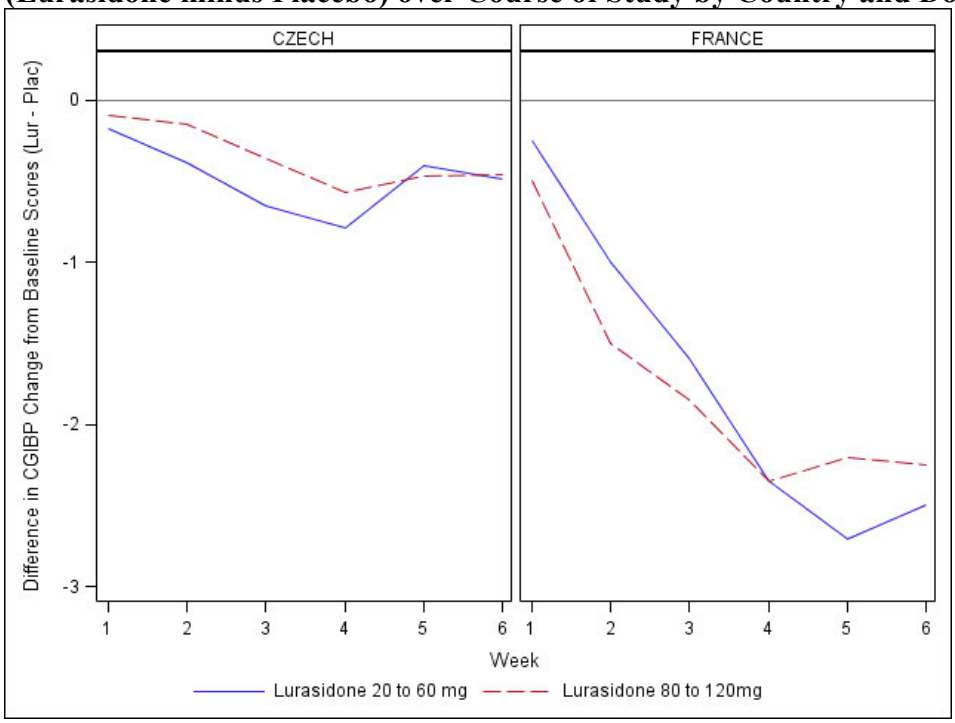


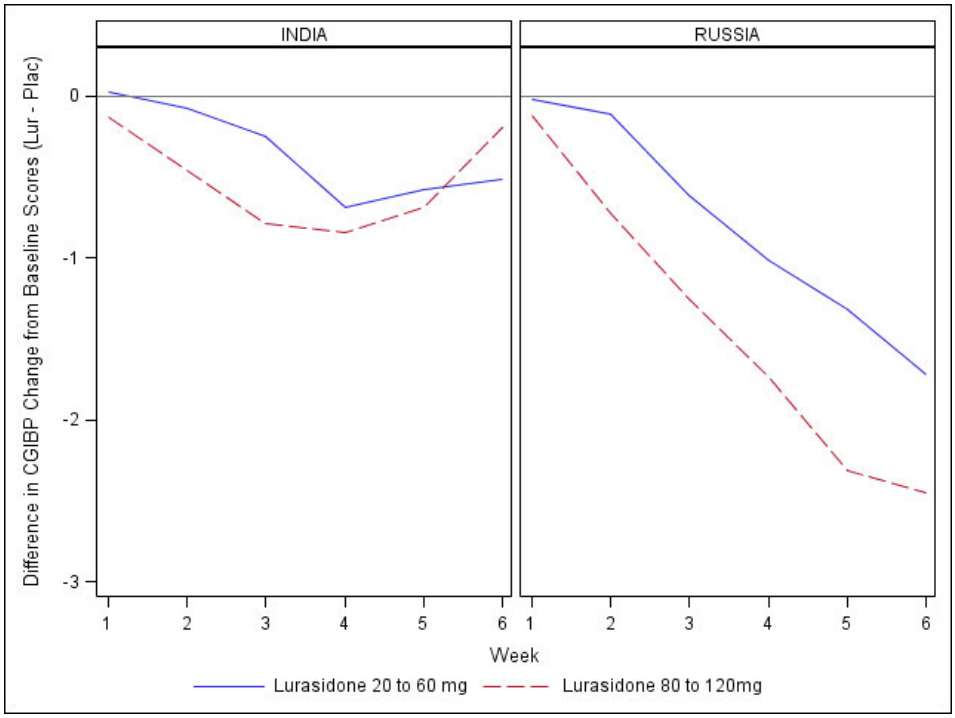
(Source: computed by reviewer; note: primary MMRM model failed for Romanian subjects)

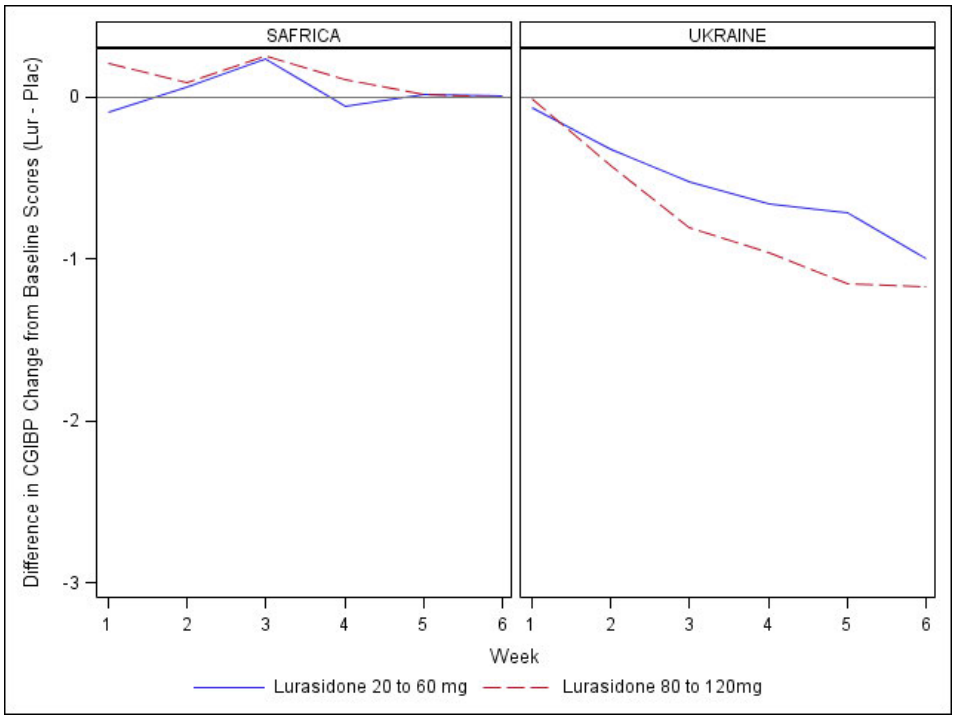
Russian and French patients appear to benefit most (at least numerically) from the treatment with lurasidone whereas South African, Indian, and US patients appear to benefit least when measured by change from Baseline differences in the CGI-BP-S score.

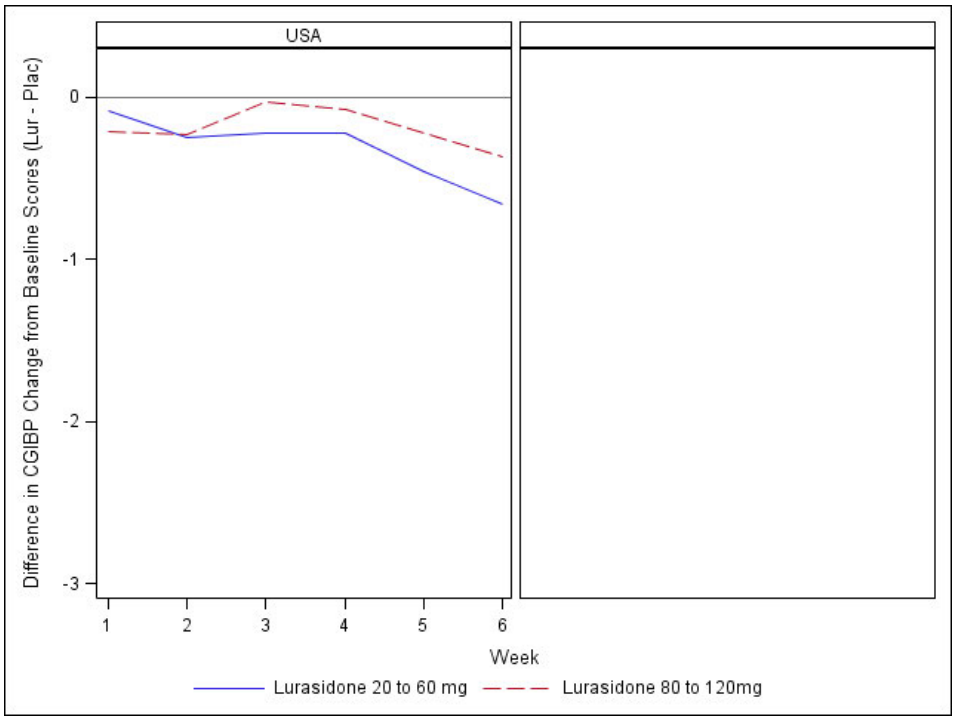
Figure A9 provides the CGI-BP-S score treatment difference estimates over the course of the 6-week study by dose and country. French, Russian and to a lesser degree Ukrainian patients exhibit an increasing treatment benefit (as measured by the CGI-BP-S). Neither dose range appears to work consistently better than the other over this 6 week period.

Figure A9: LS Mean Difference in CGI-BP-S Total Score Change from Baseline Scores (Lurasidone minus Placebo) over Course of Study by Country and Dose (MMRM)



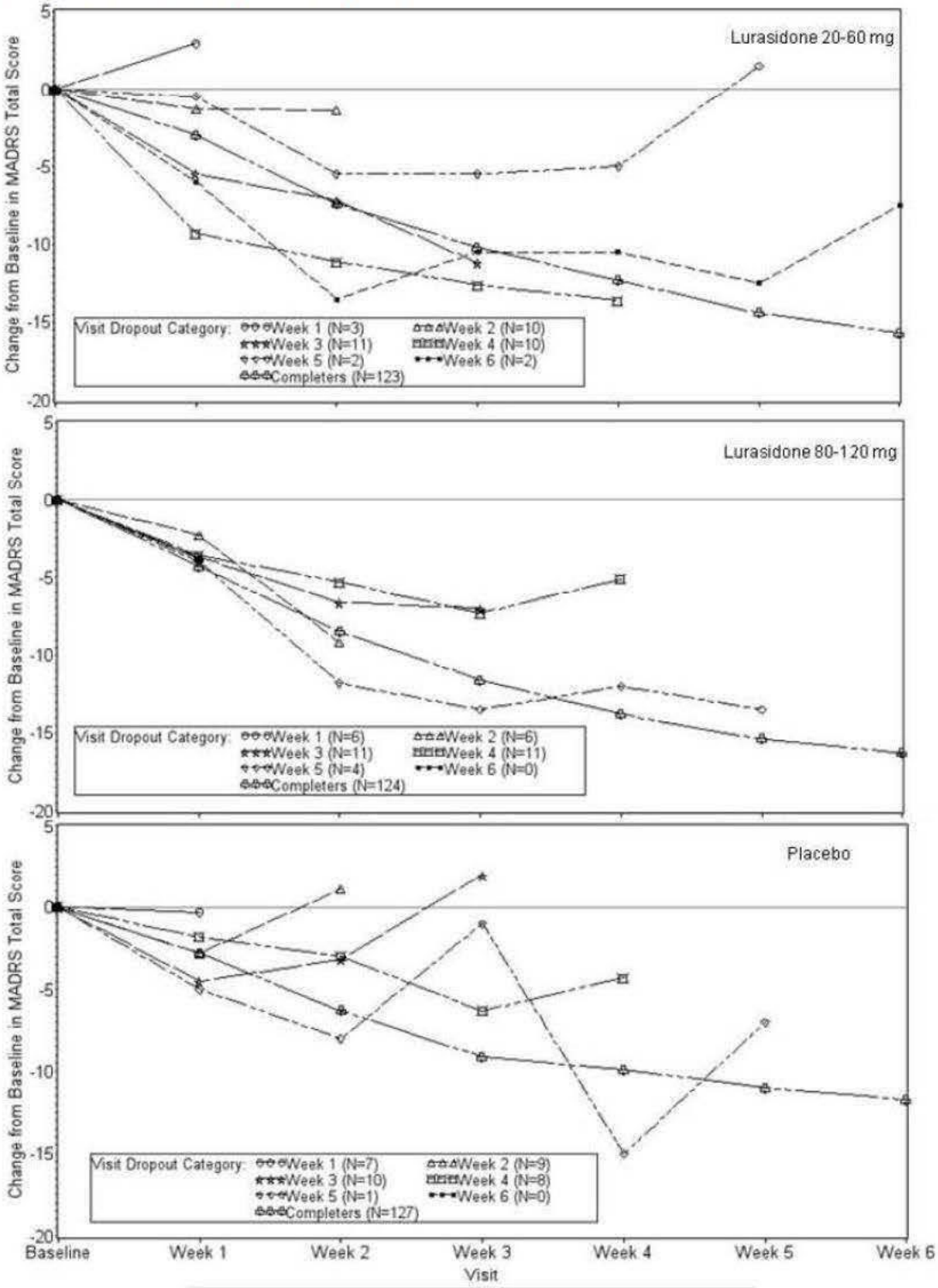






(Source: computed by reviewer; note: primary MMRM model failed for Romanian subjects)

Figure A10: Montgomery-Asberg Depression Rating Scale Total Score Change from Baseline by Visit Dropout Category



(Source: Study report p. 105)

No firm conclusions can be derived from the line plots in Figure A10. It is noteworthy though, that the dropouts tend to have smaller decreases in MADRS total score at each corresponding week compared with the completers.

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/s/

THOMAS BIRKNER
05/21/2013

PEILING YANG
05/30/2013
I concur with the review.

HSIEN MING J HUNG
05/30/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	200603
Generic Name:	Lurasidone HCL
Trade Name:	Latuda® Tablets
Strength and Dosage Form:	20 mg, 40 mg, 80 mg and 120 mg- tablets
Indication:	Schizophrenia (Atypical antipsychotic)
Sponsor:	Sunovion, Marlborough, MA
Submission Type:	Efficacy Supplement
Priority Classification:	Standard
Submission Date:	Aug 31st, 2012
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen Balimane, Ph.D.
Team Leader:	Hao Zhu, Ph.D

Memorandum

This review summarizes labeling changes for LATUDA during this review cycle and provides the scientific rationale for these changes.

1. In section 2.5, the following statement is included: "Grapefruit and grapefruit juice should be avoided in patients taking LATUDA [*see Drug Interactions (7.1)*]."

A dedicated grapefruit juice interaction study has not been conducted. Our recommendation is based on the current knowledge of lurasidone metabolism and grapefruit juice associated CYP3A4 inhibition.

Grapefruit and grapefruit juice are thought to significantly increase exposure of a CYP3A4 substrate with low bioavailability, because they mainly inhibit presystemic CYP3A4 enzymes in a mechanism-based manner and the inhibition may last up 3 days (1-3). LATUDA is known to be a low oral bioavailability compound (estimated systemic bioavailability is less than 20% based on OCP review dated 10/26/2010) that is highly metabolized by CYP3A4 enzymes. Therefore, significant increase in lurasidone exposure is anticipated in patients receiving LATUDA and taking grapefruit or grapefruit juice. Since a dedicated interaction study was not conducted, the magnitude of increase in lurasidone exposure in patients also taking grapefruit or grapefruit juice is hard to predict accurately. However, per the current drug-drug interaction guidance, grapefruit/grapefruit juice may be considered as a strong inhibitor or a moderate inhibitor based on brand, concentration, dose, and preparation. It has been shown that a strong CYP3A4 inhibitor (i.e., ketoconazole) and a moderate CYP3A4 inhibitor (i.e., diltiazem) increased lurasidone exposure by 9 fold and 2 fold, respectively (OCP review dated 10/26/2010). In addition, dose related adverse events, such as akathisia and extrapyramidal symptoms, have been observed in the clinical trials (Current label of LATUDA). Thus, taking grapefruit or

grapefruit juice in patients receiving LATUDA is likely to significantly increase the risk of potential adverse events. Dose adjustment to control the risk is difficult due to the variable magnitude and prolonged duration of the inhibition. Hence, we recommend that grapefruit and grapefruit juice should be avoided in patients taking LATUDA.

2. In "Dosage and Administration" section of Highlights and in sections 2.5 and 7.1, the following statement is added: "Concomitant Use of a Moderate CYP3A4 Inducer: It may be necessary to increase the dose of LATUDA (2.5, 7.1)"

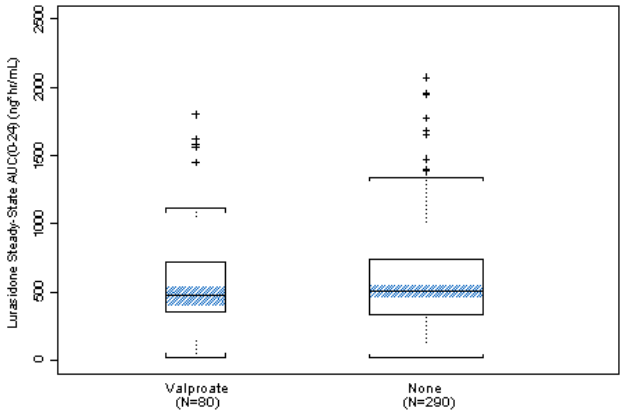
Based on the drug interaction studies, LATUDA is recommended not to be concomitantly taken with strong CYP3A4 inducers since its exposure reduces in a clinically meaningful and significant way with strong CYP3A4 inducers (rifampin reduces LATUDA exposure by more than 80%)(OCP review dated 10/26/2010). A dedicated drug interaction study is not performed with a moderate CYP3A4 inducer. However, with a greater than 80% reduction in exposure of LATUDA with Rifampin (strong CYP3A4 inducer), it is highly likely that moderate inducers will also cause clinically meaningful reduction in exposure of LATUDA. Thus, the label has been modified to instruct the physicians regarding a potential need to increase the dose of LATUDA when given concomitantly with moderate CY3A4 inducers.

3. In Section 7.1 for drug interaction with Valproate, the following statement is included: "It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies, valproate levels were not affected by lurasidone, and lurasidone concentrations were not affected by valproate."

Though a dedicated drug-drug interaction study between LATUDA and valproate was not performed, sparse pharmacokinetic samples obtained from the currently submitted studies (Studies D1050-235 and D1050-236) were applied to assess the effect of the two drugs on each other's exposure. Based on population pharmacokinetic modeling and simulation, it seems that lurasidone exposure was unchanged when co-administrated with valproate. In addition, by comparing the valproic acid exposure from the clinical studies, valproate exposure was unchanged when co-administered with LATUDA.

- **Impact of Valproate on Lurasidone Concentrations:** The distribution and mean value of estimated lurasidone steady state $AUC_{(0-24)}$ in subjects administered lurasidone with valproate were similar to those in subjects administered lurasidone with placebo. Figure 1 presents simulated 80 mg/day exposure data; considering the linear lurasidone pharmacokinetic profile, these data can be extrapolated across the lurasidone 20-120 mg/day dose range.

Figure 1: Estimated Lurasidone Exposure (80 mg/day) at Steady-State Comparing Monotherapy and Adjunct Therapy with Valproate



- **Impact of Lurasidone on Valproate Concentrations:**

Valporate concentrations collected in the adjunctive therapy trials (Study D1050235 and D1050292) were used to assess the potential interaction between lurasidone and valproate. In the adjunctive treatment arm (lurasidone + valporate), lurasidone was added in patients stabilized with valporate. A direct comparison of trough valopric acid concentrations between baseline and various visits during the treatment was performed. The results showed approximately less than 10% change in valporic acid concentration across 6 weeks of treatment duration, given no dose adjustment of valporate was performed in the treatment arm. In addition, a comparison of trough valporic acid concentration between the adjunctive treatment group (lurasidone + valporate) and placebo group (placebo + valporate) was performed. With comparable background dose and concentration of valporate between the two groups, the difference in valporic acid concentration between the two groups after lurasidone was added was less than 10% across all visits. Thus, data from 2 independent studies (D1050235 and D1050292) demonstrating a lack of change in valproic acid exposure on co-administration with lurasidone confirms that lurasidone does not impact the pharmacokinetics of valproic acid.

References:

1. Grapefruit juice and drug labeling, OCP scientific round, Sang Chung, apr 12, 2012
2. The grapefruit juice story, David Greenblatt, FDA seminar, 2013
3. Drug-grapefruit juice interactions, Mayo Clin Proc, 75, 933-942, 2000

Appendix

1. Impact of Valproate on Lurasidone Concentrations:

The impact of valproate on lurasidone concentration was evaluated based on modeling and simulation.

The simulation is based on a population pharmacokinetic model that was submitted to the agency during the original NDA submission (Study report: M1050005). The model is a three compartment model with first-order absorption, absorption lag time, and first-order elimination. Dr. Bhattaram and Dr. Wang reviewed this model report and concluded that this model is acceptable. In the current submission, the sponsor included sparse pharmacokinetic data from the recently conducted studies (Studies D1050-235 and D1050-236) and updated the model by using microconstants (e.g., K_{12} etc) (Study M1050011). Several additional covariate effects were identified based on the new data. The final model is shown as follows.

$$ka_{i,j} = 1.17 \cdot (1 + -0.250)^{ASN_i} \cdot (1 + 1.23)^{FAST_{i,j}} \cdot (1 + 0.331)^{LOWFAT_{i,j}} \cdot (1 + -0.400)^{NGT_i} \cdot e^{\eta ka_i}$$

$$ALAG1 = 0.422$$

$$TVCL_i = 199 \cdot (1 + -0.372)^{ASN_i} \cdot (1 + -0.128)^{SEXR} \cdot (1 + -0.200)^{NGT_i}$$

$$TVV2_i = 716 \cdot \left(\frac{BWT_i}{80}\right)^{0.432}$$

$$V2/F_i = TVV2_i \cdot e^{\eta V2/F_i}$$

$$k_i = \left(\frac{TVCL_i}{TVV2_i}\right) \cdot e^{\eta k_i}$$

$$k_{24_i} = 0.136 \cdot e^{\eta k24_i}$$

$$k_{42_i} = 0.00765$$

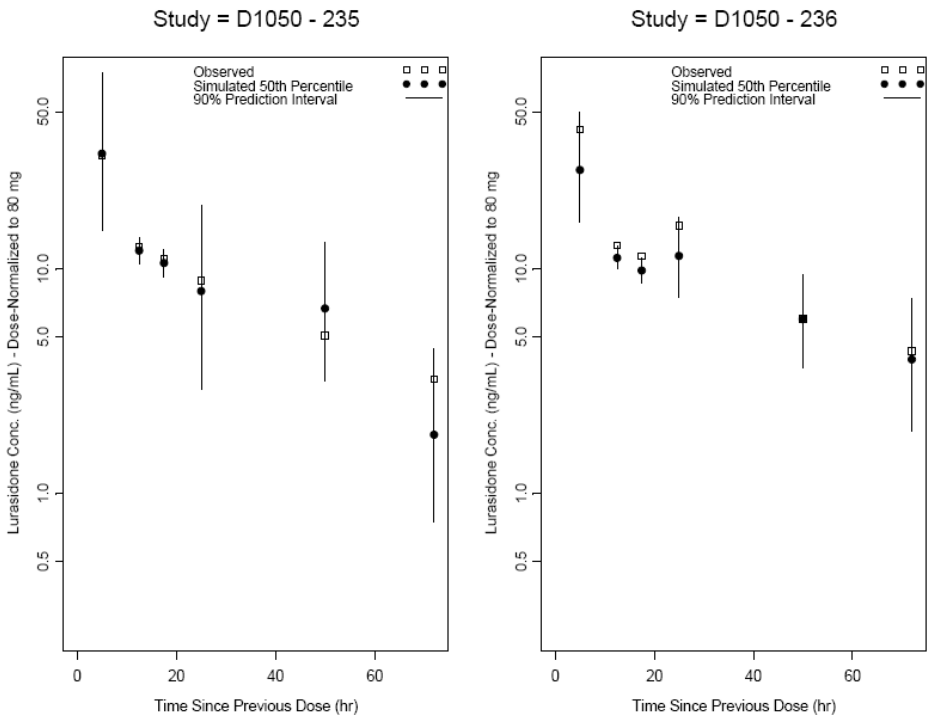
$$k_{23_i} = 0.111 \cdot e^{\eta k23_i}$$

$$k_{32_i} = (k_{42i} + 0.0957)$$

$$F1_{i,j} = 1 \cdot (1 + -0.536)^{FAST_{i,j}} \cdot (1 + -0.153)^{NGT_i}$$

A predictive check was conducted to assess model performance with the data from the new studies (Figure 2). The updated model appears to reasonably describe the observed data.

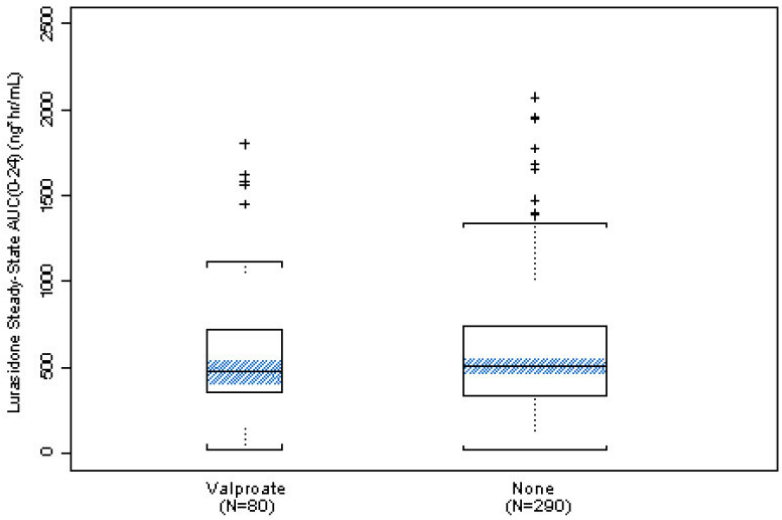
Figure 2: Observed and Predicted Distribution of the Median Lurasidone Concentrations in Studies D1050-235 and D1050-236 Based on Final Combined Model



(Source: Figure 4 Study report M1050011)

Based on the established model, AUC(0-24) at steady state was predicted through simulations at the dose of 80 mg/day. The results indicated no effect of valporate on lurasidone exposure. Since the lurasidone follows linear pharmacokinetic profile over the dose of 20 to 160 mg/day, the findings can be extrapolated into different dose groups.

Figure 3: Estimated Lurasidone Exposure (80 mg/day) at Steady-State Comparing Monotherapy and Ajunctive Therapy with Valproate



(Source: Figure 1 Response to Food and Drug Administration Information Request, June 11, 2013)

2. **Impact of Lurasidone on Valproate (divalproex) Concentrations:**

The impact of lurasidone on valproate was assessed by the change from baseline in valproate concentrations (at week 1 thru week 6) on co-administration with lurasidone or placebo in study D1050235 and D1050292.

For study D1050235, baseline mean divalproex (75.01 mg/L and 72.03 mg/L for lurasidone and placebo, respectively) serum levels were well balanced across treatment groups. During the study minor changes from the baseline values occurred; however the differences in the changes between the lurasidone and placebo groups were small. The mean divalproex levels were maintained throughout the study at the protocol-defined therapeutic range (50 to 125 mg/L for divalproex).

As shown in Table 1, the majority of subjects at Week 6 remained within the target valproate concentration range of 50 to 125 mg/L in either the lurasidone + divalproex group or placebo + divalproex group. The majority of subjects in the both groups at Week 6 maintained serum valproic acid concentrations as where they were at Baseline (50 to <75 mmol/L, 75 to <100, and 100 to 125 mg/L). In summary, after 6 weeks of dosing, there was less than 1% change in mean valproic acid exposure (compared to baseline levels) in subjects concomitantly dosed with lurasidone. This lack of change in valproic acid exposure confirms that lurasidone does not impact the pharmacokinetics of valproic acid.

Table 1: Serum divalproex (valproic acid) concentrations in presence of lurasidone or placebo

Visit/ Value	Statistic	Lurasidone 20-120 mg + Valproic Acid (N=89)	Placebo + Valproic Acid (N=87)
Serum Valproic Acid Concentration (mg/L)			
Baseline	n	89	87
	Mean (SD)	75.01 (25.898)	72.03 (26.575)
	Median	76.50	74.40
	Min, Max	1.0, 140.1	7.1, 126.2
Week 6			
Change from Baseline	n	70	76
	Baseline Mean (SD)	73.43 (24.671)	71.09 (26.932)
	Mean (SD)	-0.54 (31.788)	-1.09 (28.865)
	Median	3.80	0.65
	Min, Max	-85.6, 96.4	-99.0, 51.1

Similarly, for study D1050292, The majority of subjects at Week 6 (Table 2) remained within the target valproate concentration range of 50 to 125 mg/L in either the lurasidone + divalproex group or placebo + divalproex group. As shown in Table 2, after 6 weeks of dosing, there was less than 2% change in mean valproic acid exposure (compared to baseline levels) in subjects concomitantly dosed with lurasidone. This lack of change in valproic acid exposure confirms that lurasidone does not impact the pharmacokinetics of valproic acid.

Table 2: Serum valproic acid concentrations on week 6 in presence of lurasidone or placebo

Serum Valproic Acid Concentration - Change from Baseline and Categorical Summary by Visit and Run-in Status
Intent-to-Treat Population

Analysis Level = All Subjects

Visit/ Value	Statistic	Treatment Group: Lurasidone 20-120 mg + Valproic Acid (N=120)	Treatment Group: Placebo + Valproic Acid (N=109)
Serum Valproic Acid Concentration (mg/L)			
Week 6			
Observed	n	102	92
	Mean (SD)	67.84 (29.481)	70.55 (25.185)
	Median	72.00	70.00
	Min, Max	3.5, 150.0	3.6, 126.7
Change from Baseline	n	102	92
	Baseline Mean (SD)	68.82 (26.325)	73.84 (25.223)
	Mean (SD)	-0.98 (34.349)	-3.30 (26.995)
	Median	1.30	-4.50
	Min, Max	-113.5, 69.4	-84.0, 84.2

Note: For serum concentration, baseline is the last measurement on or before the date of first dose of study medication. LOCF endpoint is the last post-baseline measurement through the Week 6 visit day if entering the extension study or within 7 days after treatment discontinuation if not entering the extension study. At post-baseline visits and LOCF endpoint, observed values are based on those subjects with both a baseline and post-baseline measurement.

Note: Formulations of extended release valproic acid require a conversion factor for an equivalent dose of non-extended release valproic acid. A list of conversion factors for selected doses can be found in SAP Appendix 5.

Source Data: Listing 16.2.8.1 Central Clinical Chemistry Laboratory Data and 16.2.4.8 Prior and Concomitant Medications

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/s/

PRAVEEN BALIMANE
06/27/2013

VENKATESH A BHATTARAM
06/27/2013

HAO ZHU
06/27/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Division of Psychiatry Products

Name of Drug: Latuda (lurasidone) tablets (NDA 200603)

Applicant: Sunovion Pharmaceuticals, Inc.

Material Reviewed:

NDA	Supplement #	Submission Date	Receipt Date	Supplement Type	Status
200603	S-013	06-15-12	06-15-12	CBE	Approved 01-22-13
200603	S-010	08-31-12	08-31-12	PA	Pending
200603	S-011	08-31-12	08-31-12	PA	Pending

Background and Summary

1. Last approved labeling was NDA 200603/S-013 in agency letter dated 01-22-13.
2. The sponsor submitted two efficacy supplements on 08-31-12 proposing the new indications treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy to lithium or valproate.

Review

This supplement proposes the addition of two new indications, and the following changes:

Highlights:

(b) (4)

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/s/

ANN J SOHN
06/28/2013

PAUL A DAVID
06/28/2013

M E M O R A N D U M

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

AMENDED CLINICAL INSPECTION SUMMARY

DATE:	June 27, 2013
TO:	Ann Sohn, Regulatory Project Manager Mark Ritter, M.D., Clinical Reviewer Division of Psychiatry Products
FROM	John Lee, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
THROUGH:	Susan Leibenhaut, M.D., Acting Team Leader Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
	Susan Thompson, M.D., Acting Branch Chief Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections
APPLICATION:	NDA 200-603 S10
APPLICANT:	Sunovion Pharmaceuticals, Inc.
DRUG:	Latuda® (lurasidone)
NME:	No
INDICATION:	Treatment of bipolar depression as monotherapy or as adjunctive therapy to lithium or valproate

REVIEW CLASSIFICATION:	Standard
CONSULTATION REQUEST DATES:	November 5, 2012; March 4, 2013 (amended)
INSPECTION SUMMARY GOAL DATES:	April 30, 2013; March 4, 2013 (amended)
ACTION GOAL DATE:	June 30, 2013
PDUFA DUE DATE:	June 30, 2013

I. Background

Bipolar disorder is a chronic, often disabling condition with 4% lifetime incidence. Complex involvement of manic and depressive phases makes treatment difficult: standard antidepressants, although widely used, may induce mania and cyclical (bipolar) symptom acceleration. Divalproex or lithium is typically used as first-line agents, often with inadequate treatment response, and mood stabilizers plus antidepressants (or atypical agents, or both) are commonly used as second line agents. Currently, only two treatment regimens are approved to treat bipolar depression (olanzapine plus fluoxetine, and quetiapine).

Lurasidone was approved in the United States (**US**) for the treatment of schizophrenia in October 2010. Based on its selective high affinity for dopamine, serotonin, and norepinephrine receptors (low affinity for histamine or acetylcholine receptors), lurasidone may be expected to be safe and effective for schizophrenia and also for bipolar depression, with little adverse effects (including extrapyramidal effects). In the two current NDA 200-603 supplements (S-10 and S-11), Sunovion Pharmaceuticals, Inc. (Sunovion) seeks approval of lurasidone for bipolar depression, as monotherapy and as adjunctive therapy to lithium or valproate. The use as monotherapy is supported by Study D1050236, and the adjunctive use is supported by Studies D1050235 and D1050292.

Study D1050236

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Fixed-Flexible Dose, Parallel-Group Study of Lurasidone for the Treatment of Bipolar I Depression

This study enrolled 505 subjects at 24 sites in the US and 31 foreign sites: nine in India, five in Ukraine, four each in Czech Republic, Romania, Russia, and South Africa, and one in France. The study was conducted over about three years, from April 2009 to February 2012.

Study Objectives:

- To evaluate the efficacy of lurasidone in treating major depressive episodes associated with bipolar I disorder (diagnostic criteria per *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision,* **DSM-IV-TR**) using the following evaluation instruments:
  - Primary: Montgomery-Asberg Depression Rating Scale (**MADRS**)
  - Clinical Global Impression, Bipolar Version, Severity of Illness (**CGI-BP-S**)
  - Sheehan Disability Scale (**SDS**)
  - Quick Inventory of Depressive Symptomatology, Self Report (**QIDS-SR16**)
  - Young Mania Rating Scale (**YMRS**)
  - Hamilton Rating Scale for Anxiety (**HAM-A**)
  - Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form (**Q-LES-Q-SF)**
- To determine rates of treatment response (MADRS score reduction $\geq$ 50%) and symptom remission (MADRS score $\leq$ 12), and to evaluate safety:
  - Adverse events (**AEs**), serious AEs (**SAEs**), electrocardiogram (**ECG**) abnormalities, and suicidality using Columbia Suicide Severity Rating Scale (**C-SSRS**)
  - Movement disorders: Abnormal Involuntary Movement Scale (**AIMS**), Barnes Akathisia Rating Scale (**BARS**), and Simpson-Angus Scale (**SAS**)

Treatment Groups and Regimen:

Following medication washout (as tolerated) for at least three days before randomization, subjects were randomized (double-blinded) in equal ratio to placebo and two lurasidone dose arms. Based on clinical response, dose was adjusted weekly by one dose level; dose reductions could be more frequent than weekly and up to two dose levels at a time.

- Lurasidone 20 to 60 mg/day: initial dose 20 mg (Days 1-7) and flexible dosing thereafter (clinical response to 20, 40, or 60 mg)
- Lurasidone 80 to 120 mg/day: initial dose 20 mg (Days 1/2), titration to 40 mg (Days 3/4), 60 mg (Days 5/6), and 80 mg (Day 7), flexible dosing thereafter (clinical response to 80, 100, or 120 mg)

Inclusion Criteria: screening and baseline

- Subjects 18 to 75 years of age (65 in Czech Republic) with bipolar I disorder, most recent episode depressed with or without rapid cycling (episodes in the last 12 months $\geq$ four and < eight)
- Current episode of major depression: confirmed and documented, $\geq$ four weeks and < 12 months, MADRS score $\geq$ 20 and YMRS score $\leq$ 12
- Lifetime history of at least one bipolar manic or mixed manic episode confirmed by reliable informant, no psychotic features (DSM-IV-TR criteria)

Exclusion Criteria: screening and baseline

- Diagnosis of an Axis I or Axis II disorder other than bipolar I disorder that was the primary focus of treatment within three months before screening
- History of non-response to an adequate (six-week) trial of three or more antidepressants (with or without mood stabilizers) during the current episode
- MADRS item 10 (suicidal thoughts) score $\geq$ four; imminent risk of suicide or injury to self, others, or property; or laboratory test results outside the reference range (at screening only)

Efficacy Endpoints/Analyses: missing data not imputed

- Primary: Change in score (baseline and Day 42): MADRS (after six weeks of treatment)
- Change in score (baseline and Day 42): CGI-BP-S, SDS, QIDS-SR16, HAM-A, and Q-LES-Q-SF
- Subject proportion: AE of mania/hypomania or YMRS score $\geq$ 16 at final or consecutive visits
- Subject proportion (MADRS scores): clinical response ($\geq$ 50% reduction) and remission ($\leq$ 12)

Safety Endpoints/Analyses: missing data imputed using last observation carried forward (LOCF)

- Proportions of subjects with AEs, discontinuations due to AEs, and SAEs
- Frequency and severity of suicidality using the C-SSRS
- Movement disorders assessed by the AIMS, BARS, and SAS
- Vital signs, weight, physical exams, ECG, and laboratory measures

Major Study Results:

Mean (least square) MADRS scores decreased by 15, 15, and 11 for the 20-60 mg, 80-120 mg, and placebo groups, respectively ($p < 0.001$). Lurasidone therapy was well tolerated at either dose level and safety observations were consistent with those of previous schizophrenia studies. The sponsor claims that flexibly dosed lurasidone (20 to 60 mg/day or 80 to 120 mg/day) therapy is safe and effective (superior to placebo) in reducing depressive symptoms of bipolar I disorder.

Study D1050235

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of Lurasidone Adjunctive to Lithium or Divalproex for the Treatment of Bipolar I Depression

This study enrolled 348 subjects at 23 US and 35 foreign sites: 10 in India, five each in Ukraine and Czech Republic, four in South Africa, three each in Poland and Russia, two each in Romania and France, and one in Germany. The study was conducted over abut three years, from May 2009 to January 2012. Study D1050235 was identical to Study D1050236 other than as shown below.

Major Study Objective:

To evaluate the efficacy of lurasidone *in combination with lithium or divalproex* in treating major depressive episodes associated with bipolar I disorder (diagnostic criteria per DSM-IV-TR) using MADRS (primary objective), CGI-BP-S, SDS, QIDS-SR16, YMRS, HAM-A, and Q-LES-Q-SF

Treatment Groups and Regimen:

Following medication washout (as tolerated) for at least three days before randomization, subjects were randomized (double-blinded) in equal ratio to placebo or lurasidone. For both arms, lithium or divalproex was continued, and randomization was stratified by co-therapy (lithium or divalproex).

- Lurasidone dosing: initially 20 mg (Days 1-3), increase to 40 mg (Days 4-6) and 60 mg (Day 7), flexible dosing thereafter (clinical response to 20, 40, or 60 mg)
- Lithium or divalproex doses were adjusted to keep trough levels within protocol-specified range. Limited use of benzodiazepines was permitted for the first three weeks and prohibited thereafter.

Inclusion Criteria:

- Verification of continuous treatment with lithium or divalproex for $\geq$ 28 days prior to screening by a reliable informant (all preparations of lithium, divalproex, or valproic acid permitted)
- Lithium or divalproex levels within protocol-defined range at screening: 0.6 to 1.2 mEq/L for lithium ($\geq$ 0.4 mEq/L permitted with medical monitor approval if 0.6 mEq/L or higher was judged to be intolerable or unsafe) and 50 to 125 ug/mL for divalproex

Major Study Results:

Mean (least square) MADRS scores decreased by 17 and 14 for lurasidone and placebo groups, respectively ($p = 0.005$). Lurasidone therapy was well tolerated, and safety observations were consistent with those of previous schizophrenia studies. The combination of either lithium or divalproex with lurasidone did not have an impact on AEs. The sponsor claims that flexibly dosed lurasidone therapy (20 to 120 mg daily) in combination with lithium or divalproex is safe and effective (superior to placebo plus lithium or divalproex) in relieving bipolar depression.

Study D1050292

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of Lurasidone Adjunctive to Lithium or Divalproex for the Treatment of Bipolar I Depression in Subjects Demonstrating Non-Response to Treatment with Lithium or Divalproex Alone

This study (second adjunctive study in treatment-refractory bipolar depression) was conducted over 18 months (December 2010 - August 2012) in 356 subjects at 71 sites in 10 countries: 22 (sites) in US, 10 in India, 8 in Slovakia, 7 in Ukraine, 5 in Lithuania, 4 each in Canada, Columbia, Czech Republic, and Japan, and 3 in Peru.

Major Study Objective:

The primary study objective was to compare lurasidone (20 - 120 mg/day, flexible dosing) with placebo as an adjunctive agent to lithium or divalproex for the treatment of major depressive episodes associated with bipolar I disorder in subjects unresponsive to lithium or divalproex alone.

Treatment Groups and Regimen:

Subjects were randomized using interactive voice response system (**IVRS**) in equal ratio to either lurasidone (20 to 120 mg/day) or placebo, both in combination with lithium or divalproex co-therapy. Randomization was stratified by lithium or divalproex.

- Subjects were tapered off of psychotropic medications except lithium or divalproex, with either of which treatment was required for a minimum of 28 days with drug levels demonstrated to be within the protocol-specified (therapeutic) range.
- Lurasidone 20, 40, 60, 80, 100, or 120 mg/day, once daily oral dosing for 6 weeks. Initially 20 mg/day (Days 1-3), increased to 40 mg/day (Days 4-6), and flexibly dosed thereafter (Weeks 2-6).
- Dose adjustments weekly by one dose level, dose reductions for tolerability or safety more frequently and by more than one dose level (maximum of two dose levels per adjustment) beginning at Day 7.
- Dose adjustments of lithium or divalproex were permitted during the study to ensure trough level within protocol-specified range

Inclusion Criteria: screening and baseline

- Subjects 18 to 75 years of age with bipolar I disorder, most recent episode depressed with or without rapid cycling (≥ 4 episodes, < 8 in last 12 months) without psychotic features (DSM-IV-TR criteria, confirmed by MINI, current episode confirmed and documented).
- Lifetime history of at least one bipolar manic or mixed manic episode; reliable informant to confirm history (strongly recommended); current major depressive episode ≥ 4 weeks and < 12 months; MADRS total score ≥ 20, YMRS total score ≤ 12
- Lithium or divalproex therapy (minimum 28 days with therapeutic drug levels), most recent depression episode (with or without rapid cycling, ≥ 4 total with < 8 episodes in the previous 12 months) without psychotic features (DSM-IV-TR criteria) as measured by MADRS total score

Exclusion Criteria: screening and baseline

- Diagnosis of an Axis I or Axis II disorder, other than bipolar I disorder, that was the primary focus of treatment within 3 months prior to Screening
- Subject scored ≥ 4 on MADRS item number 10 (suicidal thoughts) at Screening or Baseline; imminent risk of suicide or injury to self, others, or property
- History of non-response to 6 weeks of monotherapy using three or more antidepressants per labeled recommendations (therapeutic dose range) with or without mood stabilizers during current episode

Efficacy Endpoints/Analyses: missing data observations not imputed

- Primary: Mean change from baseline to Week 6 (Day 42) in MADRS total score
- Mean change from baseline to Week 6 in global severity in CGI-BP-S score (depression)
- Mixed model for repeated measures (**MMRM**) for intent-to-treat (**ITT**)

Safety Endpoints/Analyses:

- Proportions of subjects with AEs, discontinuations due to AEs, and SAEs
- Vital signs, ECG, weight, laboratory measures, and physical examinations
- Movement disorder assessment by AIMS, BARS, and SAS

Major Study Results:

- No statistical difference between lurasidone and placebo in primary efficacy endpoint (change in MADRS total score from baseline to Week 6) (-1.5 ± 1.1, p = 0.18, MMRM/ITT)
- No statistical difference between lurasidone and placebo in change from baseline in CGI-BP-S depression score at Week 6 (-0.24 ± 0.14, p = 0.095, MMRM/ITT); statistical superiority for lurasidone in MADRS and CGI-BP-S from Weeks 2-5
- Treatment-emergent AEs (**TEAEs**), ≥ 5% for lurasidone and ≥ twice placebo: akathisia (14% vs 5%) and somnolence (12% vs 5%); no deaths, 10 SAEs in 8 subjects (5 lurasidone subjects, one with 3 SAEs, 3 placebo subjects)
- Subject discontinuation rate due to TEAEs of 5.6%, TEAEs related to EPS more common for lurasidone (12%) than for placebo (8%); no increased suicidal ideation by C-SSRS (10% vs 12%) for lurasidone than for placebo. Two SAEs related to suicidal ideation reported for lurasidone, none for placebo
- Minimal changes from Baseline in weight, lipids, measures of glycemic control and prolactin were observed for subjects in the lurasidone adjunctive treatment group; no ECG abnormalities for lurasidone, including no QTc interval > 500 msec

II. GCP Inspections

DPP submitted the initial consult (November 2012) requesting two or more of seven suggested US clinical study sites to be inspected in support of this NDA review. Of the seven suggested, four were selected (randomly) among those sites with two pivotal studies (monotherapy Study D1050236 and adjunctive therapy Study D1050235) at the same site. For all sites, subject enrollment was relatively large (either or both studies), the primary clinical investigators had large numbers of INDs on file at CDER, or lacked a recent FDA inspection. For both studies, the site-specific data for efficacy, adverse events, and protocol deviations did not appear to be significantly different among the US study sites and no significant investigator conflicts of interest were noted.

Interim application review showed that, in any of the three pivotal studies (monotherapy Study D1050236 and adjunctive therapy Studies D1050235 and D1050292), the efficacy of lurasidone was not demonstrable for the major study regions, including US (40% of all subjects), Asia, and Africa. The overall positive outcomes were driven by clinical sites in Europe, particularly by two outlier Sites 191 and 618. Without the large treatment effect seen at these two sites, the efficacy of lurasidone was either statistically not robust (Study D1050236) or not demonstrable (Study D1050235). In the second adjunctive therapy Study D1050292, the overall efficacy outcome was negative; Site 191 did not participate, and Site 618 contributed only 4 subjects. Based on these interim review findings, DPP submitted a second consult (March 2013) requesting additional inspections of the two foreign efficacy outlier sites. For all three studies, adverse events and protocol deviations did not appear to be significantly different among the foreign study sites and no significant investigator conflicts of interest were noted. The overall inspection outcomes for the six sites (four US, two foreign) are shown below.

Clinical Inspections for NDA 200-603 S-10 and S-11

	Clinical Investigator	Site, Studies, Subjects	Inspection Dates, Outcome
1	Rosario Hidalgo, MD University of South Florida 3515 East Fletcher Avenue Tampa, Florida 33613-4706	Site 100 D1050236: 12 subjects D1050235: 4 subjects	Nov 27 - Dec 4, 2012 VAI
2	Raymond Manning, MD CNRI - Los Angeles, LLC 8309 Telegraph Road Pico Rivera, CA 90660	Site 094 D1050236: 20 subjects D1050235: 14 subjects	Dec 12 - 19, 2012 NAI
3	David Walling, MD Collaborative Neuroscience Network 12772 Valley View Street, Suite 3 Garden Grove, CA 92845	Site 105 D1050236: 18 subjects D1050235: 9 subjects	Dec 10 - 17, 2012 NAI
4	Howard Hassman, MD CRI Worldwide, LLC 111 North 49th Street Philadelphia, PA 19139	Site 120 D1050236: 13 subjects D1050235: 8 subjects	Dec 10 - 14, 2012 NAI
5	Michaela Klabusayova, M.D. Psychiatricka Ambulance Divadelni 616/4 602 00 Brno, Czech Republic	Site 618 D1050236 (17 subjects) D1050235 (17 subjects) D1050292 (4 subjects)	May 13 - 17, 2013 Pending (Preliminary VAI)
6	Vladimir Tochilov, M.D. City Psychiatric Hospital 2 Moika River Embankment 126 St. Petersburg 190121, Russia	Site 191 D1050236 (22 subjects) D1050235 (13 subjects)	June 3 - 7, 2013 Pending (Preliminary VAI)

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

1. Rosario Hidalgo, M.D. (Site 100)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable good clinical practice (**GCP**) regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 15 subjects were screened, 4 were enrolled, and 4 completed the study. Subject records for all enrolled subjects were reviewed completely, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 25 subjects were screened, 12 were enrolled, and 12 completed the study. Subject records for all enrolled subjects were reviewed completely, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- A Form FDA 483 was issued for the following observations:
  - Study D1050236: One subject was screened for the study one day before obtaining informed consent.

    Reviewer Comment: Informed consent should be obtained prior to enrollment into the study and not necessarily prior to screening. This observation does not warrant a Form FDA 483 citation.
  - Study D1050235: One subject was given 3 doses of erythromycin, a prohibited concomitant medication, to treat upper respiratory infection.

    Reviewer Comment:

    Three doses of the prohibited medication erythromycin were given inadvertently over 12 hours to this subject randomized to receive lurasidone plus lithium.

    Erythromycin was prohibited in the study since it inhibits CYP3A4 and prolongs the QT interval. The erythromycin doses were temporarily related to AEs of nausea and vomiting; no other AEs were observed. Erythromycin was promptly discontinued and the error was reported as a protocol violation. The report of the protocol violation in the NDA is confirmed on Protocol Deviation Listing 16.2.2.

    This isolated error appears unlikely to have affected the efficacy data for this subject. The safety data may have been affected; AEs of nausea and vomiting appears to have been due to erythromycin and not the study medication. Overall, however, this isolated error does not appear to be significant.
- Observation not cited on Form FDA 483: In Study D1050236, for Subject 23610008, Week 3 YMRS Item 5 (Irritability) and Item 6 (Speech) differed between the CRF and the NDA data listing. CRF showed Item 5 score of 2 (irritability "subjectively increased") and Item 6 score of 2 (speech "feels talkative"), whereas the NDA data listing showed corresponding scores of 0 for both items (irritability "absent" and speech "no increase").

Reviewer's Comments:

- *YMRS total score of ≥ 16 at final or consecutive visits is an important safety observation. For this subject randomized to placebo, the Week 3 YMRS total score in the NDA (score 2) is different from that noted on the CRF (score 6). This discrepancy does not appear to be significant; however, the discrepancy appears to have resulted from the sponsor's error in data handling.*
- *Extensive review of CRF data showed no other discrepancies. Although this discrepancy could not be resolved, it appears to be an isolated error without broader implications for overall data integrity.*

- Other than as noted above, endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings. Underreporting of AEs was not observed.
- All subjects signed the informed consent document. Drug accountability was well documented. IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity:

The single minor deficiency observed at this site (use of prohibited medication) is reported in the NDA as a protocol violation. Data from this study site appear reliable.

2. Raymond Manning, M.D. (Site 094)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 23 subjects were screened, 14 were enrolled, and 12 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 26 subjects were screened, 20 were enrolled, and 15 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Underreporting of AEs was not observed. Drug accountability was well documented.
- Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

3. David Walling, M.D. (Site 105)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 42 subjects were screened, 9 were enrolled, and 6 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 43 subjects were screened, 18 were enrolled, and 14 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Underreporting of AEs was not observed. Drug accountability was well documented.

  Reviewer's Comments:

  Two of the nine subjects enrolled in Study D1050235 were not listed on subject enrollment log: Subject 23510528 (lurasidone) and Subject 23510538 (placebo). This minor isolated deficiency was not noted at inspection (noted post-inspection, comparison of inspectional finding versus NDA data listing), and therefore was neither discussed verbally nor cited on Form FDA 483. Other than as an isolated example of imperfect record keeping, this deficiency does not appear to be significant.

- Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

4. Howard Hassman, M.D. (Site 120)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 38 subjects were screened, 8 were enrolled, and 8 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

- Subjects, D1050236: 28 subjects were screened, 13 were enrolled, and 13 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor deficiencies were verbally discussed (not cited on Form FDA 483):
  - In Study D1050236, for Subject 23612008, the source record for Week 1 CGI-BP showed mania score 2, and not 1 as reported in the corresponding NDA data listing.
  - In Study D1050235, for Subject 23512036, the source record for Visit 2 HAM-A showed gastrointestinal symptom score 0 (question 11), genitourinary symptom score 2 (question 12), and total score 13. These source scores of 0, 2, and 13 differed from the corresponding scores of 2, 1, and 14 reported in the corresponding NDA data listing.

    Reviewer's Comments:

    These two minor discrepancies between source records and the NDA data listing presumably resulted from data entry errors (source data accurate, NDA data inaccurate). The errors involved secondary endpoints and appear trivial in significance. Follow-up investigation indicated that the observed discrepancies were isolated and did not suggest an underlying systematic deficiency in data handling; no other data discrepancies were observed.

- Other than as noted above, endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings. Underreporting of AEs was not observed.
- All subjects signed the informed consent document. Drug accountability was well documented. IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity: The observed deficiencies appear to be minor and isolated, and are not expected to have an impact on study results. Data from this study site appear reliable.

5. Michaela Klabusayova, M.D. (Site 618)

a. What was inspected: Given the review concerns about this site as an efficacy outlier, the inspection was conducted with special attention to potentially unblinded study conduct and/or biased data collection favoring lurasidone over placebo.

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 20 subjects were screened, 17 were enrolled, and 17 completed the study. Subject records for all 20 subjects were reviewed in detail.
- Subjects, D1050236: 18 subjects were screened, 18 were enrolled, and 17 completed the study. Subject records for all 18 subjects were reviewed in detail.

- Subjects, D1050292: 4 subjects were screened, 4 were enrolled, and 4 completed the study. Subject records for all 4 subjects were reviewed in detail.

b. General observations and comments:

- A Form FDA 483 was issued for the following observation:

  Study D1050236, Subject 23661815: The subject was given clarithromycin to treat pharyngotonsilitis, a prohibited medication (cytochrome P450 3A4 inhibitor). The clinical investigator did not consult the medical monitor about the use of clarithromycin, as specified in the study protocol.

- Other than as noted above, no significant deficiencies were observed. Evidence suggestive of unblinding was not observed. All endpoint evaluations were performed by apparently adequately trained and qualified study personnel.

  - All subjects signed the (appropriate) informed consent document.
  - Endpoint data were verifiable and underreporting of AEs was not observed.
  - Drug accountability was well documented.
  - IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity:

The observed deficiency appears to be an isolated finding of minor significance unlikely to have a significant impact on the study outcome. Evidence of unblinding or biased endpoint assessment was not observed. The data from this study site appear reliable.

Note: The establishment inspection report has not been received from the field office and the final inspection outcome classification remains pending. The findings noted above are based on preliminary communication with the field investigator.

6. Vladimir Tochilov, M.D. (Site 191)

a. What was inspected: Given the review concerns about this site as an efficacy outlier, the inspection was conducted with special attention to potentially unblinded study conduct and/or biased data collection favoring lurasidone over placebo.

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subject records review: records for all enrolled subjects were reviewed in detail.

b. General observations and comments:

- A Form FDA 483 was issued for the following observation:

  Study D1050235: For nine subjects, the study records did not contain audio recordings of the MADRS interviews, as specified in the protocol (amended 17 July 2009). This requirement was subsequently removed from the protocol (amended 18 February 2011).

- Other than as noted above, no significant deficiencies were observed. Evidence suggestive of unblinding was not observed. All endpoint evaluations were performed by apparently adequately trained and qualified study personnel.
  - All subjects signed the (appropriate) informed consent document.
  - Endpoint data were verifiable and underreporting of AEs was not observed.
  - Drug accountability was well documented.
  - IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity:

The observed deficiency appears to be an isolated finding of minor significance unlikely to have a significant impact on the study outcome. Evidence of unblinding or biased endpoint assessment was not observed. The data from this study site appear reliable.

Note: The establishment inspection report has not been received from the field office and the final inspection outcome classification remains pending. The findings noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four US clinical study sites that participated in Studies D1050235 and D1050235 were initially selected for GCP inspection. The sites were selected randomly among those US sites with both pivotal studies at the same site, relatively large subject enrollment, and remote (or no) prior FDA inspection history. At all four study sites, the observed deficiencies were limited to minor, apparently isolated deficiencies. No significant deficiencies were seen at Site 94 (Manning) and at Site 105 (Walling). At Site 120 (Hassman), the deficiency observations were discussed verbally without issuing a Form FDA 483. At Site 100 (Hidalgo), a Form FDA 483 was issued. None of the deficiencies are expected to have an important impact on the study outcome. The data from the four inspected clinical study sites appear reliable.

Interim NDA review indicated significant (unexplained) increased lurasidone efficacy in Europe relative to the rest of the world (US, Asia, and Africa). Two European efficacy outlier sites, Site 191 (Tochilov, Russia) and Site 618 (Klabusayova, Czech Republic), were additionally inspected to further investigate the interim review result. Inspectional findings relevant to the interim review were not observed at these two sites, including no evidence of unblinding, biased data collection, or other significant GCP deficiencies. The data from these two sites also appear reliable.

Notes:

1. An original Clinical Inspection Summary (CIS) for this application was finalized in DARRTS on February 11, 2013. This amended CIS contains: (1) preliminary information for two additional foreign site inspections and (2) updated final classification outcome for Site 105 (Walling).
2. For Sites 618 (Klabusayova) and 191 (Tochilov), the establishment inspection report has not been received from the field office and the final inspection outcome classification remains pending. An addendum to this amended CIS will be forwarded to DPP if the inspection outcome classification changes or if additional observations of clinical or regulatory significance are discovered after receipt and review of the final inspection report.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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/s/

JONG HOON LEE
06/27/2013

SUSAN LEIBENHAUT
06/27/2013

SUSAN D THOMPSON
06/27/2013

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

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

Memorandum

Date: **June 24, 2013**

To: Ann Sohn, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD
Team Leader, OPDP

Subject: **NDA #200603**
Latuda® (lurasidone hydrocholoride) Tablets

OPDP has reviewed the draft product labeling for Latuda® (lurasidone hydrocholoride) Tablets (Latuda) as requested in the consult from DPP dated June 21, 2013.

Reference is made to OPDP's memo dated June 12, 2013 indicating that we would not be providing comments on this label during this review cycle due to DPP's decision to issue a Complete Response letter. However, as DPP has reconsidered this decision and is now moving forward with labeling negotiations, OPDP has provided comments directly on the version of the draft PI below that was provided by Ann Sohn via email on June 20, 2013.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

APPEARS THIS WAY ON ORIGINAL

51 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSANNAH O'DONNELL
06/24/2013

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

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

Memorandum

Date: **June 12, 2013**

To: Ann Sohn, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD
Team Leader, OPDP

Subject: **NDA #200603**
Latuda® (lurasidone hydrocholoride) Tablets

OPDP acknowledges receipt of the October 11, 2012, consult request from DPP for proposed product labeling (PI) for Latuda. OPDP notes that DPP indicated on June 11, 2013, that final labeling negotiations will not be initiated during the current review cycle because a Complete Response letter will be issued. Therefore, OPDP will not provide comments on the proposed PI during this review cycle.

OPDP requests that DPP submit a new consult request during a subsequent review cycle to provide comments regarding labeling for this application.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

Thank you!

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/s/

SUSANNAH O'DONNELL
06/12/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 11, 2013

TO: Ann Sohn, Regulatory Project Manager
Mark Ritter, M.D., Clinical Reviewer
Division of Psychiatry Products

FROM John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 200-603 S10

APPLICANT: Sunovion Pharmaceuticals, Inc.

DRUG: Latuda® (lurasidone)

NME: No

INDICATION: Treatment of bipolar depression as monotherapy or as adjunctive therapy to lithium or valproate

REVIEW CLASSIFICATION:	Standard
CONSULTATION REQUEST DATE:	November 5, 2012
INSPECTION SUMMARY GOAL DATE:	April 30, 2013
ACTION GOAL DATE:	June 30, 2013
PDUFA DUE DATE:	June 30, 2013

I. Background

Bipolar disorder is a chronic, often disabling condition with 4% lifetime incidence. Complex involvement of manic and depressive phases makes treatment difficult: standard antidepressants, although widely used, may induce mania and cyclical (bipolar) symptom acceleration. Divalproex or lithium is typically used as first-line agents, often with inadequate treatment response, and mood stabilizers plus antidepressants (or atypical agents, or both) are commonly used as second line agents. Currently, only two treatment regimens are approved to treat bipolar depression (olanzapine plus fluoxetine, and quetiapine).

Lurasidone was approved in the United States (**US**) for the treatment of schizophrenia in October 2010. Based on its selective high affinity for dopamine, serotonin, and norepinephrine receptors (low affinity for histamine or acetylcholine receptors), lurasidone may be expected to be safe and effective for schizophrenia and also for bipolar depression, with little adverse effects (including extrapyramidal effects). In the two current NDA 200-603 supplements (S-10 and S-11), Sunovion Pharmaceuticals, Inc. (Sunovion) seeks approval of lurasidone for bipolar depression, as monotherapy and as adjunctive therapy to lithium or valproate. The monotherapy and adjunctive uses are supported (respectively) by Study D1050236 (S-10) and Study DI050235 (S-11).

Study D1050236

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Fixed-Flexible Dose, Parallel-Group Study of Lurasidone for the Treatment of Bipolar I Depression

This study enrolled 505 subjects at 24 sites in the US and 31 foreign sites: nine in India, five in Ukraine, four each in Czech Republic, Romania, Russia, and South Africa, and one in France. The study was conducted over about three years, from April 2009 to February 2012.

Study Objectives:

- To evaluate the efficacy of lurasidone in treating major depressive episodes associated with bipolar I disorder (diagnostic criteria per *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision,* **DSM-IV-TR**) using the following evaluation instruments:
  - Primary: Montgomery-Asberg Depression Rating Scale (**MADRS**)
  - Clinical Global Impression, Bipolar Version, Severity of Illness (**CGI-BP-S**)
  - Sheehan Disability Scale (**SDS**)
  - Quick Inventory of Depressive Symptomatology, Self Report (**QIDS-SR16**)
  - Young Mania Rating Scale (**YMRS**)
  - Hamilton Rating Scale for Anxiety (**HAM-A**)
  - Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form (**Q-LES-Q-SF)**
- To determine rates of treatment response (MADRS score reduction $\geq$ 50%) and symptom remission (MADRS score $\leq$ 12), and to evaluate safety:
  - Adverse events (**AEs**), serious AEs (**SAEs**), electrocardiogram (**ECG**) abnormalities, and suicidality using Columbia Suicide Severity Rating Scale (**C-SSRS**)
  - Movement disorders: Abnormal Involuntary Movement Scale (**AIMS**), Barnes Akathisia Rating Scale (**BARS**), and Simpson-Angus Scale (**SAS**)

Treatment Groups and Regimen:

Following medication washout (as tolerated) for at least three days before randomization, subjects were randomized (double-blinded) in equal ratio to placebo and two lurasidone dose arms. Based on

clinical response, dose was adjusted weekly by one dose level; dose reductions could be more frequent than weekly and up to two dose levels at a time.

- Lurasidone 20 to 60 mg/day: initial dose 20 mg (Days 1-7) and flexible dosing thereafter (clinical response to 20, 40, or 60 mg)
- Lurasidone 80 to 120 mg/day: initial dose 20 mg (Days 1/2), titration to 40 mg (Days 3/4), 60 mg (Days 5/6), and 80 mg (Day 7), flexible dosing thereafter (clinical response to 80, 100, or 120 mg)

Inclusion Criteria: screening and baseline

- Subjects 18 to 75 years of age (65 in Czech Republic) with bipolar I disorder, most recent episode depressed with or without rapid cycling (episodes in the last 12 months $\geq$ four and < eight)
- Current episode of major depression: confirmed and documented, $\geq$ four weeks and < 12 months, MADRS score $\geq$ 20 and YMRS score $\leq$ 12
- Lifetime history of at least one bipolar manic or mixed manic episode confirmed by reliable informant, no psychotic features (DSM-IV-TR criteria)

Exclusion Criteria: screening and baseline

- Diagnosis of an Axis I or Axis II disorder other than bipolar I disorder that was the primary focus of treatment within three months before screening
- History of non-response to an adequate (six-week) trial of three or more antidepressants (with or without mood stabilizers) during the current episode
- MADRS item 10 (suicidal thoughts) score $\geq$ four; imminent risk of suicide or injury to self, others, or property; or laboratory test results outside the reference range (at screening only)

Efficacy Endpoints/Analyses: missing data not imputed

- Primary: Change in score (baseline and Day 42): MADRS (after six weeks of treatment)
- Change in score (baseline and Day 42): CGI-BP-S, SDS, QIDS-SR16, HAM-A, and Q-LES-Q-SF
- Subject proportion: AE of mania/hypomania or YMRS score $\geq$ 16 at final or consecutive visits
- Subject proportion (MADRS scores): clinical response ($\geq$ 50% reduction) and remission ($\leq$ 12)

Safety Endpoints/Analyses: missing data imputed using last observation carried forward (LOCF)

- Proportions of subjects with AEs, discontinuations due to AEs, and SAEs
- Frequency and severity of suicidality using the C-SSRS
- Vital signs and ECG measurements
- Movement disorders assessed by the AIMS, BARS, and SAS
- Weight, laboratory measures, and physical examinations

Major Study Results

Mean (least square) MADRS scores decreased by 15, 15, and 11 for the 20-60 mg, 80-120 mg, and placebo groups, respectively ($p < 0.001$). Lurasidone therapy was well tolerated at either dose level and safety observations were consistent with those of previous schizophrenia studies. The sponsor claims that flexibly dosed lurasidone (20 to 60 mg/day or 80 to 120 mg/day) therapy is safe and effective (superior to placebo) in reducing depressive symptoms of bipolar I disorder.

Study D1050235

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of Lurasidone Adjunctive to Lithium or Divalproex for the Treatment of Bipolar I Depression

This study enrolled 348 subjects at 23 sites in the US and 35 foreign sites: 10 in India, five each in Ukraine and Czech Republic, four in South Africa, three each in Poland and Russia, two each in Romania and France, and one in Germany. The study was conducted over abut three years, from May 2009 to January 2012. Study D1050235 was identical to Study D1050236 other than as shown below.

Study Objectives:

- To evaluate the efficacy of lurasidone *in combination with lithium or divalproex* in treating major depressive episodes associated with bipolar I disorder (diagnostic criteria per DSM-IV-TR) using MADRS (primary objective), CGI-BP-S, SDS, QIDS-SR16, YMRS, HAM-A, and Q-LES-Q-SF

Treatment Groups and Regimen:

Following medication washout (as tolerated) for at least three days before randomization, subjects were randomized (double-blinded) in equal ratio to *placebo or lurasidone. For both arms, lithium or divalproex was continued, and randomization was stratified by co-therapy (lithium or divalproex).*

- Lurasidone dosing: *initial dose 20 mg (Days 1-3), increase to 40 mg (Days 4-6) and 60 mg (Day 7), flexible dosing thereafter (clinical response to 20, 40, or 60 mg)*
- *Lithium or divalproex doses were adjusted to keep trough levels within protocol-specified range. Limited use of benzodiazepines was permitted for the first three weeks and prohibited thereafter.*

Inclusion Criteria:

- *Verification of continuous treatment with lithium or divalproex for $\geq$ 28 days prior to screening by a reliable informant (all preparations of lithium, divalproex, or valproic acid permitted)*
- *Lithium or divalproex levels within protocol-defined range at screening: 0.6 to 1.2 mEq/L for lithium ($\geq$ 0.4 mEq/L permitted with medical monitor approval if 0.6 mEq/L or higher was judged to be intolerable or unsafe) and 50 to 125 ug/mL for divalproex*

Major Study Results

Mean (least square) MADRS scores decreased by 17 and 14 for lurasidone and placebo groups, respectively (p = 0.005). Lurasidone therapy was well tolerated, and safety observations were consistent with those of previous schizophrenia studies. *The combination of either lithium or divalproex with lurasidone did not have an impact on AEs. The sponsor claims that flexibly dosed lurasidone therapy (20 to 120 mg daily) in combination with lithium or divalproex is safe and effective (superior to placebo plus lithium or divalproex) in relieving bipolar depression.*

II. GCP Inspections

DPP had submitted a consult requesting two or more of seven suggested clinical study sites to be inspected in support of this NDA review. Of the seven suggested, four were selected as shown in the table below. The sites were selected randomly among those with both pivotal studies at the same site, relatively large subject enrollment in either study, and large numbers of CDER INDs or no (or remote) prior FDA inspection history. For both studies, the site-specific data for efficacy, adverse events, and protocol deviations did not appear to be significantly different among the study sites and no significant investigator conflicts of interest were noted.

Clinical Inspections for NDA 200-603 S-10 and S-11

	Clinical Investigator	Site, Studies, Subjects	Inspection Dates, Outcome
1	Rosario Hidalgo, MD University of South Florida 3515 East Fletcher Avenue Tampa, Florida 33613-4706	Site 100 D1050236: 12 subjects D1050235: 4 subjects	Nov 27 - Dec 4, 2012 VAI
2	Raymond Manning, MD CNRI - Los Angeles, LLC 8309 Telegraph Road Pico Rivera, CA 90660	Site 094 D1050236: 20 subjects D1050235: 14 subjects	Dec 12 - 19, 2012 NAI
3	David Walling, MD Collaborative Neuroscience Network 12772 Valley View Street, Suite 3 Garden Grove, CA 92845	Site 105 D1050236: 18 subjects D1050235: 9 subjects	Dec 10 - 17, 2012 Pending Preliminary NAI
4	Howard Hassman, MD CRI Worldwide, LLC 111 North 49th Street Philadelphia, PA 19139	Site 120 D1050236: 13 subjects D1050235: 8 subjects	Dec 10 - 14, 2012 NAI

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

1. Rosario Hidalgo, M.D. (Site 100)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable good clinical practice (**GCP**) regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 15 subjects were screened, 4 were enrolled, and 4 completed the study. Subject records for all enrolled subjects were reviewed completely, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 25 subjects were screened, 12 were enrolled, and 12 completed the study. Subject records for all enrolled subjects were reviewed completely, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- A Form FDA 483 was issued for the following observations:
  - Study D1050236: One subject was screened for the study one day before obtaining informed consent.

    Reviewer Comment: Informed consent should be obtained prior to enrollment into the study and not necessarily prior to screening. This observation does not warrant a Form FDA 483 citation.
  - Study D1050235: One subject was given 3 doses of erythromycin, a prohibited concomitant medication, to treat upper respiratory infection.

    Reviewer Comment:

    Three doses of the prohibited medication erythromycin were given inadvertently over 12 hours to this subject randomized to receive lurasidone plus lithium.

    Erythromycin was prohibited in the study since it inhibits CYP3A4 and prolongs the QT interval. The erythromycin doses were temporarily related to AEs of nausea and vomiting; no other AEs were observed. Erythromycin was promptly discontinued and the error was reported as a protocol violation. The report of the protocol violation in the NDA is confirmed on Protocol Deviation Listing 16.2.2.

    This isolated error appears unlikely to have affected the efficacy data for this subject. The safety data may have been affected; AEs of nausea and vomiting appears to have been due to erythromycin and not the study medication. Overall, however, this isolated error does not appear to be significant.
- Observation not cited on Form FDA 483: In Study D1050236, for Subject 23610008, Week 3 YMRS Item 5 (Irritability) and Item 6 (Speech) differed between the CRF and the NDA data listing. CRF showed Item 5 score of 2 (irritability "subjectively increased") and Item 6 score of 2 (speech "feels talkative"), whereas the NDA data listing showed corresponding scores of 0 for both items (irritability "absent" and speech "no increase").

  Reviewer Comment:

  YMRS total score of $\geq$ 16 at final or consecutive visits is an important safety observation. For this subject randomized to placebo, the Week 3 YMRS total score in the NDA (score 2) is different from that noted on the CRF (score 6). This discrepancy does not appear to be significant; however, the discrepancy appears to have resulted from the sponsor's error in data handling. Extensive review of CRF data showed no other discrepancies. Although this discrepancy could not be resolved, it appears to be an isolated error without broader implications for overall data integrity.
- Other than as noted above, endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings. Underreporting of AEs was not observed.
- All subjects signed the informed consent document. Drug accountability was well documented. IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity:

The single minor deficiency observed at this site (use of prohibited medication) is reported in the NDA as a protocol violation. Data from this study site appear reliable.

2. Raymond Manning, M.D. (Site 094)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 23 subjects were screened, 14 were enrolled, and 12 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 26 subjects were screened, 20 were enrolled, and 15 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Underreporting of AEs was not observed. Drug accountability was well documented.
- Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

3. David Walling, M.D. (Site 105)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 42 subjects were screened, 9 were enrolled, and 6 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 43 subjects were screened, 18 were enrolled, and 14 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Underreporting of AEs was not observed. Drug accountability was well documented.

Reviewer Comment: Two of the nine subjects enrolled in Study D1050235 were not listed on subject enrollment log: Subject 23510528 (lurasidone) and Subject 23510538 (placebo). This minor isolated deficiency was not noted at inspection (noted post-inspection, comparison of inspectional finding versus NDA data listing), and therefore was neither discussed verbally nor cited on Form FDA 483. Other than as an isolated example of imperfect record keeping, this deficiency does not appear to be significant.

- Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 105 are based on preliminary communications with the field investigator.

4. Howard Hassman, M.D. (Site 120)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects, D1050235: 38 subjects were screened, 8 were enrolled, and 8 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.
- Subjects, D1050236: 28 subjects were screened, 13 were enrolled, and 13 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor deficiencies were verbally discussed (not cited on Form FDA 483):
  - In Study D1050236, for Subject 23612008, the source record for Week 1 CGI-BP showed mania score 2, and not 1 as reported in the corresponding NDA data listing.
  - In Study D1050235, for Subject 23512036, the source record for Visit 2 HAM-A showed gastrointestinal symptom score 0 (question 11), genitourinary symptom score 2 (question 12), and total score 13. These source scores of 0, 2, and 13 differed from the corresponding scores of 2, 1, and 14 reported in the corresponding NDA data listing.

    Reviewer Comment: These two minor discrepancies between source records and the NDA data listing presumably resulted from data entry errors (source data accurate, NDA data inaccurate). The errors involved secondary endpoints and appear trivial in significance. Follow-up investigation indicated that the observed discrepancies were isolated and did not suggest an underlying systematic deficiency in data handling; no other data discrepancies were observed.

- Other than as noted above, endpoint data were verifiable. Data matched among source records, CRFs, and NDA data listings. Underreporting of AEs was not observed.
- All subjects signed the informed consent document. Drug accountability was well documented. IRB oversight and study monitoring appeared adequate.

c. Assessment of data integrity: The observed deficiencies appear to be minor and isolated, and are not expected to have an impact on study results. Data from this study site appear reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical study sites that participated in Studies D1050235 and D1050235 were selected for GCP inspection. The sites were selected randomly among those with both pivotal studies at the same site, relatively large subject enrollment, and remote (or no) prior FDA inspection history.

At all four study sites, the observed deficiencies were limited to minor, apparently isolated deficiencies. No significant deficiencies were seen at Site 94 (Manning) and at Site 105 (Walling). At Site 120 (Hassman), the deficiency observations were discussed verbally without issuing a Form FDA 483. At Site 100 (Hidalgo), a Form FDA 483 was issued. None of the deficiencies are expected to have an important impact on the study outcome. The data from the four inspected clinical study sites appear reliable as reported in the NDA.

Note: For Site 105 (Walling), the establishment inspection report has not been received from the field office and the final inspection outcome classification remains pending. An addendum to this clinical inspection summary will be forwarded to DPP if the inspection outcome classification changes or if additional observations of clinical or regulatory significance are discovered after receipt and review of the final establishment inspection report.

{See appended electronic signature page}

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/s/

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02/11/2013

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02/11/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Labeling Review

Date:	January 25, 2013
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Latuda (Lurasidone Hydrochloride) Tablets 20 mg, 40 mg, 80 mg, and 120 mg
Application Type/Number:	NDA 200603
Applicant:	Sunovion Pharmaceuticals Inc.
OSE RCM #:	2012-2390

***** This document contains proprietary and confidential information that should not be released to the public.*****

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1 INTRODUCTION

This review evaluates the proposed insert labeling for Latuda (Lurasidone) Tablets, 20 mg, 40 mg, 80 mg, and 120 mg. On August 31, 2012, Sunovion Pharmaceuticals Inc. submitted two efficacy supplements (NDA 200603/S-010 and S-011) which seek approval for the use of Latuda in the treatment of patients with the following conditions:

- Depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy (S-010)
- Depressive episodes associated with bipolar I disorder (bipolar depression) as adjunctive therapy to lithium or valproate (S-011).

No new strengths or packaging configurations were proposed in the supplements.

1.1 REGULATORY HISTORY

Latuda was approved on October 28, 2010 for the treatment of patients with schizophrenia.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 31, 2012 submission.

- Active Ingredient: Lurasidone Hydrochloride
- Indications of Use: Treatment of schizophrenia (approved indication); treatment of depressive episodes associated with bipolar disorder (bipolar depression), both as monotherapy and as an adjunct to lithium or valproate (proposed indications)
- Route of Administration: Oral
- Dosage Form: Tablets
- Strengths: 20 mg, 40 mg, 80 mg, and 120 mg
- Dose and Frequency: Dosage range 20 mg to 120 mg per day (see Appendix A)
- How Supplied: 30, 90, and 500-count bottles; Hospital Unit Dose cartons containing 10 blister cards with 10 tablets per blister card
- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Latuda medication error reports. We also reviewed the Latuda insert labeling submitted by the Applicant on August 31, 2012.

2.1 SELECTION OF MEDICATION ERROR CASES

Since Latuda is a currently marketed product in the U.S., DMEPA searched the FAERS (FBIS) database on December 11, 2012 to identify medication error cases that might be relevant to this review of the proposed insert labeling. DMEPA used the search strategy listed in Table 1.

Table 1: FAERS (FBIS) Search Strategy	
Date	10/28/10 (date of Latuda approval) through 12/11/12
Drug Names	Active Ingredient: Lurasidone Trade Name: Latuda
MedDRA Search Strategy	HLGT: Medication Errors HLTs: Product Label Issues; Product Packaging Issues; and Product Quality Issues NEC

The FAERS (FBIS) database search identified 16 cases. Each case was reviewed for relevancy and duplication. After individual review, 15 of the 16 cases were not included in the final analysis for the following reasons:

- Intentional overdose of Latuda
- Intentional overdose of a different drug, Latuda was a concomitant medication
- Multiple drug overdose
- Overdose—the case does not state whether or not the overdose was intentional or accidental and there was not enough information provided to assess the case
- Adverse drug events not related to a medication error
- Product complaint—lack of effect
- Dose omission of a different drug, Latuda was a concomitant medication
- Wrong patient
- Duplicate case

2.2 LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed insert labeling submitted on August 31, 2012. We also compared it against the current insert labeling approved on April 26, 2012.

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously conducted a search of the FDA Adverse Events Reporting System (AERS) database on June 18, 2012 for inclusion in the Latuda FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary, dated September 10, 2012. DMEPA used the following search strategy:

- The Adverse Event Reporting System (AERS) database was searched on June 18, 2012 using the MedDRA High Level Group Terms (HLGT's) "Medication Errors" and "Product Quality Issues" along with the active ingredient name "Lurasidone" and "Lurasidone Hydrochloride", the trade name "Latuda", and the verbatim names "Latu%" and "Lura%". The time frame for this search was determined to be October 28, 2010 (approval date of Latuda) to April 30, 2012 (lock date for the 915 review). This search strategy retrieved 10 reports.

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes the results of the FAERS search and our risk assessment of the Latuda insert labeling.

3.1 MEDICATION ERRORS CASES

Following exclusions as described in Section 2.1, one Latuda medication error case remained for our detailed analysis. This case described an overdose error. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[1].

Overdose

- Case # 8271556 (version 1) described a 19 year old patient who initiated therapy with Latuda 40 mg qhs for paranoid schizophrenia. After taking 80 mg the next day, the patient had a grand mal seizure (medical history included seizure disorder) and required resuscitation. He was hospitalized and recovered. Latuda was discontinued. There was no information provided regarding the contributing factors to the overdose.

3.2 INSERT LABELING

Our review of the insert labeling identified the following deficiencies:

- Highlights of Prescribing, Dosage and Administration
  - In the table, dashes are used to express dosage ranges. Additionally, the dosage unit does not accompany each numerical dose (e.g., 40-160 mg/day).
- Full Prescribing Information, Dosage and Administration, Section 2.4 Dose Modifications in Special Populations
  - The error-prone symbol "<" (less than) is used which can be misinterpreted to mean the opposite (greater than).[2]

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

[2] Institute for Safe Medication Practices. ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations. Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf

3.3 PREVIOUSLY COMPLETED REVIEW

Our June 18, 2012 AERS search did not identify any cases that provide new safety information requiring a change to the labeling. Additionally, there were no issues identified that impact this review of efficacy supplements S-010 and S-011.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes the proposed insert labeling can be improved to minimize the potential for confusion that can lead to medication errors. Based on this review, DMEPA provides comments in Section 4.1 below for DPP's consideration.

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Highlights of Prescribing Information, Dosage and Administration Section

   In the dosage table, dashes are used to express dosage ranges which can be misinterpreted as periods. Additionally, the dosage unit does not accompany each numerical dose (e.g., 40-160 mg/day) but could be included to provide clarity. Thus, we recommend that dash marks should be replaced with the word "to" and all doses be accompanied by their dosage unit. For example, revise "40-160 mg/day" to read: "40 mg/day to 160 mg/day"

2. Full Prescribing Information, Dosage and Administration, Section 2.4 Dose Modifications in Special Populations

   The error-prone symbol "<" (less than) is used, which can be misinterpreted to mean the opposite (greater than). Therefore, consider replacing the symbol "<" with the words "less than".

If you have further questions or need clarifications, please contact Sandra Rimmel, OSE Project Manager, at 301-796-2445.

APPENDICES

APPENDIX A. LATUDA PROPOSED DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION

(b) (4)

APPENDIX B. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

LORETTA HOLMES
01/25/2013

SCOTT M DALLAS on behalf of IRENE Z CHAN
01/25/2013

SCOTT M DALLAS
01/25/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 200603 BLA#	NDA Supplement #:S-010 and S-011 BLA Supplement #	Efficacy Supplement Type SE- 1
Proprietary Name: Latuda Established/Proper Name: lurasidone HCl Dosage Form: tablet Strengths: 20 mg, 40 mg, 80 mg, 120 mg		
Applicant: Sunovion Pharmaceuticals, Inc. Agent for Applicant (if applicable): Bridget Walton		
Date of Application: 8/31/12 Date of Receipt: 8/31/12 Date clock started after UN: 8/31/12		
PDUFA Goal Date: 6/30/13	Action Goal Date (if different):	
Filing Date: 10/30/12	Date of Filing Meeting: 10/11/12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) n/a		
Proposed indication(s)/Proposed change(s): depressive episodes associated with bipolar I disorder monotherapy, depressive episodes associated with bipolar I disorder adjunctive to lithium or valproate		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 61292	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff:*			X	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/17/12

BLA/NDA/Supp #: 200603/S-010 and S-011

PROPRIETARY NAME: Latuda

ESTABLISHED/PROPER NAME: lurasidone HCl

DOSAGE FORM/STRENGTH: tablet/ 20 mg, 40 mg, 80 mg, 120 mg

APPLICANT: Sunovion Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): depressive episodes associated with bipolar I disorder monotherapy, depressive episodes associated with bipolar I adjunctive to lithium or valproate

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ann Sohn	
	CPMS/TL:	Keith Kiedrow	
Cross-Discipline Team Leader (CDTL)	Bob Levin		
Clinical	Reviewer:	Mark Ritter	
	TL:	Bob Levin	
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Islam Younis	
	TL:	Hao Zhu	
Biostatistics	Reviewer:	Thomas Birkner	
	TL:	Peiling Yang	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sonia Tabacova	
	TL:	Aisar Atrakchi	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Chhagan Tele	
	TL:		
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Division Director, Thomas Laughren **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN J SOHN
10/11/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

RISK ASSESSMENT AND RISK MITIGATION REVIEWS(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	May 24, 2013
Reviewer(s):	Jason Bunting, PharmD, Risk Management Analyst Division of Risk Management
Team Leader	Reema Mehta, PharmD, MPH Division of Risk Management
Division Director	Claudia Manzo, PharmD Division of Risk Management
Subject:	Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	Latuda® (lurasidone HCl)
Therapeutic Class:	Atypical antipsychotics
Dosage and Route:	20 mg, 40 mg, 80 mg, and 120 mg oral tablets
Application Type/Number:	NDA 200603
Submission Number:	Supplement 010 and Supplement 011
Applicant/sponsor:	Sunovion Pharmaceuticals, Inc.
OSE RCM #:	2012-2403

1 INTRODUCTION

This review documents DRISK's evaluation to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) for Latuda® (lurasidone) oral tablets of two supplemental New Drug Applications (sNDAs) to NDA 200603, Supplement-010 and Supplement-011. The proposed indications, for Supplement-010 and Supplement-011, are for the treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and for the treatment of patients with depressive episodes associated with bipolar I disorder as adjunctive therapy to lithium or valproate, respectively. The Sponsor, Sunovion Pharmaceuticals, Inc, did not submit a proposed REMS for either of these supplements, nor is there a REMS for the currently approved indication.

1.1 BACKGROUND

Latuda (lurasidone) is an atypical antipsychotic that is currently approved for the treatment of patients with schizophrenia. The Sponsor has proposed Latuda be approved for the treatment of patients with depressive episodes associated with bipolar I disorder both as monotherapy and as adjunctive therapy to lithium or valproate.

Lurasidone is an antagonist with high affinity binding at the dopamine D_2 receptors and the 5-HT serotonin receptors, 5-HT_{2A} and 5-HT_7. It also binds with moderate affinity at the human α_{2C} adrenergic receptors, is a partial agonist at serotonin 5-HT_{1A} receptors, and is an antagonist at the α_{2A} adrenergic receptors.

Latuda is available as 20 mg, 40 mg, 80 mg, and 120 mg oral tablets. The recommended starting dose of Latuda for schizophrenia is 40 mg once daily and the maximum recommended dose is 160 mg daily. The proposed starting dose of Latuda for bipolar depression is 20 mg once daily as monotherapy or as adjunctive therapy with lithium or valproate and the maximum dose is 120 mg daily.

Latuda has a boxed warning for an increased risk of mortality in elderly patients with dementia-related psychosis. An analysis of 17 placebo-controlled trials revealed an increased risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Most deaths were cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. There is no REMS for the currently approved indication.

Other atypical antipsychotics include: olanzapine, asenapine, clozapine, risperidone, quetiapine, paliperidone, aripiprazole, ziprasidone, and iloperidone. The atypical antipsychotics indicated for the treatment of depressive episodes associated with bipolar I disorder include: quetiapine, as monotherapy, and olanzapine, when used in combination with fluoxetine.

1.2 REGULATORY HISTORY

On October 28, 2010, Latuda was approved for the treatment of patients with schizophrenia. The application for Latuda was not referred to an FDA advisory

committee because this drug is not the first in its class and the safety profile is similar to that of other drugs approved for schizophrenia. A REMS was not required at the time of initial approval of Latuda and no new safety information has arisen since approval warranting the need for a REMS.

On August 31, 2012, the Sponsor submitted two efficacy supplements, Supplement-010 and Supplement-011, for the treatment of depressive episodes associated with bipolar I disorder as monotherapy and adjunctive therapy to lithium or valproate, respectively. The application was filed for both supplements 60 days later and classified as a standard review with a PDUFA action date of June 30, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Sunovion Pharmaceuticals Inc. Summary of Clinical Safety for Latuda (lurasidone), received August 31, 2012
- Sunovion Pharmaceuticals Inc. draft Prescribing Information for Latuda (lurasidone), received August 31, 2012

3 REVIEW FINDINGS FOR LATUDA

3.1 OVERVIEW OF CLINICAL PROGRAM

Latuda was studied in patients with depressive episodes associated with bipolar I disorder in two randomized, 6-week, double-blind, placebo-controlled, flexible-dose, phase-III studies to support the clinical safety and efficacy of Latuda in Supplement-010 (study D1050236) and Supplement-011 (study D1050235). In study D1050236, 505 patients were randomized in a 2:1 ratio to receive Latuda alone (n=331) or placebo (n=168); six patients were randomized, but not exposed. In study D1050235, 348 patients were randomized in a 1:1 ratio to receive Latuda (n=183) or placebo (n=163) as adjunctive therapy with lithium or valproate; two patients were randomized to placebo, but discontinued study. Dosing in both studies was flexible and ranged from 20 mg to 120 mg of Latuda daily. The primary endpoint of the studies was the mean change from baseline to week six on the Montgomery-Asberg Depression Rating Scale (MADRS) and the secondary endpoint was mean change from baseline to week six on the Clinical Global Impressions – Severity: Bipolar Version (CGI-BP-S) scale.

Clinical safety was also supported by an ongoing open-label, 6-month extension study (study D1050256), three ongoing serious adverse events studies (studies D1050295, D1050296, and D1050298), a recently completed clinical pharmacology study (study D1050294), the Sunovion postmarketing database for Latuda, and published literature.

Key Efficacy Findings: In both the monotherapy and adjunctive therapy studies, the mean change in MADRS score at week six had decreased by -15.4 to -17.1 in the Latuda treated group as compared to -10.7 to -13.5 for the placebo group. Additionally, the mean change in CGI-BP-S score at week six had decreased by -1.71 to -1.96 in the Latuda treated group as compared to -1.14 to -1.51 for the placebo group.

Key Safety Findings: The most frequent treatment-emergent adverse events (TEAEs) reported in clinical trials that occurred in ≥5% of treatment subjects and at a higher frequency than in the placebo group were:

Treatment-emergent Adverse Events	Monotherapy		Adjunctive Therapy	
	Latuda (N=331) n (%)	Placebo (n=168) n (%)	Latuda (n=183) n (%)	Placebo (n=163) n (%)
Nausea	46 (13.9%)	13 (7.7%)	32 (17.5%)	18 (11.0%)
Parkinsonism	21 (6.3%)	4 (2.4%)	26 (14.2%)	14 (8.6%)
Somnolence	35 (10.6%)	11 (6.5%)	20 (10.9%)	9 (5.5%)
Akathisia	31 (9.4%)	4 (2.4%)	14 (7.7%)	7 (4.3%)

A total of 29 (5.8%) subjects in the monotherapy study, 20 (6.0%) Latuda treated and 9 (5.4%) placebo treated, and 22 (6.4%) subjects in the adjunctive study, 11 (6.0%) Latuda treated and 11 (6.7%) placebo treated, discontinued study drug as a result of TEAEs. *Reviewer Comment: This indicates that there was no difference in study discontinuation, due to TEAEs, between Latuda treated and placebo treated patients.* There were no deaths reported in the two pivotal studies.

The ongoing open-label extension study showed an overall adverse event profile similar to the two pivotal studies. There were two deaths in the open-label extension study; however, the causes of death were not considered to be related to Latuda (death due to suicide and a traffic accident).

The demonstrated safety profile for Latuda based on the available safety data is consistent with the known safety profile for other atypical antipsychotics.

4 DISCUSSION

Latuda is an atypical antipsychotic approved for the treatment of schizophrenia. There are few other oral atypical antipsychotics currently approved for the proposed indication (i.e., olanzapine used in combination with fluoxetine and quetiapine as monotherapy).

Latuda, as with other atypical antipsychotics, is associated tardive dyskinesia, metabolic changes, hyperprolactinemia, and potential for cognitive and motor impairment. The safety profile of Latuda, as demonstrated in the pivotal trials (study D1050236 and D1050235) is consistent with the known safety profile for the product. The most frequently reported TEAEs were mild in severity and caused discontinuation of study drug at a similar rate to placebo. No cases of death associated with the administration of Latuda have been reported.

Therefore, based on the currently available data, the benefits of Latuda for the proposed indications outweigh the risks of Latuda. Additionally, the safety profile of Latuda is similar to that of other atypical antipsychotic medications. The risks associated with Latuda and other atypical antipsychotics are mitigated through professional labeling.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Latuda. The safety profile for Latuda for the proposed indications is consistent with

the known safety for Latuda. There were no new or unique safety concerns associated with Latuda in the pivotal trials for Supplement-010 and -011. Furthermore, Latuda does not currently have a REMS for the approved indication.

Should DPP raise further concerns with the risks outlined above or identify additional risks associated with Latuda warranting more extensive risk mitigation or a formal REMS, please send a consult to DRISK.

This review serves to close the existing consult request for Latuda under NDA 200-603, Supplement-010 and Supplement-011. Please notify DRISK if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JASON A BUNTING
05/24/2013

CLAUDIA B MANZO
05/24/2013
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-603/S010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200603 SUPPL # 10, 11 HFD # 130

Trade Name Latuda

Generic Name lurasidone hydrochloride

Applicant Name Sunovion Pharmaceuticals, Inc.

Approval Date, If Known June 28, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

S-010: A Randomized, 6-week, double-blind, placebo-controlled, fixed-flexible dose, parallel-group study of lurasidone for the treatment of bipolar I depression (Study D1050236)

S-011: A Randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel-group study of lurasidone adjunctive to lithium or divalproex for the the treatment of bipolar I depression (Study D1050235)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Study D1050236: a randomized, double-blind, placebo-controlled trial of lurasidone monotherapy in bipolar depression.

2. Study D1050235: a randomized, double-blind, placebo-controlled trial of lurasidone adjunctive therapy (with lithium or valproate) in bipolar depression.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 103427	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 103427	YES ☒	! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Ann Sohn
Title: Regulatory Project Manager
Date: 6/28/13

Name of Office/Division Director signing form: OND/ODE1/Mitchell V. Mathis, M.D.
Title: Director (acting), Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN J SOHN
06/28/2013

MITCHELL V Mathis
06/28/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 200603 BLA #	NDA Supplement # 10, 11 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Latuda Established/Proper Name: lurasidone hydrochloride Dosage Form: Tablet		Applicant: Sunovion Pharmaceuticals, Inc. Agent for Applicant (if applicable): Bridget Walton
RPM: Ann Sohn		Division: Psychiatry Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 30, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	6/28/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 6/28/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	8/31/12
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 6/28/13 ☒ DMEPA 1/25/13 ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 6/24/13 ☐ SEALD Memo 6/27/13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	10/11/12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/1/13 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 6/28/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/8/13, 6/20/13, 6/27/13
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	5/30/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 5/24/13
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 2/11/13, 6/27/13

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 5/30/13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 6/27/13
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/10/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 10/2/12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/2/12
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

ANN J SOHN
06/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Ann Sohn/RPM, OND/DPP/301-796-2232

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
06/21/13		200603/S-010, S-011	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Latuda (lurasidone HCl)	Standard	Antipsychotic	

NAME OF FIRM:	
Sunovion Pharmaceuticals, Inc.	PDUFA Date: June 28, 2013

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA200603\0076
\\CDSESUB1\EVSPROD\NDA200603\0077

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

SIGNATURE OF REQUESTER
Ann Sohn, RPM
301-796-2232
Ann.sohn@fda.hhs.gov

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL ☐ HAND

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/s/

ANN J SOHN
06/21/2013

MITCHELL V Mathis
06/21/2013

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date:	March 4, 2013
To:	Ann Meeker-O'Connell, Acting Division Director, DGCPC Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB Susan Thompson, M.D., Acting Branch Chief, GCPAB Janice Pohlman, M.D., M.P.H., Team Leader GCPAB Susan Leibenhaut, M.D. Acting Team Leader, GCPAB CDER OSI PM Track Division of Good Clinical Practice Compliance Office of Scientific Investigations, OC/CDER
Through:	Mark Ritter, M.D., Medical Officer, Division of Psychiatry Products Robert Levin, M.D., Medical Team Leader, Division of Psychiatry Products Mitchell Mathis, M.D., Director, Division of Psychiatry Products
From:	Ann Sohn/Regulatory Project Manager/ Division of Psychiatry Products
Subject:	Request for Additional (Foreign) Clinical Site Inspections

I. General Information

Application: NDA 200603 / S-010 and S-011
IND: 61292, 103427
Applicant/Applicant contact information (to include phone/email):

Sunovion Pharmaceuticals, Inc.
Bridget Walton, MS, RAC
Director, Regulatory Affairs
201-228-8333 (office)
Bridget.walton@sunovion.com

Drug Proprietary Name: Latuda
Generic Drug Name: Lurasidone
NME or Original BLA: No
Review Priority: Standard
Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No

Proposed New Indications:

1) Major Depressive episodes associated with Bipolar I Disorder – Monotherapy (S-010)
2) Major Depressive episodes associated with Bipolar I Disorder – Adjunctive therapy (S-11)

PDUFA: June 30, 2013
Inspection Summary Goal Date: May 15, 2013

II. Study Protocols and Sites

Name and Address Contact (phone, email)	Site Number Protocol (Subjects)	Major Endpoints to be Verified
Vladimir Tochilov City Psychiatric Hospital #2 of St. Nikolay Chudotvorets Pchyhiary and Narcology Moika River Embankment 126 St. Petersburg 190121, Russia	**Site 191** D1050235 (13 subjects) D1050236 (22 subjects)	Primary: MADRS Secondary: CGI-BP
Michaela Klabusayova Psychiatricka ambulance Divadelni 616/4 Brno – Mesto 602 00 Czech Republic	**Site 618** D1050235 (17 subjects) D1050236 (17 subjects) D1050292 (4 subjects)	Primary: MADRS Secondary: CGI-BP

III. Site Selection Rationale

The European sites listed above are significant outliers with large treatment effects, as measured by the Montgomery Asberg Depression Rating Scale (MADRS). In addition, Site 191 demonstrates an unusual pattern of homologous decline in symptom severity among all subjects within the site. Furthermore, after removing pairs of some of these highly influential sites, the overall results of Study 235 are negative. The overall positive effects in both studies (235 and 236) are driven by positive findings at the European sites. Furthermore, both studies were negative in US sites. US subjects account for only approximately 40% of all subjects in both studies. For both studies, the findings were also negative in Asia and Africa. We have concerns about the pattern of these findings and the possibility of problems with reliability of the data.

Foreign Inspections (*please check all that apply*):

___ Insufficient domestic data

___ Only foreign data

_X_ Conflicting domestic and foreign data

_X_ Serious concerns, including suspicion of fraud, scientific misconduct, or significant human subject protection violations

_X_ Other: In both studies, the results are negative for the US sites, the Asian sites, and the African sites. Only 40% of subjects are from US sites. The results are driven by data from European sites. There are significant outliers with large treatment effects in European sites, and there are unusual patterns of efficacy results in some outlier sites. Study 235 is negative overall after removal of Sites 191 and 618.

Five or More Sites: Please refer to the reasons listed above.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified *(if applicable)*:

For specific data that need to be verified, please provide a data table.

Should you require any additional information, please contact RPM Ann Sohn at 301-796-2232 or clinical team leader Robert Levin at 301-796-1110.

CONCURRENCE:

Robert Levin, M.D.	Medical Team Leader
Mark Ritter, M.D.	Medical Reviewer
Mitchell Mathis, M.D.	Division Director (foreign or $\geq$ 5 sites)

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/s/

ANN J SOHN
03/04/2013

MITCHELL V Mathis
03/04/2013

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: February 22, 2013

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
John Lee, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Mark Ritter/ Medical Officer/Division of Psychiatry Products
Robert Levin/Medical Team Leader/ Division of Psychiatry Products
Mitchell Mathis/Director/ Division of Psychiatry Products

From: Ann Sohn/Regulatory Project Manager/ Division of Psychiatry Products

Subject: **Request for Additional, Foreign Clinical Site Inspections**

I. General Information

Application#: NDA 200603/S-010 and S-011
IND#: 61292, 103427
Applicant/Applicant contact information (to include phone/email):
Sunovion Pharmaceuticals, Inc.
Bridget Walton, MS, RAC
Director, Regulatory Affairs
201-228-8333 (office)
Bridget.walton@sunovion.com

Drug Proprietary Name: Latuda
Generic Drug Name: Lurasidone
NME or Original BLA: No
Review Priority: Standard
Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No

Proposed New Indications:

OSI/DGCPC Consult
version: 01/16/2013

1) Major Depressive episodes associated with Bipolar I Disorder – Monotherapy (S-010)
2) Major Depressive episodes associated with Bipolar I Disorder – Adjunctive therapy to lithium or valproate (S-11)

PDUFA: June 30, 2013
Action Goal Date:
Inspection Summary Goal Date: May 15, 2013

II. Protocol/Site Identification

In order of importance: 191, 618, 237, 238, 240, 190, 192

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site 191: Russia Tochilov, Vladimir City Psychiatric Hospital #2 of St. Nikolay Chudotvorets Pchyhiary and Narcology Moika River Embankment 126 St. Petersburg 190121	D1050- 235 236	 13 22	Primary: MADRS Key Secondary: CGI-BP
Site 618: Czech Republic Klabusayova, Michaela Psychiatricka ambulance Divadelni 616/4 Brno – Mesto 602 00	235 236	17 17	Primary: MADRS Key Secondary: CGI-BP
Site 237: Ukraine Bitenskyy, Valeriy Odesa Regional Psychoneurological Dispensary Department #1,2 27, Kanatna Odesa 65014	235 236	5 13	Primary: MADRS Key Secondary: CGI-BP
Site 238: Ukraine Rymsha, Sofiya Reg. Psych. Hosp.n.a.O.Yuschenko, Dept #21 VNMU n.a. M. Pirogov Chair of Psychiatry, Gen. and Med. Psychology 109, Pirogov Str. Vinnitsia 21018	235 236	6 10	Primary: MADRS Key Secondary: CGI-BP
Site 240: Ukraine Verbenko, Viktoriya CRI" Cl. Psych. Hosp. #1", Fem. Psych. Dept.#2, Male Psych. Dept. #1 Chair of Psychiatry, Psychotherapy and Narcology Crimean SMU n.a. S.I. Georgiyevskyy 27, Rozy Luxembourg Str. Simferopol 95006	235 236	6 10	Primary: MADRS Key Secondary: CGI-BP

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site 190: Russia Kozlovsky, Vladimir Psychoneurology Dispensary #4 Psychiatric 6, Pudozhskaya Str. St. Petersburg 197110	235 236	2 4	Primary: MADRS Key Secondary: CGI-BP
Site 192: Russia Vid, Viktor Bekhterev Scientific Research Psychoneurological Institute Rehabilitation Therapy of Psychiatric Patients 3, Bekhterev Str. St. Petersburg 193019	235 236	4 4	Primary: MADRS Key Secondary: CGI-BP

III. Site Selection/Rationale

The European sites listed above are significant outliers with large treatment effects, as measured by the Montgomery Asberg Depression Rating Scale (MADRS). In addition, Site 191 demonstrates an unusual pattern of homologous decline in symptom severity among all subjects within the site. Furthermore, after removing pairs of some of these highly influential sites, the overall results of Study 235 are negative. The overall positive effects in both studies (235 and 236) are driven by positive findings at the European sites. Furthermore, both studies were negative in US sites. US subjects account for only approximately 40% of all subjects in both studies. For both studies, the findings were also negative in Asia and Africa. We have concerns about the pattern of these findings and the possibility of problems with reliability of the data.

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
X Domestic and foreign data show conflicting results pertinent to decision-making
X There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
_X_ Other: In both studies, the results are negative for the US sites, the Asian sites, and the African sites. Only 40% of subjects are from US sites. The results are driven by data from European sites. There are significant outliers with large treatment effects in European sites, and there are unusual patterns of efficacy results in some outlier sites. After removing some pairs of these highly influential European sites from the analysis, Study 235 is negative overall (after removal of sites 191 and 618). We have not conducted analyses removing more than 2 influential sites at a time.

Five or More Inspection Sites:
Please refer to the reasons listed above.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact RPM Ann Sohn at 301-796-2232 or clinical team leader Robert Levin at 301-796-1110.

Concurrence: (as needed)

Robert Levin, M.D.	Medical Team Leader
Mark Ritter, M.D.	Medical Reviewer
Mitchell Mathis, M.D.	Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

ANN J SOHN
02/25/2013

MITCHELL V Mathis
02/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200603/S-010 and S-011

INFORMATION REQUEST

Sunovion Pharmaceuticals, Inc.
Attention: Bridget Walton, MS, RAC, Director
Regulatory Affairs
One Bridge Plaza
Suite 510
Fort Lee, NJ 07024

Dear Ms. Walton:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latuda (lurasidone hydrochloride) 20 mg, 40 mg, 80 mg, and 120 mg tablets.

We are reviewing your submissions and have the following requests and comments regarding studies **D1050235, D1050236, and D1050292.** We request a prompt written response in order to continue our evaluation of your supplemental applications.

[1] **Supplement 11 for the adjunctive therapy study (D1050235**)
The US demonstrated an unfavorable trend in efficacy outcomes for the primary and the key secondary measures. Please evaluate the potential factors/sources that may account for the observed heterogeneity across regions, particularly the unfavorable trend in the US.

[2] **Supplement 10 for the monotherapy study (D1050236)**
Although the US demonstrated a favorable trend in efficacy outcomes, the observed dose-response findings are opposite to that in the non-US sites (i.e., in the US the lower dose range of 20-60 mg appeared numerically more effective than the higher range dose range of 80-120 mg). Evaluate this as well.

[3] **Both Supplements**
Please provide the results of your evaluations requested above as well as relevant SAS programs.

[4] **Study D1050292**
We request that you submit to the NDA all efficacy and safety data from Study D1050292. This will be necessary in order for us to complete the reviews of the NDA supplements. Please submit the following items pertaining to the primary and the key secondary efficacy variables:

(a) The raw as well as derived variables;
(b) SAS programs that produced the derived variables from the raw variables;

(c) SAS programs that produced efficacy outcomes;
(d) All variables related to demographics/baseline characteristics/dosing, as well as other variables needed for efficacy analysis;
(e) Include also a variable indicating whether the participant was naïve or non-naïve to lithium or divalproex at the outset of the study. Indicate whether the randomization was stratified by this variable. Conduct and submit exploratory subgroup analyses stratified by this variable if not considered during randomization.
(f) A list of serial numbers and submission dates of the protocol, SAP, amendments, and relevant meetings under IND 103,427, as well as FDA feedback pertaining to this study.
(g) The requests associated with [1] to [3] above also apply to this study.

Additional requests regarding Study **D1050292**:

- Please submit the data sets for all safety parameters.
- Provide an integrated summary of safety for adjunctive studies D1050292 and D1050235.
- Provide a list of investigators, study sites, addresses, and number of subjects at each site.
-

[5] **Audits of Sites**
Please provide any information about site audits. Were there audits of non-US sites? Were there any findings of concern for any of the sites in the three studies?

[6] **MADRS Rater Quality Control**
We note that there was a rater quality control system for MADRS ratings for all sites in studies 235 and 236. Was there a similar system for study 292? We request that you submit a summary of the quality control data obtained from the studies, as well as the metrics and analyses that were used to monitor sites. We also request that you provide summary data regarding the analyses by site, rater, country, and geographic region. Please provide the vendor's reports on the remote rater program, correspondences with the vendor, and results of audits. We also request you provide a summary of the RRM software used and the study thresholds used by the software to analyze site data.

For Study 235, we note that you implemented MADRS audio recordings for all non-U.S. sites as a quality control measure (refer to protocol amendment 2, dated July 17, 2009). Please provide a summary of vendor feedback given to each rater and site, including a summary of any issues noted by the vendor regarding MADRS assessments at non-US sites.

We request that you submit the requested information by March 18, 2013.

If you have questions, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
02/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200603/S-010 and S-011

INFORMATION REQUEST

Sunovion Pharmaceuticals, Inc.
Attention: Bridget Walton, MS, RAC, Director
Regulatory Affairs
One Bridge Plaza
Suite 510
Fort Lee, NJ 07024

Dear Ms. Walton:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latuda (lurasidone hydrochloride) 20 mg, 40 mg, 80 mg, and 120 mg tablets.

We are reviewing your submissions and have the following requests and comments regarding studies **D1050235, D1050236, and D1050292.** We request a prompt written response in order to continue our evaluation of your supplemental applications.

[1] **Supplement 11 for the adjunctive therapy study (D1050235**)
The US demonstrated an unfavorable trend in efficacy outcomes for the primary and the key secondary measures. Please evaluate the potential factors/sources that may account for the observed heterogeneity across regions, particularly the unfavorable trend in the US.

[2] **Supplement 10 for the monotherapy study (D1050236)**
Although the US demonstrated a favorable trend in efficacy outcomes, the observed dose-response findings are opposite to that in the non-US sites (i.e., in the US the lower dose range of 20-60 mg appeared numerically more effective than the higher range dose range of 80-120 mg). Evaluate this as well.

[3] **Both Supplements**
Please provide the results of your evaluations requested above as well as relevant SAS programs.

[4] **Study D1050292**
We request that you submit to the NDA all efficacy and safety data from Study D1050292. This will be necessary in order for us to complete the reviews of the NDA supplements. Please submit the following items pertaining to the primary and the key secondary efficacy variables:

(a) The raw as well as derived variables;
(b) SAS programs that produced the derived variables from the raw variables;

(c) SAS programs that produced efficacy outcomes;
(d) All variables related to demographics/baseline characteristics/dosing, as well as other variables needed for efficacy analysis;
(e) Include also a variable indicating whether the participant was naïve or non-naïve to lithium or divalproex at the outset of the study. Indicate whether the randomization was stratified by this variable. Conduct and submit exploratory subgroup analyses stratified by this variable if not considered during randomization.
(f) A list of serial numbers and submission dates of the protocol, SAP, amendments, and relevant meetings under IND 103,427, as well as FDA feedback pertaining to this study.
(g) The requests associated with [1] to [3] above also apply to this study.

Additional requests regarding Study **D1050292**:

- Please submit the data sets for all safety parameters.
- Provide an integrated summary of safety for adjunctive studies D1050292 and D1050235.
- Provide a list of investigators, study sites, addresses, and number of subjects at each site.

If you have questions, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
02/21/2013

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: November 2, 2012

To: Lauren Iacono-Connors, Ph.D., Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Mark Ritter, Medical Officer, Division of Psychiatry Products
Robert Levin, Medical Team Leader, Division of Psychiatry Products
Thomas Laughren, Director, Division of Psychiatry Products

From: Ann Sohn, Regulatory Project Manager, Division of Psychiatry Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 200603/S-010 and S-011
IND#: 61292
Applicant/ Applicant contact information (to include phone/email):
Sunovion Pharmaceuticals, Inc.
One Bridge Plaza North, Suite 510
Fort Lee, NJ 07024
Regulatory Contact: Bridget Walton 201-228-8333 (office), 201-310-0156 (cell)
Email: Bridget.walton@sunovion.com
Drug Proprietary Name: Latuda
Generic Drug Name: lurasidone hydrochloride
NME or Original BLA (Yes/No): no
Review Priority (Standard or Priority): standard

Study Population includes < 17 years of age (Yes/No): no
Is this for Pediatric Exclusivity (Yes/No): no

Proposed New Indication(s): treatment of depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy (S-010) and as adjunctive therapy to lithium or valproate (S-011)

PDUFA/BsUFA:
Action Goal Date: June 30, 2013
Inspection Summary Goal Date: April 30, 2013

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Hassman, Howard, Site 120 CRI Worldwide, LLC Kirkbride Division 111 N 49th Street Philadelphia, PA 19139	D1050235 D1050236	8 13	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)
Hidalgo, Rosario, Site 100 University of South Florida 3515 E Fletcher Ave. Tampa, Florida 33613-4706	D1050235 D1050236	4 12	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)
Tran-Johnson, Tram Site 103 California Neuropsychopharmacology Clinical Research Institute 446 26th Street, 6th Floor San Diego,CA 92102	D1050235 D1050236	6 10	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)
Manning, Raymond, Site 094 CNRI – Los Angeles, LLC 8309 Telegraph Road Pico Rivera, California 90660	D1050235 D1050236	14 20	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)
Dempsey, Glen Site 080 Albuquerque Neuroscience Inc. 101 Hospital Loop Suite209 Albuquerque, NM 87109	D1050235 D1050236	1 10	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Weisler, Site 106 Richard H.Weisler &Associates 700 Spring Forest Road Suite125 Raleigh, NC 27609	D1050235 D1050236	7 9	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therapy)
Walling, David Site 105 Collaborative Neuroscience Network Inc. 12772 Valley View Street Suite 3 Garden Grove, CA 92845	D1050235 D1050236	9 18	Bipolar Depression (monotherapy) Bipolar Depression (Adjunctive therap)

III. Site Selection/Rationale

We would appreciate having inspections for two of the above sites. All of these sites participated in both studies, and they enrolled a large number of subjects. At this point, we do not have particular concerns about any of the sites in the two studies. Thank you.

Domestic Inspections:

Reasons for inspections (please check all that apply):

X Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

None Requested

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

.

Should you require any additional information, please contact Ann Sohn at 301-796-2232 or Mark Ritter at 301-796-2165.

Concurrence: (as needed)

Robert Levin, M.D., Medical Team Leader
Mark Ritter, M.D. Medical Reviewer

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/s/

ANN J SOHN
11/05/2012

THOMAS P LAUGHREN
11/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200603/S-010 and S-011

FILING COMMUNICATION

Sunovion Pharmaceuticals, Inc.
Attention: Bridget Walton, MS, RAC
Director, Regulatory Affairs
One Bridge Plaza, Suite 510
Fort Lee, NJ 07024

Dear Ms. Walton:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received August 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Latuda (lurasidone hydrochloride) 20 mg, 40 mg, 80 mg, and 120 mg tablets.

These supplemental applications propose the following additional indications: treatment of patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy to lithium or valproate.

We have completed our filing review and have determined that your supplemental applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these supplemental applications are considered filed 60 days after the date we received your supplemental application. The review classification for these supplemental applications is **Standard**. Therefore, the user fee goal date is June 30, 2013.

We are reviewing your supplemental applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 14, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Clinical Pharmacology
Submit lurasidone plasma concentration data collected in studies D1050235 and D1050236 in SAS transport format.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

THOMAS P LAUGHREN
10/15/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 200603 s10/s11 **Applicant: Sunovion** **Stamp Date: 08/31/2012**

Drug Name: Lurasidone **NDA/BLA Type: supplements**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Thomas Birkner	10/12/2012
Reviewing Statistician	Date
Peiling Yang	10/12/2012
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

THOMAS BIRKNER
10/12/2012

PEILING YANG
10/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE/DMEPA

FROM: Ann Sohn, OND/DPP, 301-796-2232

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/11/12		200603/S-010, S-011	New supplements	8/31/12

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Latuda (lurasidone HCl)	standard	antipsychotic	

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ✓ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Links to EDR submissions:
\\CDSESUB1\EVSPROD\NDA200603\0076
\\CDSESUB1\EVSPROD\NDA200603\0077

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Ann Sohn, Regulatory Project Manager Ann.sohn@fda.hhs.gov	✓MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

ANN J SOHN
10/11/2012

THOMAS P LAUGHREN
10/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Ann Sohn/RPM, OND/DPP/301-796-2232

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
10/11/12		200603/S-010, S-011	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Latuda (lurasidone HCl)	Standard	Antipsychotic	

NAME OF FIRM:	
Sunovion Pharmaceuticals, Inc.	PDUFA Date: June 28, 2013

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA200603\0076
\\CDSESUB1\EVSPROD\NDA200603\0077

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

SIGNATURE OF REQUESTER
Ann Sohn, RPM
301-796-2232
Ann.sohn@fda.hhs.gov

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL ☐ HAND

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/s/

ANN J SOHN
10/11/2012

THOMAS P LAUGHREN
10/11/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200603 **Applicant: Sunovion** **Stamp Date: 8/31/2012**

Drug Name: Latuda® (lurasidone HCl) tablets **NDA/BLA Type: sNDA**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		Cross-referenced from the original NDA
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N.A. (the formulation to be marketed is not different from the formulation used in the toxicology studies)
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N.A. (all pivotal pharm/tox studies are cross-referenced from the original NDA)
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N.A. (no special nonclinical studies/data were requested by the Division during pre-submission discussions)

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			To be reviewed
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?	√		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N.A.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sonia Tabacova 10/11/2012

Reviewing Pharmacologist Date

Aisar Atrakchi

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

SONIA A TABACOVA
10/11/2012

AISAR H ATRAKCHI
10/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200603/S-010 and S-011

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENTS

Sunovion Pharmaceuticals, Inc.
Attention: Bridget Walton, MS, RAC, Director
Regulatory Affairs
One Bridge Plaza
Suite 510
Fort Lee, NJ 07024

Dear Ms. Walton:

We have received your Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 200603

SUPPLEMENT NUMBER: 010 AND 011

PRODUCT NAME: Latuda (lurasidone HCl) tablets 20 mg, 40 mg, 80 mg, and 120 mg

DATE OF SUBMISSION: AUGUST 31, 2012

DATE OF RECEIPT: AUGUST 31, 2012

These supplemental applications propose additional indications of treatment in patients with depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy to lithium or valproate.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on OCTOBER 30, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have questions, please email me at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann Sohn, Pharm.D., LCDR USPHS
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ANN J SOHN
08/31/2012