CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204447Orig1s020

Trade Name:	TRINTELLIX
Generic or Proper Name:	vortioxetine
Sponsor:	Takeda Pharmaceuticals
Approval Date:	October 19, 2018
Indication:	TRINTELLIX is indicated for the treatment of major depressive disorder (MDD)

CENTER FOR DRUG EVALUATION AND RESEARCH

204447Orig1s020

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology** • **Clinical Microbiology/Virology**	**X**
Product Quality Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s020

APPROVAL LETTER

NDA 204447 S-020

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Takeda Pharmaceuticals, USA, Inc.
Attention: Kinnari Shaw
Senior Manager, Global Regulatory Affairs, Marketed Products
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Shaw:

Please refer to your supplemental new drug application (sNDA) dated and received January 14, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trintellix (vortioxetine) Tablets.

This Prior Approval supplemental new drug application provides for updates to labeling to reflect efficacy and safety results from study Lu AA21004-402: A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder.

APPROVAL & LABELING

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

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

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

Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

Your January 20, 2020, submission contains the final report for the following postmarketing commitment listed in the September 30, 2013 approval letter.

2084-6 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vortioxetine in the treatment of adults with major depressive disorder in the US. This trial must include a placebo group and several fixed doses and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of vortioxetine. Because the short-term trials appear to show that higher doses have demonstrated better treatment effects in the US population compared to the rest of the

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

world, it is important to establish the dose-response for maintenance in the US. This trial should randomize patients on stable doses of vortioxetine to several different doses (e.g., 5 mg, 10 mg, and 20 mg) of vortioxetine (and to placebo) during the maintenance phase.

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

We remind you that there are postmarketing requirements listed in the September 30, 2013, approval letter that are still open.

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, email Jasmeet (Mona) Kalsi, Senior Regulatory Project Manager, at Jasmeet.Kalsi@FDA.HHS.GOV.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
11/13/2020 03:58:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s020

LABELING

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

TRINTELLIX (vortioxetine) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **TRINTELLIX has not been evaluated for use in pediatric patients (8.4).**

----------RECENT MAJOR CHANGES----------
Dosage and Administration, Maintenance/ Continuation/Extended Treatment (2.2) Removed 11/2020

----------INDICATIONS AND USAGE----------
TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults (1).

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 10 mg administered orally once daily without regard to meals (2.1).
- The dose should then be increased to 20 mg/day, as tolerated (2.1).
- Consider 5 mg/day for patients who do not tolerate higher doses (2.1).
- TRINTELLIX can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible (2.2).
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
TRINTELLIX is available as 5 mg, 10 mg and 20 mg immediate release tablets (3).

----------CONTRAINDICATIONS----------
- Hypersensitivity to vortioxetine or any components of the TRINTELLIX formulation (4).
- Monoamine Oxidase Inh bitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue (4).

----------WARNINGS AND PRECAUTIONS----------
- *Serotonin Syndrome* has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with TRINTELLIX, both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue TRINTELLIX and initiate supportive treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.3).
- Activation of Mania/Hypomania can occur with antidepressant treatment. Screen patients for bipolar disorder (5.4).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.5).
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong Inhibitors of CYP2D6: Reduce TRINTELLIX dose by half when coadministered (2.5, 7.1).
- Strong CYP Inducers: Consider dose increase of TRINTELLIX dose when coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose (2.6, 7.1).

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Third trimester use may increase risk for persistent pulmonary hypertension and withdrawal in the newborn (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

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 trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

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 (5.1)]*.

TRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended starting dose is 10 mg administered orally once daily without regard to meals. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses.

2.2 Discontinuing Treatment

Although TRINTELLIX can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of TRINTELLIX 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of TRINTELLIX 15 mg/day or 20 mg/day *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

2.3 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with TRINTELLIX to avoid the risk of Serotonin Syndrome *[see Warnings and Precautions (5.2)]*. Conversely, at least 21 days should be allowed after stopping TRINTELLIX before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)]*.

2.4 Use of TRINTELLIX with Other MAOIs Such as Linezolid or Methylene Blue

Do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)]*.

In some cases, a patient already receiving TRINTELLIX therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or

intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, TRINTELLIX should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 21 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with TRINTELLIX may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)]*.

The risk of administering methylene blue by nonintravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with TRINTELLIX is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

2.5 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors

The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued *[see Drug Interactions (7.1), Use in Specific Populations (8.6)]*.

2.6 Use of TRINTELLIX in Patients Taking Strong CYP Inducers

Consider increasing the dose of TRINTELLIX when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of TRINTELLIX should be reduced to the original level within 14 days, when the inducer is discontinued *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

TRINTELLIX is available as immediate-release, film-coated tablets in the following strengths:

- 5 mg: pink, almond shaped biconvex film coated tablet, debossed with “5” on one side and “TL” on the other side
- 10 mg: yellow, almond shaped biconvex film coated tablet, debossed with “10” on one side and “TL” on the other side
- 20 mg: red, almond shaped biconvex film coated tablet, debossed with “20” on one side and “TL” on the other side

4 CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any component of the formulation. Hypersensitivity reactions including anaphylaxis, angioedema, and urticaria have been reported in patients treated with TRINTELLIX *[see Adverse Reactions (6.2)]*.
- The use of MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*.

  Starting TRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

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 studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with 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 trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two 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 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 1*.

Table 1. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	**Increases Compared to Placebo**
<18	14 additional cases
18 - 24	5 additional cases
Age Range	**Decreases Compared to Placebo**
25 - 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, 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 studies 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 MDD 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 MDD 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 suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRINTELLIX is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including TRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of TRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. TRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking TRINTELLIX. TRINTELLIX should be

discontinued before initiating treatment with the MAOI *[see Contraindications (4), Dosage and Administration (2.3), Drug Interactions (7.1)]*.

If concomitant use of TRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions (7.1, 7.2)]*.

5.4 Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with TRINTELLIX in premarketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use TRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.5 Angle Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.6 Hyponatremia

Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with TRINTELLIX in a premarketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of TRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications (4)]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*

- Abnormal Bleeding *[see Warnings and Precautions (5.3)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Angle Closure Glaucoma *[see Warnings and Precautions (5.5)]*
- Hyponatremia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Studies Experience

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

Patient Exposure

TRINTELLIX was evaluated for safety in 5852 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre- and postmarketing clinical studies; 2616 of those patients were exposed to TRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily; 204 patients were exposed to TRINTELLIX in a 24 to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily; and 429 patients were exposed to TRINTELLIX in a 32 week placebo-controlled maintenance study in the U.S. at doses of 5 mg, 10 mg, and 20 mg, once daily. Patients from the 6 to 8 week studies continued into 12 month open-label studies. A total of 2586 patients were exposed to at least one dose of TRINTELLIX in open-label studies, 1727 were exposed to TRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in MDD patients treated with TRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any TRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2. Common Adverse Reactions Occurring in ≥2% of Patients Treated with Any TRINTELLIX Dose and at Least 2% Greater than the Incidence in Placebo-Treated Patients					
System Organ Class Preferred Term	**TRINTELLIX 5 mg/day**	**TRINTELLIX 10 mg/day**	**TRINTELLIX 15 mg/day**	**TRINTELLIX 20 mg/day**	**Placebo**
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

* Includes pruritus generalized

Nausea

Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was two weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of TRINTELLIX treatment with 15 to 20% of patients experiencing nausea after one to two days of treatment. Approximately 10% of patients taking TRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment. In addition to the data from the MDD studies mentioned below, TRINTELLIX has been prospectively assessed for its effects in MDD patients with existing TESD induced by prior SSRI treatment and in healthy adults with normal sexual function at baseline *[see Clinical Studies (14)]*.

Voluntarily Reported Adverse Reactions of Sexual Dysfunction

In the MDD 6 to 8 week controlled trials of TRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their self-reported ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed TESD when treated with TRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	**TRINTELLIX 10 mg/day** N=94:86†	**TRINTELLIX 15 mg/day** N=57:67†	**TRINTELLIX 20 mg/day** N=67:59†	**Placebo** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

* Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

Adverse Reactions Following Abrupt Discontinuation of TRINTELLIX Treatment

Discontinuation symptoms have been prospectively evaluated in patients taking TRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of TRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests

TRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of TRINTELLIX *[see Warnings and Precautions (5.6)]*. In the six month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12 week, open-label phase, there were no clinically important changes in lab test parameters between TRINTELLIX and placebo-treated patients.

Weight

TRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the six month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during

the initial 12 week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients.

Vital Signs
TRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo

Gastrointestinal disorders — dyspepsia

Nervous system disorders — dysgeusia

Vascular disorders — flushing

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of TRINTELLIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal system — acute pancreatitis

Immune system disorders — hypersensitivity reactions (including anaphylaxis and urticaria)

Metabolic disorders — weight gain

Nervous system disorders — seizure

Skin and subcutaneous tissue disorders — rash, generalized rash

Psychiatric disorders — aggression, agitation, anger, hostility, irritability

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with TRINTELLIX

Table 4: Clinically Important Drug Interactions with TRINTELLIX

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of SSRIs and SNRIs including TRINTELLIX with MAOIs increases the risk of serotonin syndrome.
Intervention	Concomitant use of TRINTELLIX is contraindicated: • With an MAOI intended to treat psychiatric disorders or within 21 days of stopping treatment with TRINTELLIX. • Within 14 days of stopping an MAOI intended to treat psychiatric disorders. • In a patient who is being treated with linezolid or intravenous methylene blue. *[see Dosage and Administration (2.3, 2.4), Contraindications (4), Warnings and Precautions (5.2)].*
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue

Other Serotonergic Drugs	
Clinical Impact	Concomitant use of TRINTELLIX with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when TRINTELLIX is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of TRINTELLIX and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)].*
Examples	Other SNRIs, SSRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort
Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of TRINTELLIX with strong CYP2D6 inhibitors increases plasma concentrations of vortioxetine.
Intervention	Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor is coadministered *[see Dosage and Administration (2.5)].*
Examples	bupropion, fluoxetine, paroxetine, quinidine
Strong CYP Inducers	
Clinical Impact	Concomitant use of TRINTELLIX with a strong CYP inducer decreases plasma concentrations of vortioxetine.
Intervention	Consider increasing the TRINTELLIX dose when a strong CYP inducer is coadministered. The maximum dose is not recommended to exceed three times the original dose *[see Dosage and Administration (2.6)].*
Examples	rifampin, carbamazepine, phenytoin
Drugs that Interfere with Hemostasis (antiplatelets agents and anticoagulants)	
Clinical Impact	Drugs that Interfere with Hemostasis (antiplatelets agents and anticoagulants)
Intervention	Inform patients of the increased risk of bleeding associated with the concomitant use of TRINTELLIX and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[see Warnings and Precautions (5.3), Drug Interactions (7.2)]*.
Examples	aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein	
Clinical Impact	TRINTELLIX is highly bound to plasma protein. The concomitant use of TRINTELLIX with another drug that is highly bound to plasma protein may increase free concentrations of TRINTELLIX or other tightly-bound drugs in plasma.
Intervention	Monitor for adverse reactions and reduce dosage of TRINTELLIX or other protein bound drugs as warranted *[see Drug Interactions (7.2)]*.
Examples	warfarin

7.2 Effect of TRINTELLIX on Other Drugs

Other CNS Active Agents

No clinically relevant effect was observed on steady-state lithium exposure following coadministration with multiple daily doses of TRINTELLIX. Multiple doses of TRINTELLIX did

not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam *[see Clinical Pharmacology (12.3)]*.

A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg) *[see Clinical Pharmacology (12.3)]*.

Drugs That Interfere with Hemostasis
Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of TRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin. Coadministration of aspirin 150 mg/day with multiple daily doses of TRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Clinical Pharmacology (12.3)]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions (5.3), Drug Interactions (7.1)]*.

Highly Protein Bound Drugs
In a clinical study with coadministration of TRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein bound drug, no significant change in INR was observed *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are limited human data on TRINTELLIX use during pregnancy to inform any drug-associated risks. However, there are clinical considerations regarding neonates exposed to SSRIs and SNRIs, including TRINTELLIX, during the third trimester of pregnancy *[see Clinical Considerations]*. Vortioxetine administered to pregnant rats and rabbits during the period of organogenesis at doses ≥15 times and 10 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight and delayed ossification. No malformations were seen at doses up to 77 times and 58 times the MRHD, respectively. Vortioxetine administered to pregnant rats during gestation and lactation at oral doses ≥20 times the MRHD resulted in a decrease in the number of live-born pups and an increase in early postnatal pup mortality. Decreased pup weight at birth to weaning occurred at 58 times the MRHD and delayed physical development occurred at ≥20 times the MRHD. These effects were not seen at 5 times the MRHD *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

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

Clinical Considerations
Disease-associated Maternal and/or Embryo/Fetal Risk
A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal Adverse Reactions
Exposure to serotonergic antidepressants, including TRINTELLIX, in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). Monitor neonates who were exposed to TRINTELLIX in the third trimester of pregnancy for PPHN and drug discontinuation syndrome *[see Data]*.

Data
Human Data
Third Trimester Exposure
Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. These findings are based on postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly, a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 - 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Animal Data
In pregnant rats and rabbits, no malformations were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, in rats and rabbits, respectively. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses of 40 and 120 mg/kg (20 and 58 times the MRHD, respectively) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

8.2 Lactation

Risk Summary
There is no information regarding the presence of vortioxetine in human milk, the effects on the breastfed infant, or the effects on milk production. Vortioxetine is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRINTELLIX and any potential adverse effects on the breastfed child from TRINTELLIX or from the underlying maternal condition.

Data

Animal Data

Administration of [^{14}C]-vortioxetine to lactating rats at an oral dose of 20 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, resulted in drug-related material in milk secretion. Milk to plasma ratio in lactating rats was 1, 1.2, 0.5, and 0.5 at 2, 6, 24, and 72 hours post dose.

8.4 Pediatric Use

Clinical studies on the use of TRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRINTELLIX in the pediatric population have not been established.

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 1)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.6)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher vortioxetine plasma concentrations than extensive CYP2D6 metabolizers *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Human Experience

There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In premarketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of TRINTELLIX in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

There have been postmarketing reports of overdoses of TRINTELLIX. The most frequently reported symptoms with overdoses up to 80 mg (four times the maximum recommended daily dose) were nausea and vomiting. With overdoses greater than 80 mg, a case of serotonin syndrome in combination with another serotonergic drug, and a case of seizure, have been reported.

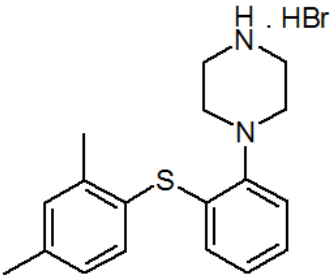
10.2 Management of Overdose

No specific antidotes for TRINTELLIX are known. In managing overdosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

TRINTELLIX is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr), an antidepressant. Vortioxetine HBr is known

chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. The empirical formula is $C_{18}H_{22}N_2S$, HBr with a molecular weight of 379.36 g/mol. The structural formula is:



Vortioxetine HBr is a white to very slightly beige powder that is slightly soluble in water.

Each TRINTELLIX tablet contains 6.355 mg, 12.71 mg or 25.42 mg of vortioxetine HBr equivalent to 5 mg, 10 mg, or 20 mg of vortioxetine, respectively. The inactive ingredients in TRINTELLIX tablets include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating which consists of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg and 20 mg) and iron oxide yellow (10 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

12.2 Pharmacodynamics

Vortioxetine binds with high affinity to the human serotonin transporter (Ki=1.6 nM), but not to the norepinephrine (Ki=113 nM) or dopamine (Ki>1000 nM) transporters. Vortioxetine potently and selectively inhibits reuptake of serotonin (IC50=5.4 nM). Vortioxetine binds to 5-HT3 (Ki=3.7 nM), 5-HT1A (Ki=15 nM), 5-HT7 (Ki=19 nM), 5-HT1D (Ki=54 nM), and 5-HT1B (Ki=33 nM), receptors and is a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

In humans, the mean 5-HT transporter occupancy, based on the results from two clinical PET studies using 5-HTT ligands ([^{11}C]-MADAM or [^{11}C]-DASB), was approximately 50% at 5 mg/day, 65% at 10 mg/day and approximately 80% at 20 mg/day in the regions of interest.

Effect on Cardiac Repolarization

The effect of vortioxetine 10 mg and 40 mg administered once daily on QTc interval was evaluated in a randomized, double-blind, placebo-, and active-controlled (moxifloxacin 400 mg), four-treatment-arm parallel study in 340 male subjects. In the study the upper bound of the one-sided 95% confidence interval for the QTc was below 10 ms, the threshold for regulatory concern. The oral dose of 40 mg is sufficient to assess the effect of metabolic inhibition.

Effect on Driving Performance

In a clinical study in healthy subjects, TRINTELLIX did not impair driving performance, or have adverse psychomotor or cognitive effects following single and multiple doses of 10 mg/day.

12.3 Pharmacokinetics

Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steady-state plasma concentrations are typically achieved within two weeks of dosing.

Absorption

The maximal plasma vortioxetine concentration (C_{max}) after dosing is reached within 7 to 11 hours postdose (T_{max}). Steady-state mean C_{max} values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%.

Effect of Food

No effect of food on the pharmacokinetics was observed.

Distribution

The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate or severe) or renal (mild, moderate, severe, ESRD) impairment is observed.

Elimination

Metabolism

Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers *[see Dosage and Administration (2.5)]*.

Excretion

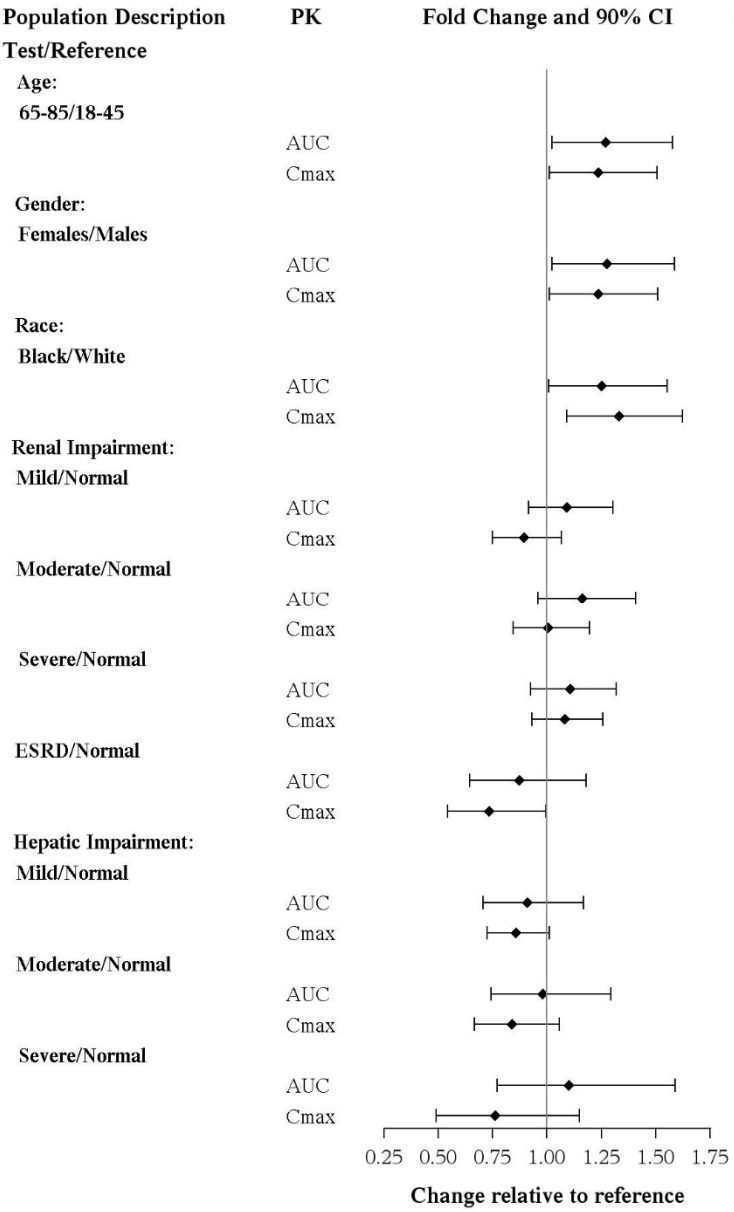
Following a single oral dose of [^{14}C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild, moderate or severe) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

Specific Populations

No clinically significant differences in the exposures of vortioxetine were observed based on age, gender, ethnicity, renal function, or hepatic function.

The effects of intrinsic patient factors on the pharmacokinetics of vortioxetine are presented in *Figure 1*.

Figure 1. Impact of Intrinsic Factors on Vortioxetine PK



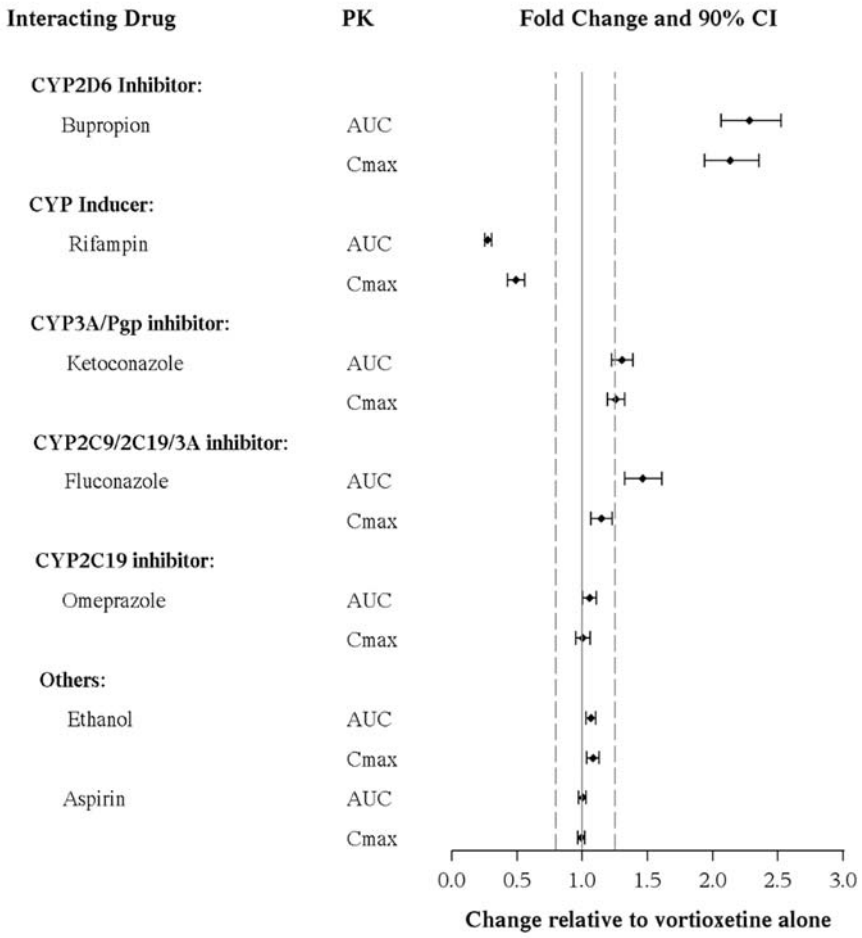
Drug Interaction Studies

Clinical Studies

Other Drugs on TRINTELLIX

The effects of other drugs on vortioxetine exposure are summarized in *Figure 2*.

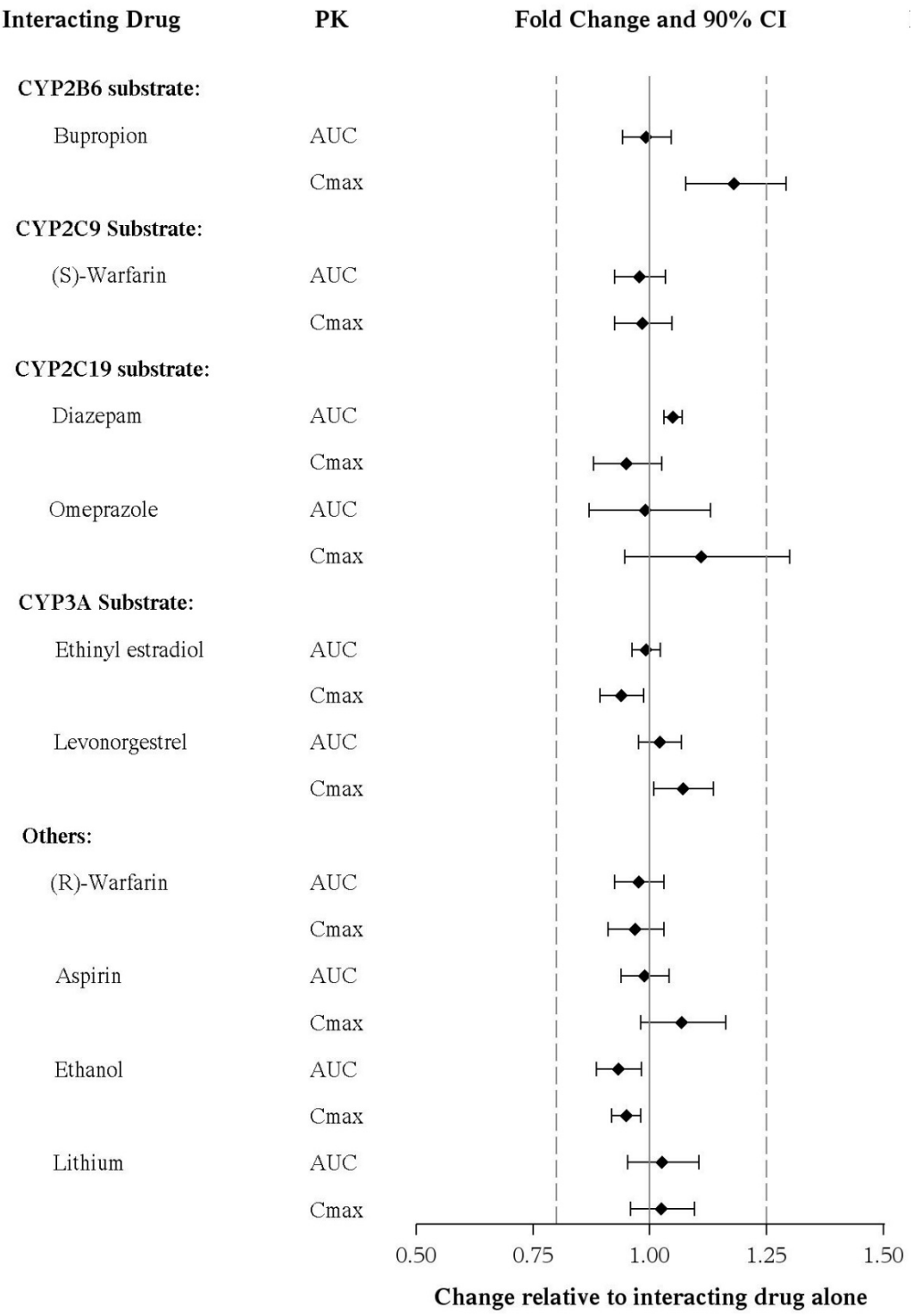
Figure 2. Impact of Other Drugs on Vortioxetine PK



TRINTELLIX on Other Drugs

The effects of vortioxetine on the exposures of other drugs are summarized in *Figure 3*.

Figure 3. Impact of Vortioxetine on PK of Other Drugs



In Vitro

Vortioxetine and its metabolite(s) are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, P-gp, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. As such, no clinically relevant interactions with drugs metabolized/transported by these CYP enzymes or transporters would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic

administration of TRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of TRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which CD-1 mice and Wistar rats were given oral doses of vortioxetine up to 50 and 100 mg/kg/day for male and female mice, respectively, and 40 and 80 mg/kg/day for male and female rats, respectively, for two years. The doses in the two species were approximately 12, 24, 20, and 39 times, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

In rats, the incidence of benign polypoid adenomas of the rectum was statistically significantly increased in females at doses 39 times the MRHD, but not at 15 times the MRHD. These were considered related to inflammation and hyperplasia and possibly caused by an interaction with a vehicle component of the formulation used for the study. The finding did not occur in male rats at 20 times the MRHD.

In mice, vortioxetine was not carcinogenic in males or females at doses up to 12 and 24 times, respectively, the MRHD.

Mutagenicity

Vortioxetine was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay in cultured human lymphocytes, and an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Treatment of rats with vortioxetine at doses up to 120 mg/kg/day had no effect on male or female fertility, which is 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of TRINTELLIX in treatment for MDD was established in six, 6 to 8 week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

Adults (aged 18 years to 75 years)

The efficacy of TRINTELLIX in patients aged 18 years to 75 years was demonstrated in five, 6 to 8 week, placebo-controlled studies (Studies 1 to 5 in *Table 5*). In these studies, patients were randomized to TRINTELLIX 5 mg, 10 mg, 15 mg or 20 mg or placebo once daily. For patients who were randomized to TRINTELLIX 15 mg/day or 20 mg/day, the final doses were titrated up from 10 mg/day after the first week.

The primary efficacy measures were the Hamilton Depression Scale (HAMD-24) total score in Study 2 and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in all other studies. In each of these studies, at least one dose group of TRINTELLIX was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement *(see Table 5)*. Subgroup analysis by age, gender or race did not suggest any clear evidence of differential responsiveness. Two studies of the 5 mg dose in the U.S. (not represented in *Table 5*) failed to show effectiveness.

Elderly Study (aged 64 years to 88 years)
The efficacy of TRINTELLIX for the treatment of MDD was also demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study of TRINTELLIX in elderly patients (aged 64 years to 88 years) with MDD (Study 6 in *Table 5*). Patients meeting the diagnostic criteria for recurrent MDD with at least one previous major depressive episode before the age of 60 years and without comorbid cognitive impairment (Mini Mental State Examination score <24) received TRINTELLIX 5 mg or placebo.

Table 5. Primary Efficacy Results of 6 Week to 8 Week Clinical Trials

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
Study 1 [MADRS] Non-US Study	TRINTELLIX (5 mg/day)‡	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	TRINTELLIX (10 mg/day)‡	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	TRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	TRINTELLIX (10 mg/day)‡	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	TRINTELLIX (15 mg/day)‡	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	TRINTELLIX (20 mg/day)‡	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	TRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	TRINTELLIX (20 mg/day)‡	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	TRINTELLIX (10 mg/day)	154	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	TRINTELLIX (20 mg/day)‡	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	TRINTELLIX (5 mg/day)‡	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
† Difference (drug minus placebo) in least-squares mean change from baseline.
‡ Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse).

Time Course of Treatment Response
In the 6 to 8 week placebo-controlled studies, an effect of TRINTELLIX based on the primary efficacy measure was generally observed starting at Week 2 and increased in subsequent weeks with the full antidepressant effect of TRINTELLIX generally not seen until Study Week 4 or later. *Figure 4* depicts time course of response in U.S. based on the primary efficacy measure (MADRS) in Study 5.

Figure 4. Change from Baseline in MADRS Total Score by Study Visit (Week) in Study 5

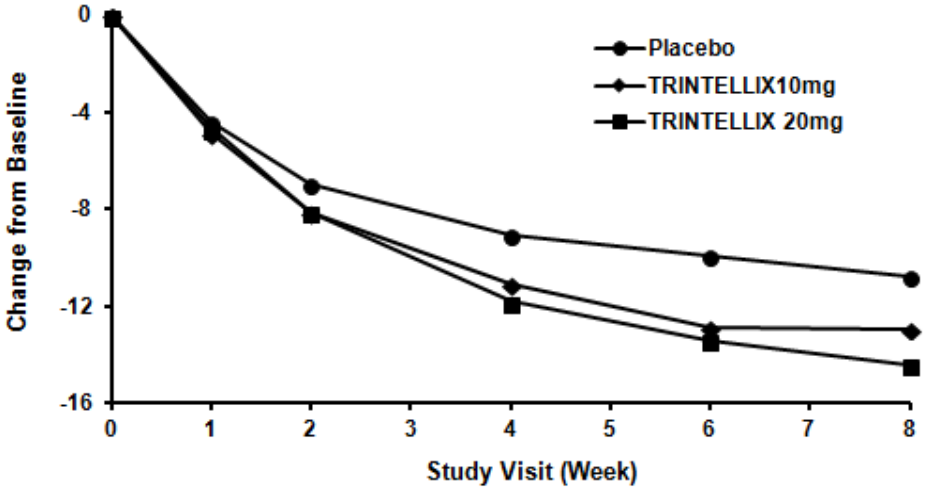
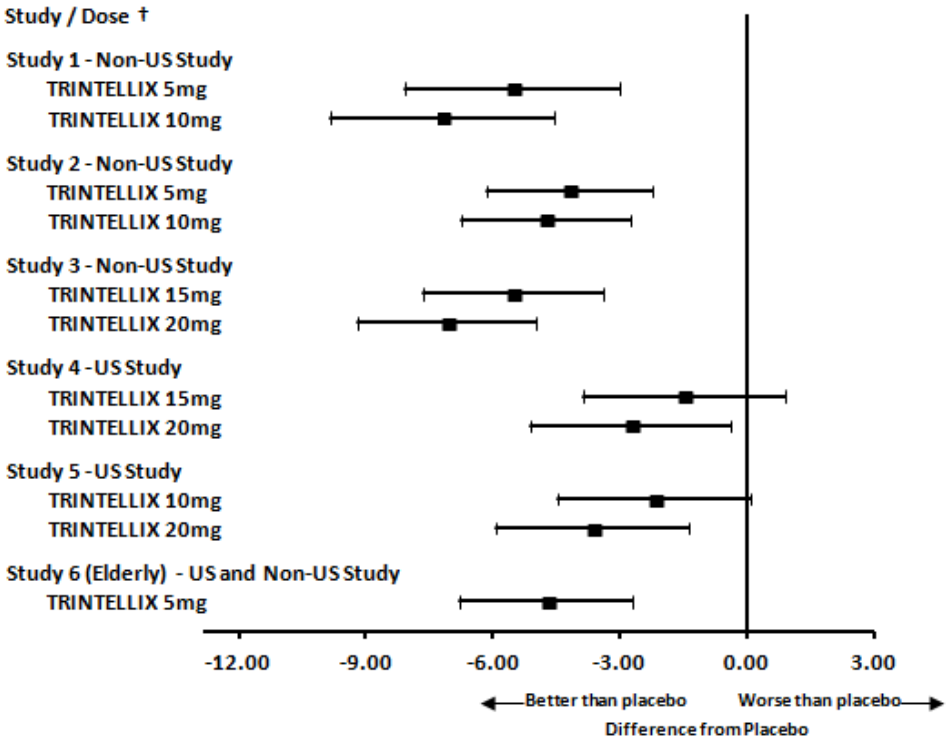


Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8



† Results (point estimate and unadjusted 95% confidence interval) are from mixed model for repeated measures (MMRM) analysis. In Studies 1 and 6, the primary analysis was not based on MMRM and in Studies 2 and 6 the primary efficacy measure was not based on MADRS.

Digit Symbol Substitution Test in Major Depressive Disorder

Two, eight week, randomized, double-blind, placebo-controlled studies were conducted to evaluate the effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST) during the treatment of acute MDD. The DSST is a neuropsychological test that most specifically measures processing speed, an aspect of cognitive function that may be impaired in MDD. Patients are asked to match nine symbols with their corresponding number (1 to 9) according to a key; the score is the correct number of matches achieved in 90 seconds. For reference, the mean score for healthy 45 to 54 year-old subjects is 50 (SD=15).

Study 7 randomized adult patients meeting the diagnostic criteria for recurrent MDD to receive TRINTELLIX 10 mg, TRINTELLIX 20 mg, or placebo once daily. Study 8 randomized adult patients meeting the diagnostic criteria for recurrent MDD and reporting subjective difficulty concentrating or slow thinking to receive a flexible dose of TRINTELLIX (10 or 20 mg) or placebo once daily. Neither study included patients whose MDD was in remission yet who continued to experience difficulty concentrating or slow thinking. Patients' mean age was 46 (SD=12) and 45 (SD=12) in Study 7 and 8, respectively. In both studies, patients in the TRINTELLIX group had a statistically significantly greater improvement in number of correct responses on the DSST *(Table 6)*; depressed mood as assessed by change from baseline in MADRS total score also improved in both studies.

Table 6. Effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST)

Study No.	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[§] (95% CI)
Study 7	TRINTELLIX (10 mg/day)[‡]	193	42.0 (12.6)	9.0 (0.6)	4.2 (2.5, 5.9)
	TRINTELLIX (20 mg/day)[‡]	204	41.6 (12.7)	9.1 (0.6)	4.3 (2.6, 5.9)
	Placebo	194	42.4 (13.8)	4.8 (0.6)	--
Study 8	TRINTELLIX (10/20 mg/day)[‡]	175	42.1 (11.9)	4.6 (0.5)	1.8 (0.3, 3.2)
	Placebo	167	43.0 (12.3)	2.9 (0.5)	--

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

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

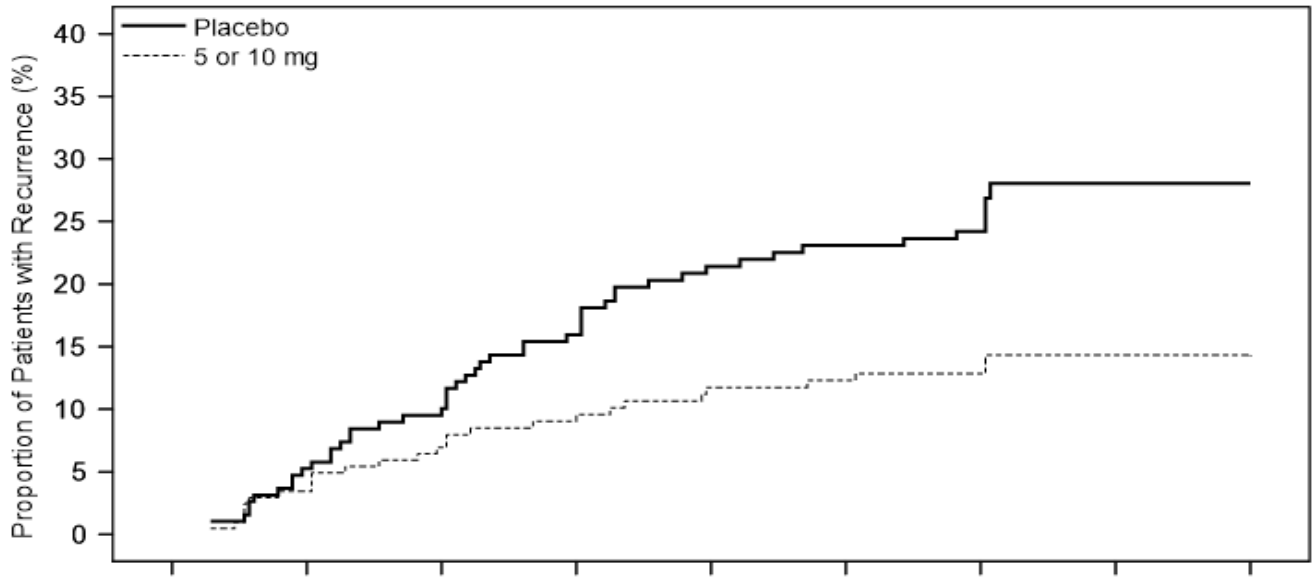
[‡] Doses are statistically significantly superior to placebo.

The effects observed on DSST may reflect improvement in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage over other antidepressants on the DSST.

Maintenance Studies

In a non-U.S. maintenance study (Study 9 in *Figure 6*), 639 patients meeting DSM-IV-TR criteria for MDD received flexible doses of TRINTELLIX (5 mg or 10 mg) once daily during an initial 12 week open-label treatment phase; the dose of TRINTELLIX was fixed during Weeks 8 to 12. Three hundred ninety six (396) patients who were in remission (MADRS total score ≤10 at both Weeks 10 and 12) after open-label treatment were randomly assigned to continuation of a fixed dose of TRINTELLIX at the final dose they responded to (about 75% of patients were on 10 mg/day) during the open-label phase or to placebo for 24 to 64 weeks. Approximately 61% of randomized patients satisfied remission criterion (MADRS total score ≤10) for at least four weeks (since Week 8), and 15% for at least eight weeks (since Week 4). Patients on TRINTELLIX experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo. Recurrence of depressive episode was defined as a MADRS total score ≥22 or lack of efficacy as judged by the investigator.

Figure 6. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 9)

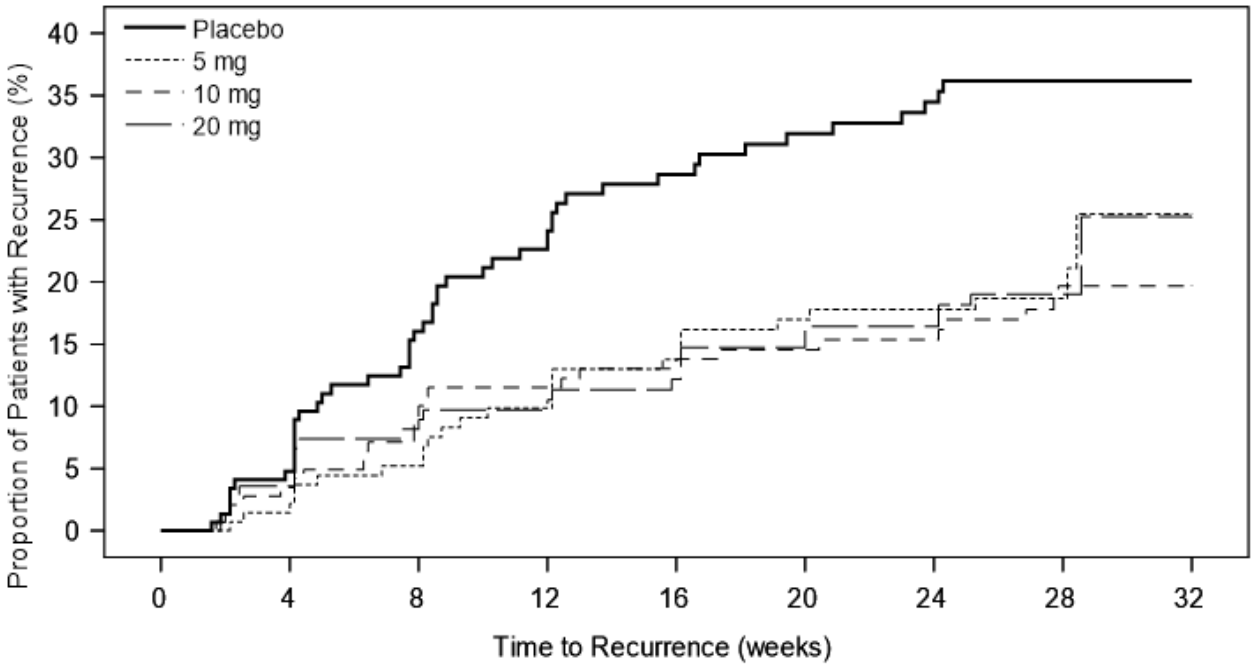


No. of Patients Maintained

TRINTELLIX (5 or 10 mg)	204	195	180	170	162	157	118	2	1
Placebo	192	180	168	155	142	138	114	1	1

In a U.S.-based maintenance study (Study 10 in *Figure 7*), 1106 patients meeting DSM-IV-TR criteria for MDD were treated with a fixed dose of TRINTELLIX 10 mg once daily during an initial 16 week open-label treatment phase. Five hundred and eighty (580) patients who were in remission (MADRS total score ≤12 at both Weeks 14 and 16) after open-label treatment were randomized in a 1:1:1:1 ratio to TRINTELLIX 5 mg/day, 10 mg/day, 20 mg/day, or placebo daily for 32 weeks. The definition of recurrence of depressive episodes was the same as for Study 9. For all three doses of TRINTELLIX evaluated, patients treated with TRINTELLIX experienced a statistically significantly longer time to recurrence of depressive episodes than did patients treated with placebo.

Figure 7. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 10)



No. of Patients Maintained

TRINTELLIX 20 mg	144	127	116	110	104	98	97	67	0
TRINTELLIX 10 mg	145	136	122	117	113	108	105	66	0
TRINTELLIX 5 mg	140	131	123	115	109	101	94	67	0
Placebo	151	138	117	103	90	81	77	56	0

Prospective Evaluation of Treatment Emergent Sexual Dysfunction (TESD)

Two, randomized, double-blind, active-controlled studies were conducted to prospectively compare the incidence of TESD between TRINTELLIX and SSRIs via a validated self-rated measure of sexual function, the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). The CSFQ-14 is designed to measure illness- and medication-related changes in sexual functioning that consists of 14 items measuring sexual functioning as a total score. The CSFQ-14 consists of subscales that assess the three phases of the sexual response cycle (desire, arousal, and orgasm). Higher scores on the CSFQ-14 indicate greater sexual function and for reference, a 2-3 point change is considered clinically meaningful.

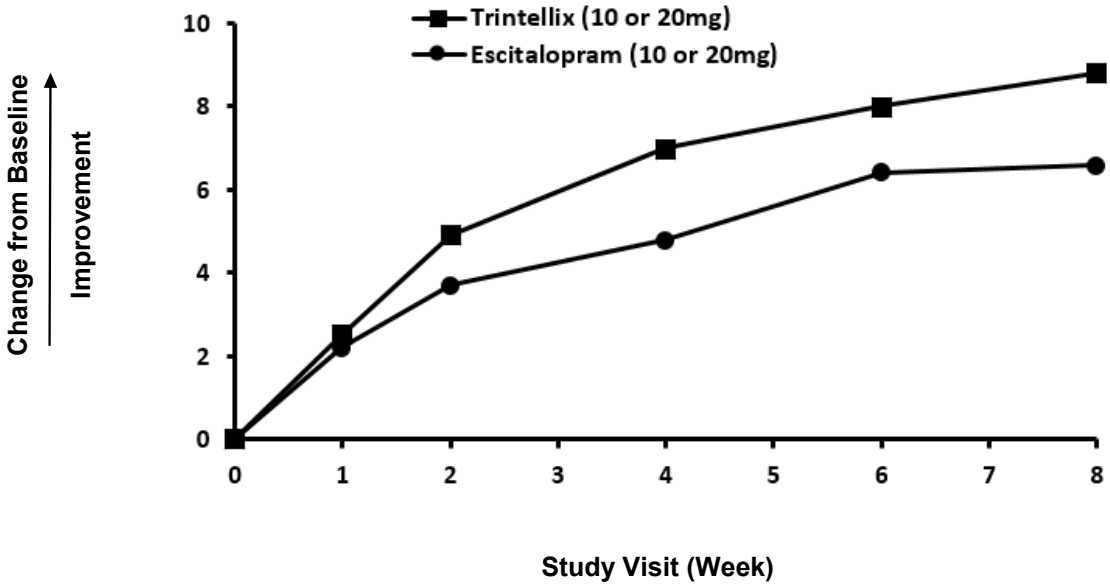
Effect of Switching from SSRI to TRINTELLIX on TESD

The effect of TRINTELLIX on TESD induced by prior SSRI treatment in MDD patients whose depressive symptoms were adequately treated was evaluated in an eight-week, randomized, double-blind, active-controlled (escitalopram), flexible-dose study (Study 11). Patients taking citalopram, sertraline, or paroxetine for at least eight weeks duration and who were experiencing sexual dysfunction attributed to their SSRI treatment were switched to TRINTELLIX (n=217) or escitalopram (n=207). For both TRINTELLIX and escitalopram, patients were started on 10 mg, increased to 20 mg at Week 1, followed by flexible dosing. The majority of subjects received the 20 mg dose of TRINTELLIX (65.6%) or the 20 mg dose of escitalopram (71.9%) during the study.

Improvement in TESD induced by prior SSRI treatment in subjects switched to TRINTELLIX was superior to the improvement observed in those subjects who switched to escitalopram (2.2 point improvement vs escitalopram on the change from Baseline in CSFQ-14 total score, with 95% confidence interval 0.48 – 4.02), after eight weeks of treatment, while both drugs

maintained the subjects' prior antidepressant response. For change from Baseline in CSFQ-14, *see Figure 8*.

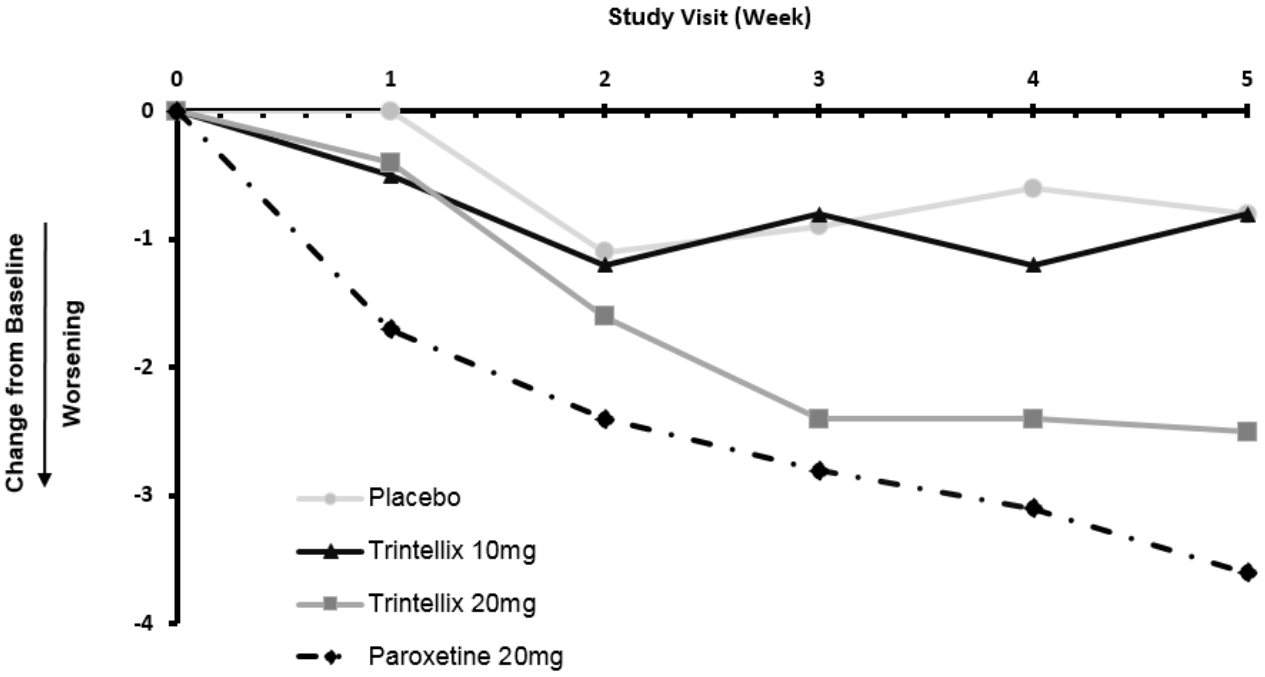
Figure 8. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Study 11



Effects in Healthy Volunteers with Normal Sexual Functioning at Baseline

In a randomized Healthy Volunteer study (Study 12) with 348 subjects aged 18 years to 40 years with normal sexual functioning without the confounding effect of depression, TESD with TRINTELLIX 10 mg (n=85), but not with TRINTELLIX 20 mg (n=91), was statistically significantly less than with paroxetine 20 mg (n=83) *[see Adverse Reactions (6.1)]*. Paroxetine 20 mg was statistically significantly worse than placebo (n=89), confirming assay sensitivity in this study. For change from Baseline in CSFQ-14, *see Figure 9*.

Figure 9. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Healthy Volunteers (Study 12)



16 HOW SUPPLIED/STORAGE AND HANDLING

TRINTELLIX tablets are available as follows:

Features	Strengths		
	5 mg	**10 mg**	**20 mg**
Color	pink	yellow	red
Debossment	"5" on one side of tablet "TL" on other side of tablet	"10" on one side of tablet "TL" on other side of tablet	"20" on one side of tablet "TL" on other side of tablet
Presentations and NDC Codes			
Bottles of 30	64764-720-30	64764-730-30	64764-750-30
Bottles of 90	64764-720-90	64764-730-90	64764-750-90
Bottles of 500	64764-720-77	64764-730-77	64764-750-77

Storage: Store at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients and their caregivers about the benefits and risks associated with treatment with TRINTELLIX and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk

Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially early during treatment and when the dose is adjusted up or down *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Discontinuation of Treatment
Patients who are on TRINTELLIX 15 mg/day or 20 mg/day may experience headache, muscle tension, mood swings, sudden outburst of anger, dizziness and runny nose if they abruptly stop their medicine. Advise patients not stopping TRINTELLIX without talking to their healthcare provider *[see Adverse Reactions (6)]*.

Concomitant Medication
Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications because of a potential for interactions. Instruct patients not to take TRINTELLIX with an MAOI or within 14 days of stopping an MAOI and to allow 21 days after stopping TRINTELLIX before starting an MAOI *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7.1)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of TRINTELLIX and triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan supplements, and St. John's Wort supplements *[see Warnings and Precautions (5.2), Drug Interactions (7.1, 7.2)]*.

Abnormal Bleeding
Caution patients about the increased risk of abnormal bleeding when TRINTELLIX is given with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation *[see Warnings and Precautions (5.3)]*.

Activation of Mania/Hypomania
Advise patients and their caregivers to look for signs of activation of mania/hypomania *[see Warnings and Precautions (5.4)]*.

Angle Closure Glaucoma
Patients should be advised that taking TRINTELLIX can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.5)]*.

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking TRINTELLIX *[see Warnings and Precautions (5.6)]*.

Nausea
Advise patients that nausea is the most common adverse reaction, and is dose related. Nausea commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients.

Alcohol
A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg/day) did not increase the impairment of mental and motor skills caused by alcohol.

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise a pregnant woman or a woman planning to become pregnant that TRINTELLIX may cause withdrawal symptoms in the newborn or persistent pulmonary hypertension of the newborn (PPHN) *[see Use in Specific Populations (8.1)]*.

Distributed and marketed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

Marketed by:
Lundbeck
Deerfield, IL 60015

LUN205 R20

MEDICATION GUIDE

TRINTELLIX (trin'-TELL-ix)

(vortioxetine) Tablets

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

TRINTELLIX and other antidepressant medicines may cause serious side effects.

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**
2. **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or 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) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions?**
   - Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

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

What is TRINTELLIX?

TRINTELLIX is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD).

It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

- Talk to your healthcare provider if you do not think that your condition is getting better with TRINTELLIX treatment.

Do not take TRINTELLIX if you:

- are allergic to vortioxetine, or any of the ingredients in TRINTELLIX. See the end of this Medication Guide for a complete list of ingredients in TRINTELLIX.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 21 days of stopping TRINTELLIX.
- Do not start TRINTELLIX if you stopped taking an MAOI in the last 14 days.

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

- have liver problems
- have or had seizures or convulsions
- have mania or bipolar disorder (manic depression)
- have low salt (sodium) levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions

- are pregnant or plan to become pregnant. It is not known if TRINTELLIX will harm your unborn baby. Taking TRINTELLIX while pregnant in your third trimester may cause your newborn baby to have withdrawal symptoms that causes a certain type of breathing problem called Persistent Pulmonary Hypertension of the Newborn (PPHN).
- are breastfeeding or plan to breastfeed. It is not known if TRINTELLIX passes into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TRINTELLIX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TRINTELLIX and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headache (e.g., triptans)
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), buspirone, or antipsychotics
- MAOIs (including linezolid, an antibiotic)
- Tramadol or fentanyl
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- aspirin
- warfarin (Coumadin, Jantoven)
- diuretics
- rifampin
- carbamazepine
- phenytoin
- quinidine

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before you take TRINTELLIX with any of these medicines, talk to your healthcare provider about serotonin syndrome. See **"What are the possible side effects of TRINTELLIX?"**.

How should I take TRINTELLIX?

- Take TRINTELLIX exactly as your healthcare provider tells you to take it.
- Take TRINTELLIX at about the same time each day.
- Your healthcare provider may need to change the dose of TRINTELLIX until it is the right dose for you.
- Do not start or stop taking TRINTELLIX without talking to your healthcare provider first. Suddenly stopping TRINTELLIX when you take higher doses may cause you to have side effects
  - o Headache
  - o Stiff muscles
  - o mood swings
  - o sudden outburst of anger
  - o dizziness or feeling lightheaded
  - o runny nose
- TRINTELLIX may be taken with or without food.
  If you take too much TRINTELLIX, call the Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of TRINTELLIX?

TRINTELLIX may cause serious side effects, including:

- **See "What is the most important information I should know about TRINTELLIX?".**
- **serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when medicines such as TRINTELLIX are taken with certain other medicines. Symptoms of serotonin syndrome may include:
  - o agitation, hallucinations, coma or other changes in mental status
  - o problems controlling your movements or muscle twitching
  - o fast heartbeat
  - o high or low blood pressure
  - o sweating or fever
  - o nausea or vomiting
  - o diarrhea

- muscle stiffness or tightness

- **abnormal bleeding or bruising.** TRINTELLIX may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a nonsteroidal anti-inflammatory drug (NSAID), or aspirin.
- **hypomania** (manic episodes). Symptoms of manic episodes include:
  - greatly increased energy
  - racing thoughts
  - unusually grand ideas
  - reckless behavior
  - severe problems sleeping
  - talking more or faster than usual
  - excessive happiness or irritability
- **visual problems**
  - eye pain
  - changes in vision
  - swelling or redness in or around the eye

  Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- **low levels of salt (sodium) in your blood.** Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. Symptoms of severe or sudden cases of low salt levels in your blood may include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels can cause death.

Common side effects in people who take TRINTELLIX include:

- nausea
- constipation
- vomiting

These are not all the possible side effects of TRINTELLIX. **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 TRINTELLIX?

Store TRINTELLIX at room temperature between 59°F to 86°F (15°C to 30°C).

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

General information about the safe and effective use of TRINTELLIX.

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

You can ask your pharmacist or healthcare provider for information about TRINTELLIX that is written for healthcare professionals.

What are the ingredients in TRINTELLIX?

Active ingredient: vortioxetine hydrobromide

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating consisting of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg and 20 mg) and iron oxide yellow (10 mg)

Distributed and Marketed by:
Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015

Marketed by:
Lundbeck, Deerfield, IL 60015

For more information, go to www.TRINTELLIX.com or call 1-877-TAKEDA-7 (1-877-825-3327).

This Medication Guide has been approved by the U.S. Food and Drug Administration LUN205 R20 Revised: April 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s020

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	204447 S-020
Priority or Standard	Standard
Submit Date(s)	January 14, 2020
Received Date(s)	January 14, 2020
PDUFA Goal Date	November 14, 2020
Division/Office	Division of Psychiatry
Review Completion Date	
Established/Proper Name	vortioxetine
(Proposed) Trade Name	Trintellix
Pharmacologic Class	Antidepressant – Selective Serotonin Reuptake Inhibitor
Code name	LuAA21004
Applicant	Takeda Development Center Americas, Inc.
Dosage form	oral tablet
Applicant proposed Dosing Regimen	5 mg, 10 mg, or 20 mg by mouth once daily
Applicant Proposed Indication(s)/Population(s)	Major Depressive Disorder/Adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000 | Major depressive disorder (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Major Depressive Disorder/Adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	370143000 | Major depressive disorder (disorder)
Recommended Dosing Regimen	5 mg, 10 mg, or 20 mg by mouth once daily

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Clinical Reviewer	David Millis
Clinical Team Leader	Martine Solages
Statistical Reviewer	Semhar Ogbagaber
Statistical Team Leader	Peiling Yang
Cross-Disciplinary Team Leader	Martine Solages
Division Director (OB)	Hsien-Ming James Hung
Division Director (signatory authority)	Tiffany R Farchione

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression - Severity
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
GCP	good clinical practice
GGT	gamma-glutamyl transferase
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	institutional review board
ITT	intent to treat
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCS	Potentially Clinically Significant
PH	proportional hazards
PK	pharmacokinetics
PMC	postmarketing commitment
PPS	per protocol set
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SOC	standard of care
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Vortioxetine (trade name: Trintellix) is an antidepressant that was approved on September 30, 2013 for the treatment of major depressive disorder (MDD) in adults. The mechanisms of action of vortioxetine are believed to be selective serotonin reuptake inhibition and inhibition of the serotonin transporter.

Under this supplemental NDA application, NDA 204447, Takeda Pharmaceuticals USA, Inc. (hereafter, "the Applicant") is seeking the addition of labeling language to describe the results of a new study designed to demonstrate maintenance of the antidepressant effect of vortioxetine. A previous maintenance study conducted at non-United States sites was submitted with the original NDA. The Applicant has completed a second maintenance of effect study, Study LuAA21004_402, to fulfill a postmarketing commitment to conduct a maintenance study in the United States in which all approved doses for vortioxetine are evaluated. Study LuAA21004_402 is the only study for which data was provided in this submission.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Our review of the efficacy data from Study LuAA21004_402 indicates that vortioxetine 5 mg, vortioxetine 10 mg, and vortioxetine 20 mg all were superior to placebo in prolonging the time to relapse of major depression in patients who demonstrated response to vortioxetine 10 mg during the open-label period of the study. These data provide evidence of maintenance effectiveness and will be included in the text of the product labeling. The completion of Study LuAA21004_402 fulfills the postmarketing commitment to conduct a maintenance study in the United States evaluating all approved vortioxetine doses.

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment
The results of randomized withdrawal study LuAA21004_402 support the efficacy of vortioxetine for maintenance treatment of MDD. The previous randomized withdrawal study evaluated only the 5-mg and 10-mg doses and was conducted at only non-United States sites. Study LuAA21004_402 demonstrated efficacy in maintenance treatment for the 5-mg, 10-mg, and 20-mg doses of vortioxetine, which covers all doses approved for marketing. Study LuAA21004_402 was conducted entirely at United States sites, so it is anticipated that the results will be more generalizable to the United States population than the results of the previous study. The risks associated with selective serotonin reuptake inhibitor (SSRI) antidepressants include suicidal ideation, serotonin syndrome, activation of mania or hypomania, weight gain, agitation and aggression, insomnia, somnolence, seizures, abnormal bleeding, hyponatremia, sexual dysfunction, and discontinuation syndrome; the current vortioxetine label includes language describing these risks. The most common adverse events noted in previous clinical trials of vortioxetine were nausea, headache, diarrhea, dry mouth, and dizziness. The safety profile for vortioxetine demonstrated in Study LuAA21004_402 was similar to the safety profile demonstrated in previous clinical trials. Postmarketing pharmacovigilance has raised the possibility of aggression and agitation as a previously unrecognized safety signal. The observed occurrences of aggression and agitation cannot be definitively demonstrated to be causally related to vortioxetine, but a causal relationship is possible. The Division of Pharmacovigilance will continue routine surveillance for episodes of aggression and agitation that may be causally related to vortioxetine. The labels of other SSRIs include text to indicate the possible occurrence of aggression or agitation. The Agency recommends updating the labeling of vortioxetine to include text indicating the occurrence of episodes of aggression or agitation in the postmarketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Major depressive disorder (MDD) is a serious and potentially life-threatening condition with high impact on social functioning, physical health, self-care, and quality of life. The disease typically has a chronic course with periods of recurrence of depressive symptoms. Severe depressive episodes can result in hospitalization or suicide.	MDD is a disabling and potentially life-threatening condition. It typically has a chronic course necessitating long-term treatment to avoid recurrences of illness.
Current Treatment Options	• Current pharmacologic treatment options include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), and antidepressants that do not fall into any of these categories. Non-pharmacologic treatment options include electroconvulsive therapy, transcranial magnetic stimulation, and psychotherapy. Antidepressants are a first-line treatment, but many patients do not respond to the first antidepressant chosen. Additionally, it is difficult to predict the tolerability of an antidepressant for a particular patient.	Treatment options are available, but efficacy and tolerability for individual patients is difficult to predict. Thus, it is beneficial to have additional antidepressant options available to prescribers.
Benefit	• A previous maintenance of efficacy study demonstrated efficacy of the 5-mg and 10-mg doses of vortioxetine compared to placebo in non-US populations. Study LuAA21004_402, submitted with this application, demonstrated efficacy of the 5-mg, 10-mg, and 20-mg doses compared to placebo in patients treated at research sites in the United States.	The maintenance of treatment efficacy demonstrated in Study LuAA21004_402 covers all doses approved for marketing and is more generalizable to the United States population than the results of the previous maintenance of efficacy study.
Risk and Risk Management	• Safety concerns associated with SSRIs include suicidal ideation, serotonin syndrome, activation of mania or hypomania, weight gain, agitation and aggression, insomnia, somnolence, seizures, abnormal bleeding, hyponatremia, sexual dysfunction, and discontinuation syndrome. The most common adverse events noted in previous clinical trials of vortioxetine were nausea, headache, diarrhea, dry mouth, and dizziness. The safety profile demonstrated for vortioxetine in Study LuAA21004_402 was similar to the safety profile	The Agency will continue surveillance for episodes of aggression, agitation, and related adverse reactions that might suggest a causal relationship for vortioxetine. Aggression, agitation, anger, hostility, and irritability will be listed in Section 6.2 of the prescribing information (Postmarketing Experience).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrated in previous clinical trials. Postmarketing pharmacovigilance revealed occurrences of aggression, agitation, anger, hostility, and irritability that might be causally related to vortioxetine. However, a causal relationship could not be definitively demonstrated.	

1.4. Patient Experience Data

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

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	Sections 7 and 8
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

MDD is a serious and life-threatening condition that affects the individual's social functioning, self-care, physical health, and quality of life. It typically has a chronic course with recurrent episodes. Severe episodes can result in hospitalization or suicide.

Because MDD is a long-term illness for many patients, maintenance therapy is recommended to prevent relapse in patients with recurrent depressive episodes. The Agency typically assesses maintenance of antidepressant effect through analysis of data from a placebo-controlled randomized withdrawal trial in which patients who demonstrate a short-term response to the drug are randomized to either a treatment group that continues taking the drug or a group that is switched to placebo. The time to the first relapse of depression is then documented for each patient in the two treatment groups. The mean time to relapse for the two treatment groups is then compared.

2.2. Analysis of Current Treatment Options

Table 1 lists the antidepressant medications currently approved for monotherapy of MDD. Non-pharmaceutical treatment modalities include electroconvulsive therapy, transcranial magnetic stimulation, and psychotherapy. Although many treatment options are available, it is currently not possible to predict which treatment will be effective for a particular patient. Patients who do not experience symptom relief from the first antidepressant prescribed may respond to an antidepressant from another class. Switching to a different antidepressant within the same class may benefit some patients because a patient may experience differences in tolerability even among antidepressants in the same class. For these reasons, there is public health benefit in expanding the range of antidepressant treatment options available to clinicians.

Table 1: Currently Approved Medications for Monotherapy of MDD

Medication Class	Approved Medications
Tricyclic Antidepressants (TCA)	imipramine, desipramine, amitryptiline, nortryptiline, doxepin, amoxapine, trimipramine, protryptiline, maprotiline
Monoamine Oxidase Inhibitors (MAOI)	phenylzine, tranylcypromine, isocarboxazid, maprotiline, selegiline patch
Selective Serotonin Reuptake Inhibitors (SSRI)	fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, vilazodone, vortioxetine
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	venlafaxine, duloxetine, desvenlafaxine, levomilnacipran
Other Antidepressants	bupropion, trazodone, nefazodone, mirtazapine

Vortioxetine is an SSRI. Safety concerns associated with this class of antidepressants include suicidal ideation, serotonin syndrome, activation of mania or hypomania, weight gain, agitation and aggression, insomnia, somnolence, seizures, abnormal bleeding, hyponatremia, sexual dysfunction, and discontinuation syndrome. The most common adverse events noted in previous clinical trials of vortioxetine were nausea, headache, diarrhea, dry mouth, and dizziness. The safety profile demonstrated for vortioxetine in Study LuAA21004_402 was similar to the safety profile demonstrated in previous clinical trials.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On September 30, 2013, vortioxetine was approved for the treatment of major depressive disorder in adults. The assessment of efficacy was based on the results from six positive short-term placebo-controlled studies and one positive long-term placebo-controlled maintenance of treatment effect study. The approved dosages for treatment of MDD are 5 mg, 10 mg, and 20 mg daily, given orally.

3.2. Summary of Presubmission/Submission Regulatory Activity

The NDA submitted by the Applicant for the original approval of vortioxetine included data from short-term efficacy studies indicating that only the 20-mg dose showed statistically significant efficacy in the adult population in the United States. The reason for the regional differences was not clear. Study 11985A, which demonstrated long-term maintenance of efficacy of vortioxetine treatment, included treatment arms only for vortioxetine 5 mg, vortioxetine 10 mg, and placebo. The study did not include a vortioxetine 20 mg arm. Additionally, Study 11985A was conducted entirely at non-United States sites. From these study results, it was not clear whether all US patients would need to receive the 20-mg dose for maintenance treatment.

At a Late-Cycle Meeting held on July 2, 2013, the Agency discussed with the Applicant the need for a relapse prevention study that would be conducted in the United States, that would further characterize the dose response relationship of vortioxetine in the United States, and that would cover all approved doses.

The original approval letter includes the following postmarketing commitment (PMC):

2084-6 *A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vortioxetine in the treatment of adults with major depressive disorder in the US. This trial must include a placebo group and several fixed doses and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of vortioxetine. Because the short-term trials appear to show that higher doses have demonstrated better treatment effects in the US population compared to the rest of the world, it is important to establish the dose-response for maintenance in the US. This trial should randomize patients on stable doses of vortioxetine to several different doses (e.g., 5 mg, 10 mg, and 20 mg) of vortioxetine (and to placebo) during the maintenance phase.*

On January 14, 2020, the Applicant submitted a supplemental New Drug Application (Supplement S-020). The supplement included the final Clinical Study Report for Study LuAA21004-402, which was conducted to fulfill PMC #2084-6 described above. The supplement also included draft labeling that would add a description of Study LuAA21004-402 to the Clinical Studies section of the label and an update to the Dosage and Administration section of the label to indicate that two maintenance studies have now been completed. The Applicant did not suggest any additional changes to the product label.

APPEARS THIS WAY ON ORIGINAL

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) had selected two sites for inspection based on criteria including high enrollments, high discontinuation rates, and high weighted treatment effect. However, the public health emergency related to the COVID-19 pandemic required that OSI prioritize inspections to Breakthrough Therapy drugs, drugs on the CDER Drug Shortages list, medical counter-measure drugs, crash cart drugs, and drugs that meet unmet medical needs to treat life-threatening or sight-threatening diseases. Because vortioxetine does not fall into any of these categories, the inspections for NDA 204447 were postponed. It was not possible to schedule the inspections such that they could be completed prior to the PDUFA due date for this application. The Agency felt that review of the application could proceed without the inspections because no research site, including the two sites initially selected, had demonstrated any obvious irregularities in conduct of the study necessitating inspection prior to reaching a conclusion on our analysis of the safety and efficacy data.

4.2. Product Quality

No new Product Quality information was submitted with this supplement.

4.3. Clinical Microbiology

No new Clinical Microbiology information was submitted with this supplement.

4.4. Devices and Companion Diagnostic Issues

Not relevant to this submission.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data were submitted with this supplement.

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

No new Clinical Pharmacology data were submitted with this supplement.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The supplement is based on the results from a single randomized withdrawal study. Details of the study design are presented in Table 2.

APPEARS THIS WAY ON ORIGINAL

Table 2: Summary of Study Design for Study 402

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
LuAA21004_402 (Study 402)	02371980	Placebo-controlled randomized withdrawal	Open-label period: vortioxetine 10 mg daily Double-blind randomized withdrawal period: vortioxetine 5 mg daily, 10 mg daily, 20 mg daily, or placebo	Primary endpoint: time in weeks from randomization to relapse of any mood event during the double-blind treatment period	Open-label period: 16 weeks Double-blind period: 28 weeks Safety follow-up: 4 weeks	Open-label period: 1106 Double-blind period: 580	Males and females aged 18 to 75 years with a current diagnosis of major depressive disorder and at least two other major depressive episodes before the current episode	74 sites in the United States

7.2. Review Strategy

The review consisted of analysis of the safety and efficacy data submitted by the Applicant in the Clinical Study Report for Study LuAA21004_402. The Clinical Study Report for Study 11985A (submitted with the original product approval) was consulted in order to document differences in the designs of the two studies. This application qualified for a streamlined review and the assessment relied on qualified data summaries rather than review of the full datasets.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study LuAA21004_402

(Study 402; ClinicalTrials.gov Identifier NCT02371980)

Overview and Objectives

Study Title: "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10, and 20 mg) in Adults with Major Depressive Disorder"

Primary Objective: To evaluate the efficacy of vortioxetine (5, 10, and 20 mg) versus placebo during the first 28 weeks of the 32-week double-blind treatment period in the prevention of relapse in patients with MDD who responded to acute treatment with vortioxetine 10 mg.

Secondary Objective: To evaluate the overall efficacy of vortioxetine versus placebo during continuation treatment of patients with MDD.

Additional Objectives:

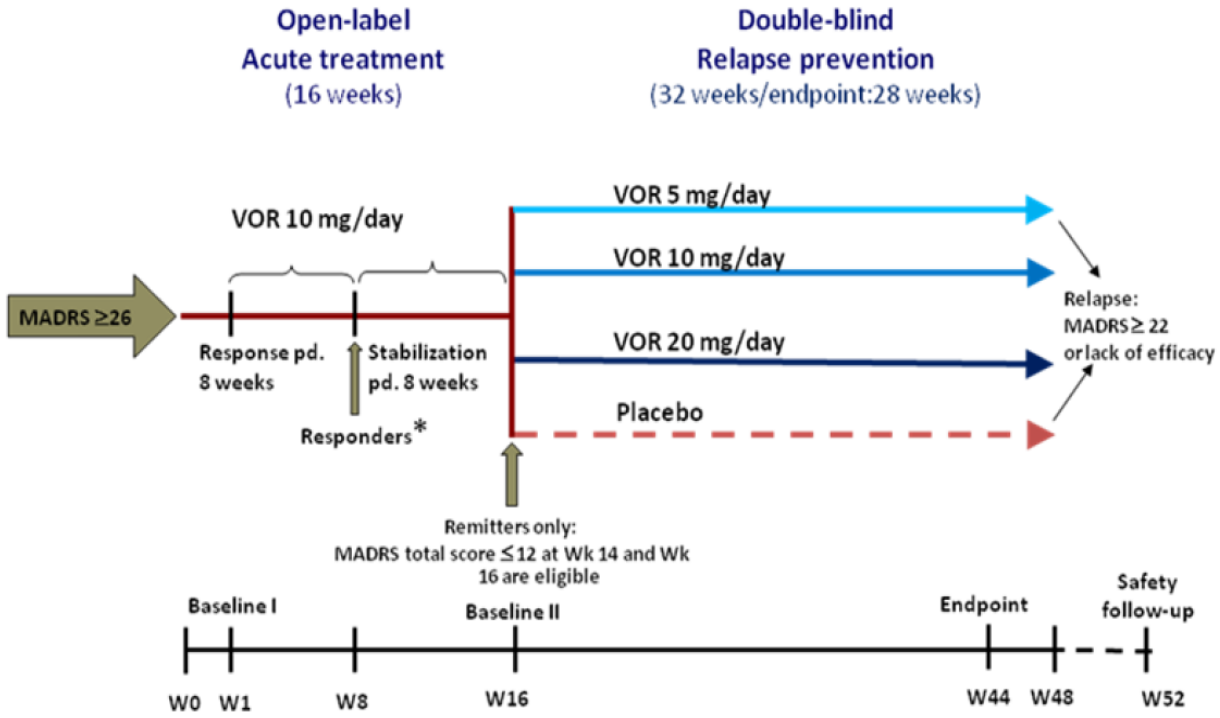
- To assess the effect of long-term treatment with vortioxetine and placebo on suicidal ideation and behavior.
- To determine the pharmacokinetic (PK) parameters of vortioxetine using a population PK approach.
- To collect and store pharmacogenomic (PGx) samples for possible exploratory investigation of drug response or disease. PGx analyses could be conducted to explore gene polymorphism relationships with drug responses, if indicated by the findings.

Safety Objective: To evaluate long-term safety and tolerability of vortioxetine versus placebo in patients with MDD.

Trial Design

Study Design Overview: Study LuAA21004-402 (Study 402) was a randomized, double-blind, placebo-controlled, phase 4 study to evaluate three fixed doses (5 mg, 10 mg, and 20 mg) of vortioxetine once daily in the prevention of relapse in adult patients with MDD who had responded to acute treatment with vortioxetine. The study included a 16-week open-label treatment period followed by a 32-week double-blind randomized treatment period. Please see Figure 1 for a schematic of the study design.

Figure 1: Study Design



VOR: vortioxetine; pd: period.
*Defined as ≥50% reduction in MADRS total score. Subjects had to remain in response throughout stabilization period.
Source: Figure 3.a of Applicant's statistical analysis plan (Page 8)

The study design had some elements that are not typical of a randomized-withdrawal study. Typically, a randomized-withdrawal study design allows for flexible dosing during the open-label period to identify a dose for each patient that is both tolerable and efficacious. In Study 402, all patients received the 10-mg dose of vortioxetine during the open-label period. Only patients who responded to the 10-mg dose were allowed to continue to the double-blind period. Patients who met criteria to continue in the study were randomized to either placebo or vortioxetine 5 mg, 10 mg, or 20 mg. Thus, the study design included either continuation on the 10-mg dose, a forced reduction from the 10-mg dose to the 5-mg dose, or a forced increase from the 10-mg dose to the 20-mg dose. An advantage of this study design is that it allows randomization of the responders into four equally-balanced treatment groups, simplifying the comparison of efficacy of the three drug doses to placebo.

A previous study, Study 11985A, demonstrated maintenance of efficacy of vortioxetine 5 mg and vortioxetine 10 mg in the treatment of MDD. The previous study used a more typical randomized-withdrawal design with flexible dosing during the open-label phase. The previous study was

conducted entirely at non-United States sites. Other design elements of Study 402 that are different from the previous maintenance of efficacy study include a longer stabilization period in the open-label phase and differences in remission criteria, relapse criteria, covariates in the primary analysis, and the time point of the primary analysis.

In previous short-term efficacy studies of vortioxetine in the United States, the 10-mg dose was numerically better than placebo but not statistically significantly different from placebo. Also in the United States, the 5-mg dose was statistically significantly different from placebo in only one study in the elderly population. The 5-mg and 10-mg doses were included in this study to collect additional data on these doses in the United States and to further evaluate their performance in maintenance of efficacy in the United States. The 20-mg dose was included because, although it is an approved dose, it had not previously been evaluated in a long-term maintenance study.

Trial Location: The study was conducted at 74 sites in the United States.

Key Inclusion Criteria:

- Male or female aged 18 to 75 years, inclusive.
- Diagnosis of recurrent Major Depressive Disorder (classification code 296.3x) as the primary diagnosis according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), with the current episode confirmed by the Mini International Neuropsychiatric Interview (MINI).
- The duration of the current episode is ≥ 8 weeks and ≤ 18 months.
- The patient had at least two other major depressive episodes before the current episode.
- Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 26 at the Screening and Baseline I visits.

Key Exclusion Criteria:

- Any current psychiatric disorder other than MDD is the primary focus of treatment.
- History of bipolar disorder, psychotic disorder, obsessive compulsive disorder, mental retardation, organic mental disorder, mental disorder due to a general medical condition, substance abuse or dependence, clinically significant neurological disorder, or neurodegenerative disorder.
- The current depressive symptoms are considered to have been resistant to two adequate antidepressant treatments of at least six weeks duration each.
- Electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation within six months prior to Screening.

- Significant risk of suicide according to the investigator's clinical judgment or has a score ≥5 on item 10 (suicidal thoughts) of the MADRS or has made a suicide attempt within the previous six months.

- Any clinically significant unstable illness.

- Known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.

- Any clinically significant abnormal vital signs or abnormal laboratory findings at Screening.

Prohibited Concurrent Medications:
The study protocol includes a list of prohibited concurrent medications. Patients were required to stop any previously prescribed antidepressants, antipsychotics, mood stabilizers, and anxiolytics (including benzodiazepines) 2 weeks prior to Week 1 of the open-label period of the study. Fluoxetine had to be discontinued 5 weeks prior to Week 1, and long-acting antipsychotics had to be discontinued 6 months prior to Week 1. The protocol prohibited any as-needed use of antidepressants, antipsychotics, mood stabilizers, or anxiolytics during the study. Sedative/hypnotic drugs had to be discontinued 2 weeks prior to Week 1. Daily use of sedatives/hypnotics was prohibited during the study. Short-term use of sedatives/hypnotics was allowed, as described below under Allowable Concurrent Medications.

Allowable Concurrent Medications:
Daily use of sedatives/hypnotics was not allowed during the study. However, the protocol allowed the use of zolpidem, eszopiclone/zopiclone, zaleplon, and ramelteon, with a maximum of two nights per week. Use of these drugs the night before a study visit was not allowed.

Procedures and Schedule

Open-Label Period

At Baseline I, patients were enrolled into a 16-week open-label treatment period during which all patients received vortioxetine 10 mg daily. Patients were seen every 2 weeks. At Week 8, patients who met the response criteria (≥ 50% reduction in MADRS total score from Baseline I) continued for an additional 8 weeks of treatment (Stabilization Period) and continued to receive vortioxetine 10 mg daily. To qualify for randomization, patients had to continue to meet response criteria at every study visit and had to meet remission criteria (MADRS total score ≤ 12) at Week 14 and Week 16. Patients who did not meet the response or remission criteria or who required a dose adjustment were withdrawn from the study and completed an early withdrawal visit.

Double-Blind Period

At Baseline II, patients who met the response and remission criteria were randomized in a 1:1:1:1 ratio into 32 weeks of treatment with vortioxetine 5 mg daily, vortioxetine 10 mg daily, vortioxetine 20 mg daily, or placebo daily. Patients were seen twice during the first month and then once monthly for the remainder of the double-blind treatment period. Relapse was defined as a MADRS total score ≥ 22 or lack of efficacy as determined by the Investigator. Patients who relapsed were withdrawn from the study and completed an early withdrawal visit.

Patients were contacted for a safety follow-up call 30 days after the last dose of study medication, whether this occurred at completion of the study or prior to early withdrawal from either the open-label or double-blind period of the study.

Table 3 depicts the schedule of assessments in Study 402.

Table 3: Schedule of Assessments, Study LuAA21004_402

	Screening	Baseline I	Open-Label Treatment							Baseline II/ Random-ization(a)	Withdrawal (b)	Follow-up ☎ call
Study Day/End of Week:		**Day 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		
Visit Windows (Days relative to Baseline I)	**Days -21 to -5**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Screening/Baseline Procedures and Assessments												
Informed consent	X											
CTSdatabase	X(c)											
Demographics, medical history, height	X											
Concurrent medical conditions	X	X (d)										
Relevant psychiatric and social history	X											
Diagnostic Validation	X											
MINI	X											
Diagnosis (DSM-IV-TR)	X											
Medication history	X											
Inclusion/exclusion criteria	X	X (d)										
Eligibility verification	X											
Stabilization criteria (e)						X	X	X	X	X		
Randomization criteria										X		
Safety Assessments												
PTE assessment (f)	X	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Body weight	X	X				X				X	X	
Physical examination	X	X								X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X (g)
Clinical laboratory tests (h)	X	X				X				X	X	
Urine drug screening	X	X								X		
ECG	X	X								X	X	
Pregnancy test (hCG) (i)	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
AE assessment			X	X	X	X	X	X	X	X	X	X (j)

	Screening	Baseline I	Open-Label Treatment							Baseline II/ Random-ization(a)	Withdrawal (b)	Follow-up ☎ call
Study Day/End of Week:		**Day 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		
Visit Windows (Days relative to Baseline I)	**Days -21 to -5**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Efficacy Assessments												
MADRS (SIGMA if site chooses to use)	X	X	X	X	X	X	X	X	X	X	X	
CGI-S		X	X	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	X	X	X	
Other Blood Sampling												
PK sampling for study medication						X				X	X	
Pharmacogenomic sampling (h)		X				X				X	X	
Clinical Supplies												
Call IWRS for Subject ID/Medication ID/subject status	X	X	X	X	X	X	X	X	X	X	X	
Dispense study medication		X (k)	X	X	X	X	X	X	X	X		
Study medication return/ accountability/compliance			X	X	X	X	X	X	X	X	X	

(a) Subjects who meet all randomization criteria please follow schedule of procedures for week 16 on schedule of study procedures for double-blind treatment period.
(b) All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(c) Obtain subject authorization, enter subject into the CTS database.
(d) Update at Baseline I.
(e) Subjects must meet response criteria from Week 8 through Week 16 and remission criteria at Weeks 14 and 16.
(f) Pretreatment event assessment occurs from the date of Screening up to the first dose of study medication.
(g)Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(h) Fasting labs must be performed at Baseline I and Baseline II (randomization).
(i) Serum hCG for female subject of childbearing potential at Screening, Baseline II (randomization) and Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(j) Two whole blood samples (3 mL per sample) will be collected predose on Day 0 for DNA isolation. Two whole blood samples (2.5 mL per sample) will be collected for RNA isolation at each time point at predose on Day 0 and weeks 8, and 16 and any early withdrawal visit during open-label. The sample for pharmacogenomics may be drawn at the earliest visit after Baseline I, if missed at visit 2 (Baseline I). Pharmacogenomics sample collection is optional for subjects. A separate Informed Consent Form will be obtained.
(k) The subjects will be instructed to take the first dose of study medication on the morning after enrollment (Baseline I).

	Baseline II/ Random-ization	Double-Blind Treatment (a)								Completion/ Withdrawal (b)	Follow-up ☎ call
End of Week:	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Windows (Days relative to Baseline II)	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5
Visit Number:	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Baseline II Procedures and Assessments											
Randomization criteria	X (c)										
Safety Assessments											
Vital signs	X	X	X	X	X	X	X	X	X	X	
Body weight	X	X		X		X		X		X	
Physical examination	X	X				X				X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X(d)
Clinical laboratory tests (e)	X	X				X				X	
Urine drug screening	X										
ECG	X					X				X	
Pregnancy test (hCG) (f)	X	X	X	X	X	X	X	X	X	X	
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X(d)
Relapse Checklist		X	X	X	X	X	X	X	X	X	
Efficacy Asssessments											
MADRS (SIGMA if site chooses to use)	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	
CGI-I	X									X	
Other Blood Sampling											
PK sampling for study medication (g)	X					X				X	
Pharmacogenonic sampling (h)	X									X	
Clinical Supplies											
Call IWRS for Subject ID/Medication ID/subject status	X	X	X	X	X	X	X	X	X	X	

	Baseline II/ Random-ization	Double-Blind Treatment (a)								Completion/ Withdrawal (b)	Follow-up ☎ call
End of Week:	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Windows (Days relative to Baseline II)	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Visit Number:	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Dispense study medication	X (i)	X	X	X	X	X	X	X	X		
Study medication return/ accountability/compliance	X	X	X	X	X	X	X	X	X	X	

(a) Subject well-being phone calls should be made every 2 weeks post Week 20 through week 46.
(b)All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(c) Confirm stabilization criteria of response and remission are met and there are no major protocol violations.
(d)Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(e) Fasting labs to be performed at Baseline II/ Randomization and Completion/Withdrawal.
(f) Serum hCG for female subject of childbearing potential at Baseline II/Randomization and Completion/Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(g) PK sampling must be taken prior to first dose of double-blind study medication.
(h) Only samples for RNA to be collected at Week 16 and Week 48 for those subjects who consented to pharmacogenomic sampling.
(i) The subjects will be instructed to take the first dose of study medication on the morning after randomization.

Source: Study Luaa21004-402 Protocol Incorporating Amendment 1, Appendix A, "Schedule of Study Procedures," pages 83-86.

Study Endpoints

Primary Efficacy Endpoint:

The endpoint of the efficacy assessment was time (in weeks) from randomization to relapse of any mood event during the 28 weeks of the 32-week double-blind treatment period. Precisely, it is the time from the first dose of the double-blind treatment period to first recurrence of any mood event.

The Applicant defined relapse (as outined in the statistical analysis plan, page 9) as:

- Depression, as signified by Montgomery-Asberg Depression Rating Scale (MADRS ≥ 22), or
- Lack of efficacy as determined by the investigator.

To control the overall type 1 error for the primary efficacy endpoint, a sequential testing procedure was performed starting from the highest dose to the lowest. That is, 20 mg versus placebo, 10 mg versus placebo, and 5 mg versus placebo were sequentially tested at significance level 0.05.

Secondary Efficacy Measures:

There were no type 1 error-controlled secondary efficacy endpoints. However, some secondary endpoints in the double-blind treatment period were explored. These included change from double-blind baseline in MADRS total score at all time points, change from double-blind baseline in Clinical Global Impression – Severity (CGI-S) total score at all time points, Clinical Global Impression – Improvement (CGI-I) score at all time points, and time from randomization to relapse during the entire 32-week double-blind treatment period, with relapse defined as MADRS score ≥ 22 or lack of efficacy as determined by the investigator.

Clinical Reviewer's Comment: Comparisons between vortioxetine and placebo for the secondary efficacy measures were considered supportive, and statistical tests for endpoints with these measures were not controlled for multiplicity.

Safety Assessments

The safety and tolerability of vortioxetine were evaluated using the following general assessments:

- Adverse events (AEs)
- Laboratory values
- Vital signs
- Weight

- Electrocardiograms (ECGs)

Statistical Analysis Plan

The primary analysis for the primary and secondary efficacy endpoints was carried out on the full-analysis set (FAS) population which included all randomized subjects who took at least one dose of double-blind study medication. All efficacy analyses were based on FAS and included treatment assignments to which subjects were randomized.

Efficacy Analyses Methods
The primary analysis for the primary efficacy endpoint was based on the comparison of the distribution of time to relapse during the first 28 weeks of the 32-week double blind treatment for vortioxetine (5, 10, 20 mg) versus that for placebo. The Applicant's primary analysis utilized Cox proportional hazards model using an exact method to handle ties, with treatment as a factor and baseline MADRS total score as the covariate. The baseline MADRS total score was administered at the beginning of the double-blind treatment phase (Baseline II). The analysis was supplemented with non-parametric plots of Kaplan-Meier estimates of relapse.

Estimated hazard ratios and 95% CIs were reported from a supportive analysis: primary Cox model analysis with treatment as a factor (baseline MADRS total score was excluded since covariate adjustment in the Cox regression model required stronger model assumptions); the standard log-rank test and the accelerated failure time models were also performed. Various distributions were studied in the parametric models (e.g., Weibull, log-normal, and log-logistic).

Secondary endpoint (exploratory): Change from double-blind Baseline II in MADRS totals score was analyzed using the mixed model for repeated measures (MMRM) model with treatment, week, baseline MADRS total score, treatment-by-week interaction as fixed effects, and center as random effect with unstructured covariance matrix. Treatment group comparisons were made at each assessment week.

The hypotheses testing in the methods above will be conducted using 2-sided tests with alpha set at 0.05 level of significance.

Statistical Reviewer's Comment: Reference is made to the statistical review (IND 076307, SN 309) wherein FDA recommended a Cox model without baseline covariate (MADRS total score) if case model assumptions were not satisfied. The Applicant provided a response (SN 314) and indicated that a sensitivity analyses would be conducted by excluding the baseline covariate. The Applicant's results in the clinical study report (CSR) included the proposed sensitivity analyses.

Sensitivity Analyses
Censored time: (i) All withdrawals (relapses or other reasons) occurring after Visit 18/Week 44 were regarded as censored observations and assigned the date of Visit 18 as censoring time;

(ii) subjects who did not relapse and withdrew before or at Visit 18 were considered non-relapsed subjects and received the date of the study drug withdrawal as censoring time. If the date was missing, the date of the last contact was used as censoring time (CSR, page 58-59).

Sensitivity analyses, using the same methodology as for the primary analysis (Cox model) was repeated with treatment as a factor. Also, time from randomization to relapse of MDD occurring during the entire 32-week double-blind treatment period was analyzed using a Cox model.

Protocol Amendments

There was one protocol amendment on September 25, 2015. The main changes to the protocol were as follows:

1. Clarification of the exclusion criteria to exclude patients with fibromyalgia, obstructive sleep apnea, chronic pain, and morbid obesity because of potential impact on assessment of the primary endpoint.

2. Addition of an exclusion criterion to exclude patients who are treatment-resistant, as defined by lack of response to at least six weeks of adequate monotherapy treatment or only responding to combination or augmentation therapy.

3. Addition of a subject registry to help restrict patients from enrolling in multiple clinical trials simultaneously.

4. Addition of PK and RNA blood sampling for patients who withdraw during the open-label period.

5. Expansion of flexibility in rater qualifications to allow non-physicians with training and experience to administer the Clinical Global Impression scales.

6. Addition of a Relapse Checklist at Visits 18 to 48 to assess potential indicators of relapse at each post-baseline visit during the double-blind period.

Other grammatical and editorial changes were made for purposes of clarification.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Study 402 CSR states that the study was conducted in compliance with the Institutional Review Board (IRB) regulations stated in Title 21 of the United States Code of Federal Regulations (CFR), Part 56, Good Clinical Practice (GCP) regulations and guidelines. The CSR also states that the ethical principles guiding conduct of the study have their origin in the

Declaration of Helsinki, the informed consent regulations stated in Title 21 CFR, Part 50, in accordance with the International Conference on Harmonization (ICH) GCP (E6) Section 4.8, and all applicable local regulations.

Financial Disclosure

No disclosable financial interests or arrangements were reported for any of the investigators participating in this study. See Section 19.2, Financial Disclosures, for details.

Patient Disposition

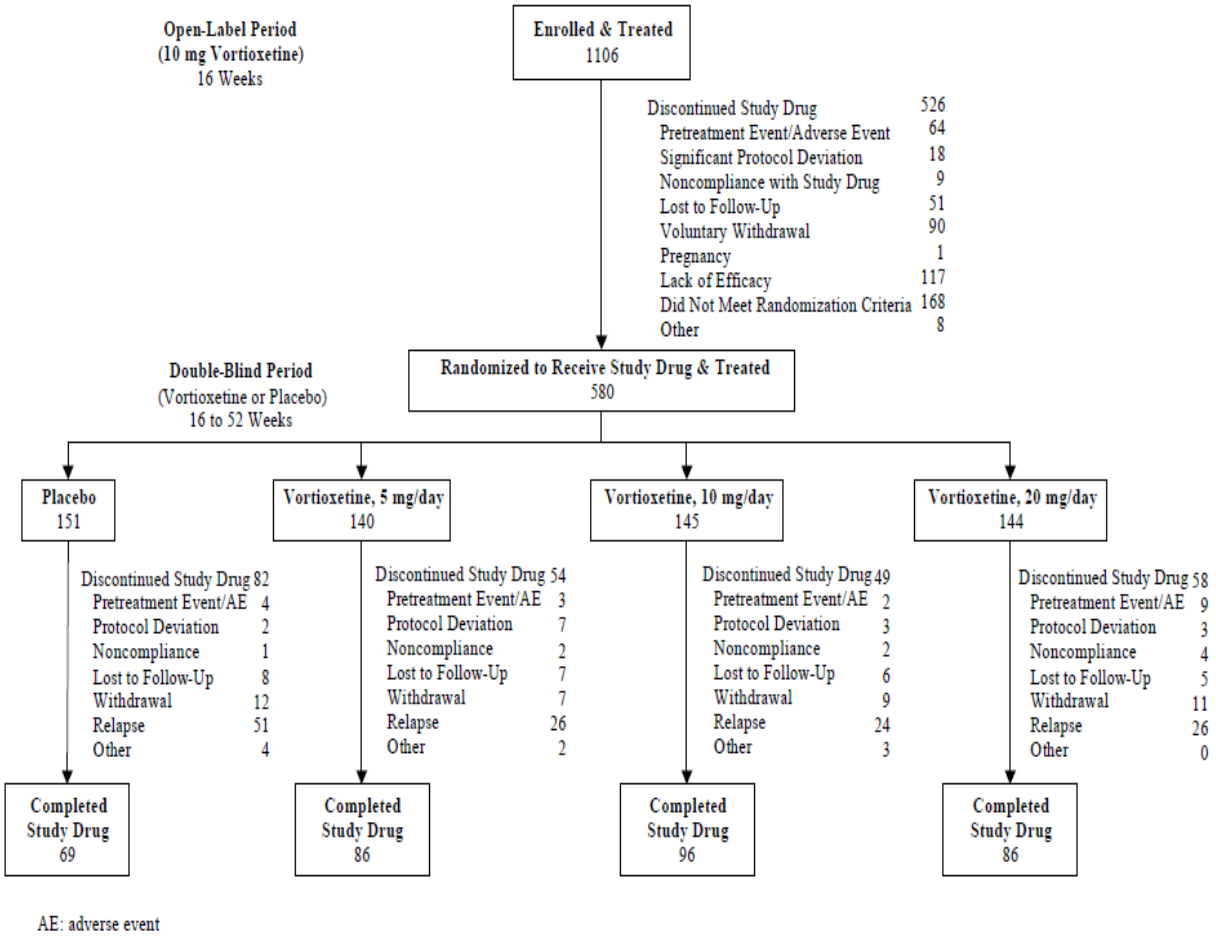
A total of 1106 patients were enrolled in the open-label vortioxetine only treatment. As shown in Table 4, 580 subjects completed the open-label treatment period and were subsequently randomized in the double-blind treatment phase. The two common reasons for discontinuation from the open-label treatment period were failure to meet randomization criteria (31.9%) and lack of efficacy (22.2%) (see Figure 2).

Table 4: Analysis Sets (All Enrolled Subjects)

	Number of Subjects (%)				
	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Vortioxetine 20 mg	Total
All enrolled subjects			1106		
Open-label safety set [a]			1106 (100.0)		
Open-label PK set [a]			588 (53.2)		
All randomized subjects	151	140	145	144	580
FAS [b]	151 (100.0)	140 (100.0)	145 (100.0)	144 (100.0)	580 (100.0)
Double-blind safety set [b]	151 (100.0)	140 (100.0)	145 (100.0)	144 (100.0)	580 (100.0)
PPS [b]	139 (92.1)	125 (89.3)	135 (93.1)	133 (92.4)	532 (91.7)
Double-blind PK set [b]	1 (0.7)*	132 (94.3)	139 (95.9)	134 (93.1)	406 (70.0)

BLQ: below the limit of quantitation; FAS: full analysis set; PK: pharmacokinetic; PPS: per protocol set.
[a]Percentages are based on the total number of enrolled subjects.
[b]Percentages are based on the total number of randomized subjects.
*The sample for this subject receiving placebo was assayed in error, and the reported value is BLQ.
Source: Table 11.a (cross-reference Table 15.1.7) of Applicant's CSR (Page 71)

Figure 2: Subject Disposition



Source: Figure 10.a (cross-reference Table 15.1.5.1 and Table 15.1.5.2) of Applicant's CSR (Page 68)

Figure 2 summarizes total number of enrolled and treated trial participants along with reasons for discontinuation by treatment group. The primary efficacy analysis set is the Full Analysis Set (FAS), which includes 580 subjects, with 151 in the placebo group, 140 in the vortioxetine 5-mg group, 145 in the vortioxetine 10-mg group, and 144 in the vortioxetine 20-mg group. Sixty-nine (45.7%) subjects in the placebo group, 86 (61.4%) subjects in the 5-mg group, 96 (66.2%) subjects in the 10 mg group, and 86 (59.7%) subjects in the 20-mg group completed the study without experiencing a relapse, with total completion rate of 58.1%. Proportion of completers was higher among the fixed vortioxetine dose groups. Overall, the most frequent reasons for discontinuation during the double-blind phase were relapse (52.3%) and withdrawal (16.0%). Specifically, among those who discontinued, a substantial number of subjects in the placebo group (62.2%) compared to vortioxetine dose groups (5-mg: 48.1%; 10-mg: 49.0%; 20-mg: 44.8%) withdrew due to relapse events related to depressive episodes. Among those who were randomized in the double-blind phase, a higher proportion of subjects in the placebo group (34.4%) experienced relapse compared to vortioxetine dose groups (5-mg: 19.3%; 10-mg: 18.6%; 20-mg: 18.8%).

Protocol Violations/Deviations

In Table 5, major protocol deviations with at least one protocol violation during the double-blind treatment period were reported for eight (5.3%) subjects in the placebo group, four (2.9%) in the vortioxetine 5-mg group, five (3.4%) in the vortioxetine 10-mg group, and eight (5.6%) in the vortioxetine 20-mg group. Key category of deviation was related to *study drug exposure < 14 days* (5.3% in placebo, 1.4% in vortioxetine 10-mg and 3.5% in vortioxetine 20-mg). The distribution of major protocol violations appeared similar across treatment groups.

Table 5: Number (%) of Subjects With Major Protocol Violations During Double-Blind Treatment Period (FAS)

	Number of Subjects (%)				
	Placebo (N=151)	Vortioxetine 5 mg (N=140)	Vortioxetine 10 mg (N=145)	Vortioxetine 20 mg (N=144)	Total (N=580)
Subjects With At Least One Major Protocol Violation	8 (5.3)	4 (2.9)	5 (3.4)	8 (5.6)	25 (4.3)
No Evaluable Baseline II MADRS Assessment	0	0	0	0	0
No Evaluable Post-Baseline II MADRS Assessment	2 (1.3)	1 (0.7)	1 (0.7)	2 (1.4)	6 (1.0)
Low Study Drug Compliance (<70%) or Missed Study Drug for 6 Consecutive Days	1 (0.7)	2 (1.4)	2 (1.4)	4 (2.8)	9 (1.6)
Double-Blind Study Drug Exposure <14 Days (a)	8 (5.3)	0	2 (1.4)	5 (3.5)	15 (2.6)
Subjects Switch Treatment During Study	0	1 (0.7)	0	0	1 (0.2)

Note 1: Violations are significant deviations during the double-blind period identified as major prior to unblinding.
Note 2: Percentages are based on the total number of subjects in each treatment group.
Note 3: Subjects are counted for each violation where the violation criteria is met.
(a) Days are computed as the last dose date - the first dose date + 1.

Source: Table 15.1.6.2 of Applicant's Tables and Figures (Page 26)

Table of Demographic Characteristics

The demographic data for the FAS double-blind subjects is presented in Table 6. The average age of patients was 45.1 years, ranging from 18 to 75 years. Most participants were White (74.5%), female (72.4%), and non-Hispanic/Latino (84.1%). The demographic characteristics and baseline measurements were approximately similar across treatment arms with respect to age, gender, race, height, weight, and BMI in the double-blind phase.

Table 6: Demographic and Baseline II Characteristics Data for Double-Blind Subjects (FAS)

	Placebo N=151	**Vortioxetine 5 mg N=140**	**Vortioxetine 5 mg N=145**	**Vortioxetine 5 mg N=144**	**Total N=580**
Age (Years)					
N	151	140	145	144	580
Mean (SD)	45.0 (13.25)	44.7 (13.90)	46.6 (12.52)	44.1 (13.21)	45.1 (13.23)
Median	47.0	46.0	49.0	45.0	46.0
Minimum, Maximum	18, 71	18, 75	18, 70	18, 70	18, 75
Median Age Categories (N[%])					
≤46 years	75 (49.7)	72 (51.4)	66 (45.5)	79 (54.9)	292 (50.3)
>46 years	76 (50.3)	68 (48.6)	79 (54.5)	65 (45.1)	288 (49.7)
Gender (N[%])					
Male	37 (24.5)	37 (26.4)	48 (33.1)	38 (26.4)	160 (27.6)
Female	114 (75.5)	103 (73.6)	97 (66.9)	106 (73.6)	420 (72.4)
Ethnicity (N[%])					
Hispanic or Latino	22 (14.6)	24 (17.1)	23 (15.9)	23 (16.0)	92 (15.9)
Non-Hispanic and Latino	129 (85.4)	116 (82.9)	122 (84.1)	121 (84.0)	488 (84.1)
Race (N[%])					
American Indian or Alaska	1 (0.7)	0	0	0	1 (0.2)
Asian	3 (2.0)	3 (2.1)	3 (2.1)	3 (2.1)	12 (2.1)
Black or African American	26 (17.2)	34 (24.3)	27 (18.6)	29 (20.1)	116 (20.0)
Native Hawaiian or Other Pacific Islander	2 (1.3)	1 (0.7)	2 (1.4)	3 (2.1)	8 (1.4)
White	117 (77.5)	98 (70.0)	111 (76.6)	106 (73.6)	432 (74.5)
Multiracial	2 (1.3)	3 (2.1)	2 (1.4)	3 (2.1)	10 (1.7)
Missing	0	1 (0.7)	0	0	1 (0.2)
Race Categories (N[%])					
White	117 (77.5)	98 (70.0)	111 (76.6)	106 (73.6)	432 (74.5)
Non-white	34 (22.5)	41 (29.3)	34 (23.4)	38 (26.4)	147 (25.3)
Missing	0	1 (0.7)	0	0	1 (0.2)
Height (cm)					
N	151	140	145	144	580
Mean (SD)	167.4 (10.30)	168.3 (9.19)	168.5 (9.21)	167.0 (9.24)	167.8 (9.50)
Median	167.0	168.0	167.0	165.0	167.0
Minimum, Maximum	145, 195	147, 193	152, 198	150, 196	145, 198
Weight (kg)					
N	151	140	145	144	580
Mean (SD)	82.24 (18.447)	81.77 (20.668)	84.47 (19.211)	85.41 (17.378)	83.47 (18.957)
Median	81.60	77.80	83.70	84.80	82.20
Minimum, Maximum	45.6, 142.7	44.0, 133.1	48.1, 148.5	44.8, 129.5	44.0, 148.5
Body Mass Index (kg/m^2)					
N	151	140	145	144	580
Mean (SD)	29.25 (5.473)	28.74 (6.429)	29.65 (5.757)	30.54 (5.337)	29.55 (5.779)

Median	29.07	27.57	29.15	30.20	29.06
Minimum, Maximum	19.0, 40.9	17.3, 48.6	17.9, 51.4	16.9, 42.6	16.9, 51.4
Smoking Classification (N[%])					
Subject has never smoked	103 (68.2)	93 (66.4)	94 (64.8)	90 (62.5)	380 (65.5)
Subject is a current smoker	27 (17.9)	25 (17.9)	30 (20.7)	27 (18.8)	109 (18.8)
Subject is an ex-smoker	21 (13.9)	22 (15.7)	21 (14.5)	27 (18.8)	91 (15.7)
Alcohol Consumption (N[%])					
Never	49 (32.5)	40 (28.6)	48 (33.1)	40 (27.8)	177 (30.5)
Once monthly or less often	37 (24.5)	43 (30.7)	36 (24.8)	38 (26.4)	154 (26.6)
Once a week	22 (14.6)	16 (11.4)	22 (15.2)	32 (22.2)	92 (15.9)
2 to 6 times per week	17 (11.3)	22 (15.7)	19 (13.1)	17 (11.8)	75 (12.9)
Daily	2 (1.3)	1 (0.7)	0	2 (1.4)	5 (0.9)
Ex-Drinker	24 (15.9)	18 (12.9)	20 (13.8)	15 (10.4)	77 (13.3)

Source: Table 10.c (cross-reference Table 15.1.8.1.2) of Applicant's CSR (Page 73-75)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were not considerable differences in mean baseline efficacy scores (MADRS and CGI-S) between randomized and non-randomized subjects in the open-label phase (see Table 7).

Table 7: Baseline I (Open-label Period) Efficacy Parameters (Randomized, Non-Randomized Set)

	Randomized N=580	Randomization Failure N=526	Overall N=1106
MADRS Total Score			
N	580	526	1106
Mean (SD)	33.6 (4.26)	34.2 (4.26)	33.9 (4.27)
Median	33.0	34.0	34.0
Minimum, Maximum	26, 50	26,47	26, 50
CGI-S Score			
N	580	526	1106
Mean (SD)	4.6 (0.56)	4.7 (0.59)	4.7 (0.58)
Median	5.0	5.0	5.0
Minimum, Maximum	4, 6	1, 6	1, 6

CGI-S: Clinical Global Impression Scale-Severity of Illness Scale; MADRS: Montgomery Asberg Depression Rating Scale.
Source: Table 11.d (cross-reference Table 15.1.8.2.1) of Applicant's CSR (Page 76)

The mean baseline efficacy parameters were similar across the four treatment groups in the double-blind period (Table 8). In addition, the mean MADRS and CGI-S total scores improved significantly from Baseline I to Baseline II (from 33.6 to 4.8 in mean MADRS total score; from 4.6 to 1.5 in mean CGI-S total score) among the randomized subjects.

Table 8: Baseline II (Double-Blind Period) Efficacy Parameters (Randomized Set)

	Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144	Total N=580
MADRS Total Score					
N	151	140	145	144	580
Mean (SD)	4.9 (3.32)	4.8 (3.38)	4.9 (3.63)	4.7 (3.62)	4.8 (3.48)
Median	5.0	4.5	4.0	5.0	5.0
Minimum, Maximum	0, 12	0, 12	0, 12	0, 12	0, 12
Median MADRS Score (N[%])					
≤5	90 (59.6)	88 (62.9)	88 (60.7)	83 (57.6)	349 (60.2)
>5	61 (40.4)	52 (37.1)	57 (39.3)	61 (42.4)	231 (39.8)
CGI-S Score					
N	151	140	145	144	580
Mean (SD)	1.5 (0.62)	1.5 (0.63)	1.6 (0.70)	1.6 (0.71)	1.5 (0.67)
Median	1.0	1.0	1.0	1.0	1.0
Minimum, Maximum	1, 3	1, 3	1, 4	1, 3	1, 4
Median CGI-S Score (N[%])					
≤1	79 (52.3)	84 (60.0)	77 (53.1)	78 (54.2)	318 (54.8)
>1	72 (47.7)	56 (40.0)	68 (46.9)	66 (45.8)	262 (45.2)
CGI-I Score					
N	151	140	145	144	580
Mean (SD)	1.2 (0.47)	1.3 (0.49)	1.3 (0.52)	1.3 (0.44)	1.3 (0.48)
Median	1.0	1.0	1.0	1.0	1.0
Minimum, Maximum	1, 4	1, 4	1, 4	1, 2	1, 4

CGI-I: Clinical Global Impression Scale-Global Improvement Scale; CGI-S: Clinical Global Impression Scale-Severity of Illness Scale; MADRS: Montgomery Asberg Depression Rating Scale.
Source: Table 11.e (cross-reference Table 15.1.8.2.2) of Applicant's CSR (Page 77)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Of the 1106 patients enrolled in the open-label period of the study, 526 patients were assessed as not eligible for randomization. Of those patients, noncompliance with study drug was the reason for ineligibility for nine patients (1.7%). Of the 580 patients randomized to the double-blind period, nine patients (1.6%) were withdrawn from the study because of treatment noncompliance.

The use of concomitant medications during the study appears to have been limited to continuation of medications for treatment of chronic medical conditions. There were no protocol deviations related to the use of prohibited concomitant medications or rescue medications during the study.

Efficacy Results – Primary Endpoint

The Biostatistics reviewer confirmed the Applicant's long-term efficacy findings. Table 9 below summarizes the efficacy results for the primary efficacy parameter, which was time from randomization to relapse during the first 28 weeks of the double-blind treatment phase. Time

to relapse was statistically significantly longer among those who were under the fixed vortioxetine doses (5, 10, 20 mg) compared to placebo (
Figure 3). The hazard ratios for all vortioxetine arms compared to placebo (0.47 to 0.52), extracted from the Cox model, were statistically significantly lower than 1 (Table 9). Subjects in vortioxetine dose groups experienced significantly reduced risk of relapse. The Kaplan-Meier curves for time to relapse support that the observed relapse rates were lower for the three vortioxetine dose groups compared to the placebo group in the double-blind period (
Figure 3). The cumulative proportion of subjects who had a relapse by each given visit is displayed in Figure 4.

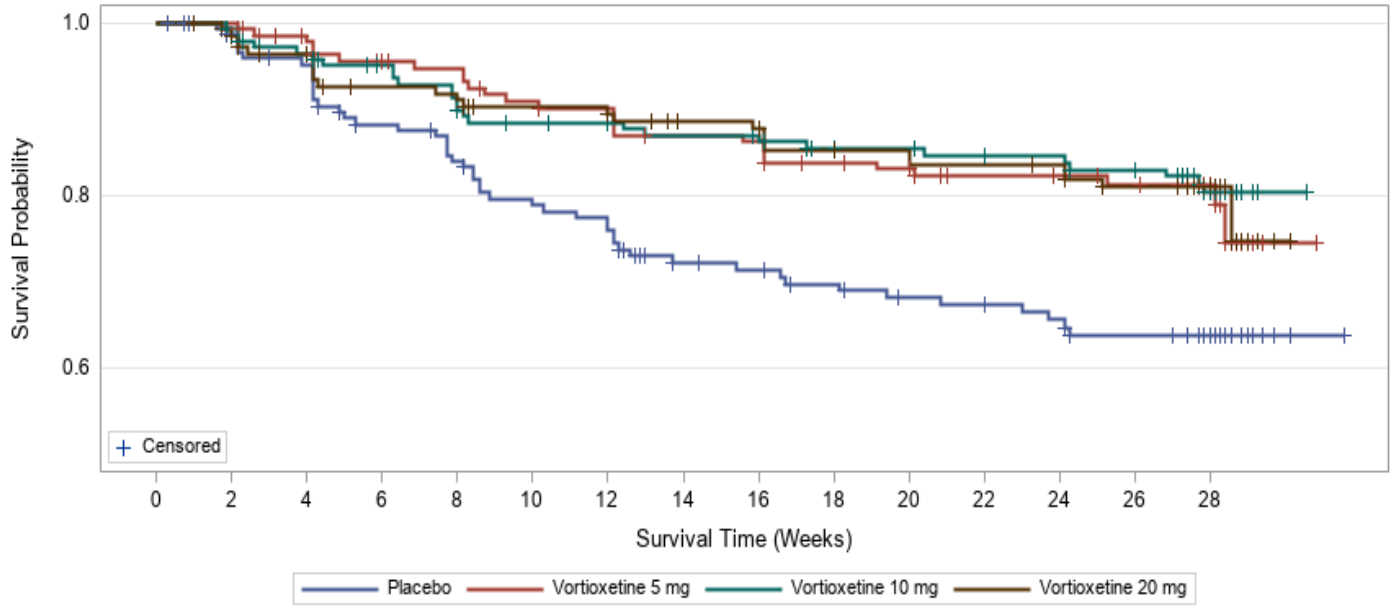
In addition, the log-rank test showed the long-term benefits of vortioxetine doses for major depression patients where the fixed dose groups separated statistically significantly from the placebo group (p = 0.001).

Table 9: Summary of Applicant's Primary Efficacy Results. Cox Model for Time to Relapse During the First 28 Weeks of Double-Blind Period (FAS)

	Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144
Time to Relapse within 28 weeks				
Number of events (%)	49 (32.5)	27 (19.3)	26 (17.9)	25 (17.4)
Number Censored (%)	102 (67.5)	113 (80.7)	119 (82.1)	119 (82.6)
Vortioxetine vs Placebo [a]				
Hazard Ratio		0.52	0.48	0.48
95% CI for Hazard Ratio		(0.32, 0.83)	(0.30, 0.77)	(0.30, 0.78)
P-value		0.006*	0.002*	0.003*

FAS: full analysis set; MADRS: MontgomeryAsberg Depression Rating Scale * indicates statistical significance at the 0.05 level. [a]: P-value, hazard ratio and 95% CI comparing Vortioxetine to Placebo were obtained using a Cox proportional hazards model with a factor for treatment and baseline II MADRS total score as a covariate, using the exact method to handle ties.
Source: Table 11.k (cross-reference Table 15.2.1.2.1) of Applicant's CSR (Page 86)

Figure 3: Kaplan Meier Estimation of Time to Relapse During the First 28 Weeks (Double-Blind-Full Analysis Set)

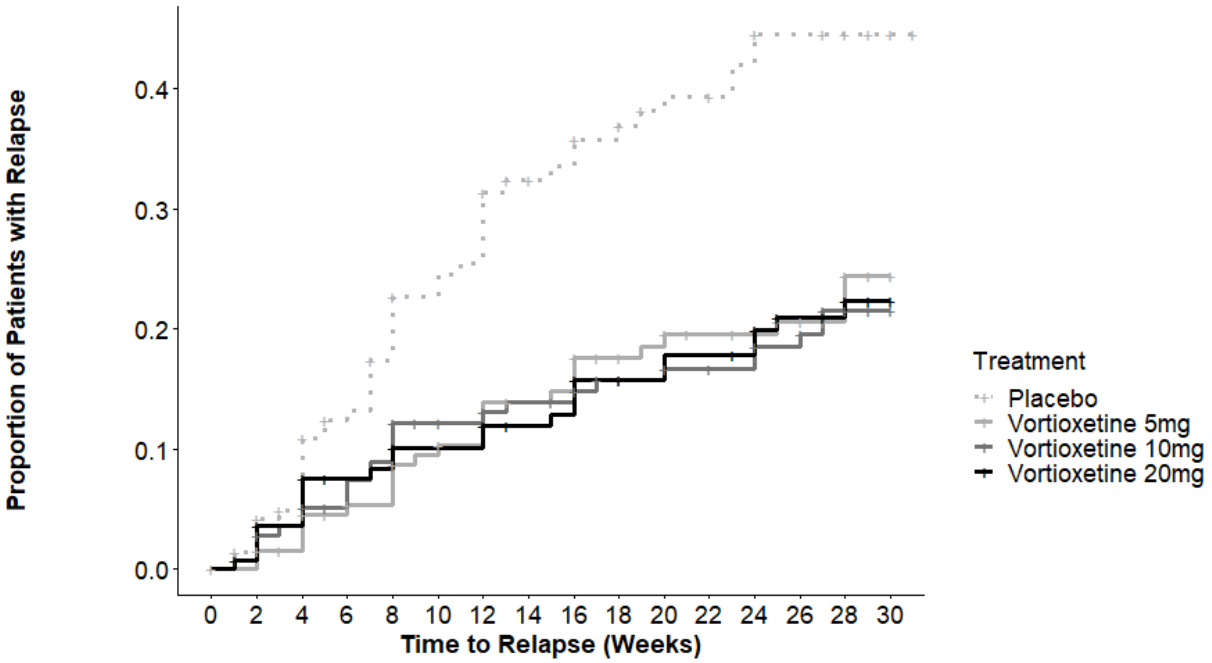


Subjects at Risk

Placebo	151	144	138	117	103	90	81	77	56
V 5 mg	140	140	131	123	115	109	101	94	67
V 10 mg	145	143	136	122	117	113	108	105	66
V 20 mg	144	138	127	116	110	104	98	97	67

Source: Applicant's Tables and Figures in CSR (Page 485, Table 15.2.1.2.3)

Figure 4: Cumulative Proportion* of Subejcts with Relapse During the First 28 Weeks (Double-Blind-Full Analysis Set)



Number of subjects at risk

Placebo	151	145	138	124	117	108	105	92	90	85	81	80	77	73	62	3
Vortioxetine 5mg	140	140	132	126	123	117	115	110	109	104	102	95	94	92	79	1
Vortioxetine 10mg	145	143	136	130	125	119	118	115	114	109	108	106	105	102	76	1
Vortioxetine 20mg	144	141	129	118	117	112	112	106	105	101	100	98	97	91	74	1

*based on Kaplan-Meier estimates.
Source: Statistical Reviewer's Result

Sensitivity and Supportive Analyses

As a sensitivity to the primary model, the Cox proportional hazards model, based on the assumption of constant hazard ratio over time, was used to compare treatment groups without adjusting for baseline MADRS. The estimated hazard ratio (vortioxetine/placebo) for each dose ranged from 0.48 to 0.51, a statistically significant risk reduction for each dose group compared to placebo.

As a secondary analysis plan, the Applicant proposed to examine: (i) Time to early discontinuation during the first 28 weeks of the double-blind period; (ii) time to relapse during the first 32 weeks of the double-blind period. The statistical analysis approach was similar to the primary endpoint. The statistical reviewer was able to replicate the Applicant's results.

(i) Time to early discontinuation during the first 28 weeks was statistically significantly longer in the fixed vortioxetine dose groups compared to the placebo group [5-mg: HR = 0.63, p = 0.009; 10-mg: HR = 0.55, p = 0.001; 20-mg: HR = 0.69, p = 0.033] (Tables and Figures, Table 15.2.4.1, page 533 of Clincial Study Report).

(ii) Time from randomization to relapse during the first 32 weeks of the double-blind treatment phase was statistically significantly longer in the fixed vortioxetine dose groups compared to the placebo group [5-mg: HR = 0.48, p = 0.002; 10-mg: HR = 0.46, p < 0.001; 20-mg: HR = 0.48, p = 0.002] (Tables and Figures, Table 15.2.1.2.5, page 487 of Clinical Study Report).

The estimated hazard ratios (HR) indicated a reduced risk of early discontinuation during the first 28 weeks and a reduced risk of relapse during the first 32 weeks for the vortioxetine groups.

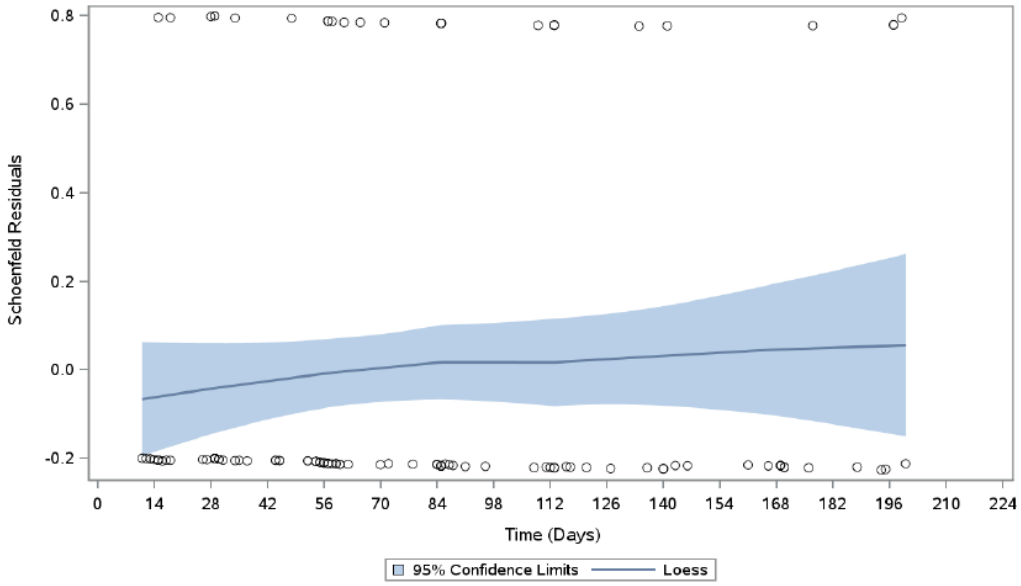
Model Diagnostic Check for Hazard Proportionality Assumption

The validity of the Cox model with a set of covariates depends on whether the assumption of proportional hazards (PH) holds. As a pre-specified sensitivity analysis, the Applicant excluded the MADRS baseline covariate from the Cox model and the hazard ratios did not differ considerably from the primary Cox model; however, this could only assess the impact of the MADRS baseline covariate. To explore whether the hazard ratio can be reasonably assumed to be a constant over time the Agency requested the Applicant to submit model diagnostics (Information Request via email July 7, 2020). The Schoenfeld's residuals plot provided by the Applicant (Figure 5, Plot A) suggests that the residuals (circles in the plot) versus time center around 0. This supports the conclusion that the observed hazard ratio did not change much over time. Plot B (produced by the statistical reviewer) suggested the effect of the baseline covariate did not change much over time. In both plots, the LOESS curve (solid curve in the shaded region) smoothed Schoenfeld's residuals; the graphical assessment approach is not a validation tool but helps to visually inspect patterns if PH assumption holds.

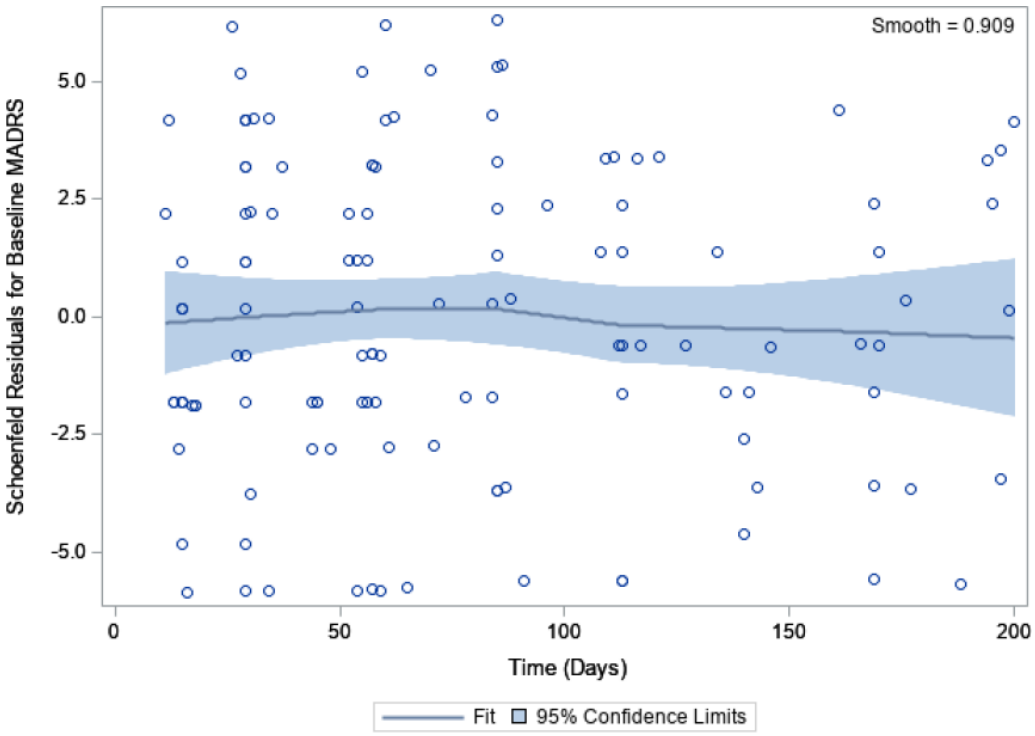
APPEARS THIS WAY
ON ORIGINAL

Figure 5: Diagnostic Plot for Cox Model for Time to Relapse During the First 28 Weeks of Double-Blind Period

Plot A: Plot of Schoenfeld Residuals for Treatment Group



Plot B: Plot of Schoenfeld Residuals for Baseline MADRS Total Score



Source: Plot A is from Applicant's Result (Information Request Response, July 10, 2020). Plot B is from FDA Statistical Reviewer's Results.

Data Quality and Integrity

The Applicant's review of the MADRS data in the database after database lock revealed that two patients randomized to the double-blind period had protocol deviations that should have excluded them from randomization. These patients did not meet the eligibility criterion for randomization that requires MADRS score ≤ 12 at the Week 14 and Week 16 visits. These two patients were removed from the per-protocol analysis set.

Clinical Reviewer's comment: We do not anticipate that the inclusion of these two patients in the double-blind full analysis set would affect the results of the efficacy analysis. We did not perform a separate efficacy analysis on the per-protocol analysis set.

Exploratory Subgroup Analyses: Gender, Race, Age, and Geographic Region

The specified primary efficacy analyses models were used to investigate the treatment effect in the subgroups. Across most of the subgroups, vortioxetine doses showed numerical improvement compared to placebo in reducing risk of relapse to depression (see Table 10 and Figure 6). The statistical reviewer has confirmed Applicant's results.

This section presents the Applicant's exploratory subgroup analysis by sex (male, female), age (≤ 46 years, > 46 years) and race (White, non-White). The Cox proportional hazards model was used to inspect the treatment effect. The age cut-off (46 years) used by the Applicant appears to be a convenient data-driven choice. In this trial only 5.2% of subjects are older than 65 years old, so results of subgroup analysis by age are not discussed in this review.

In general, results from subgroup analyses were consistent between genders and between races, in the sense that all trended in favor of vortioxetine. However, approximately 72% of the patients were female and approximately 75% in this trial were White. The sample size in each tretament group in some of the subgroups might be too small for meaningful comparisons.

Table 10: Subgroup Analysis: Cox Model for Time to Relapse During the First 28 Weeks of Double-Blind Period (FAS)

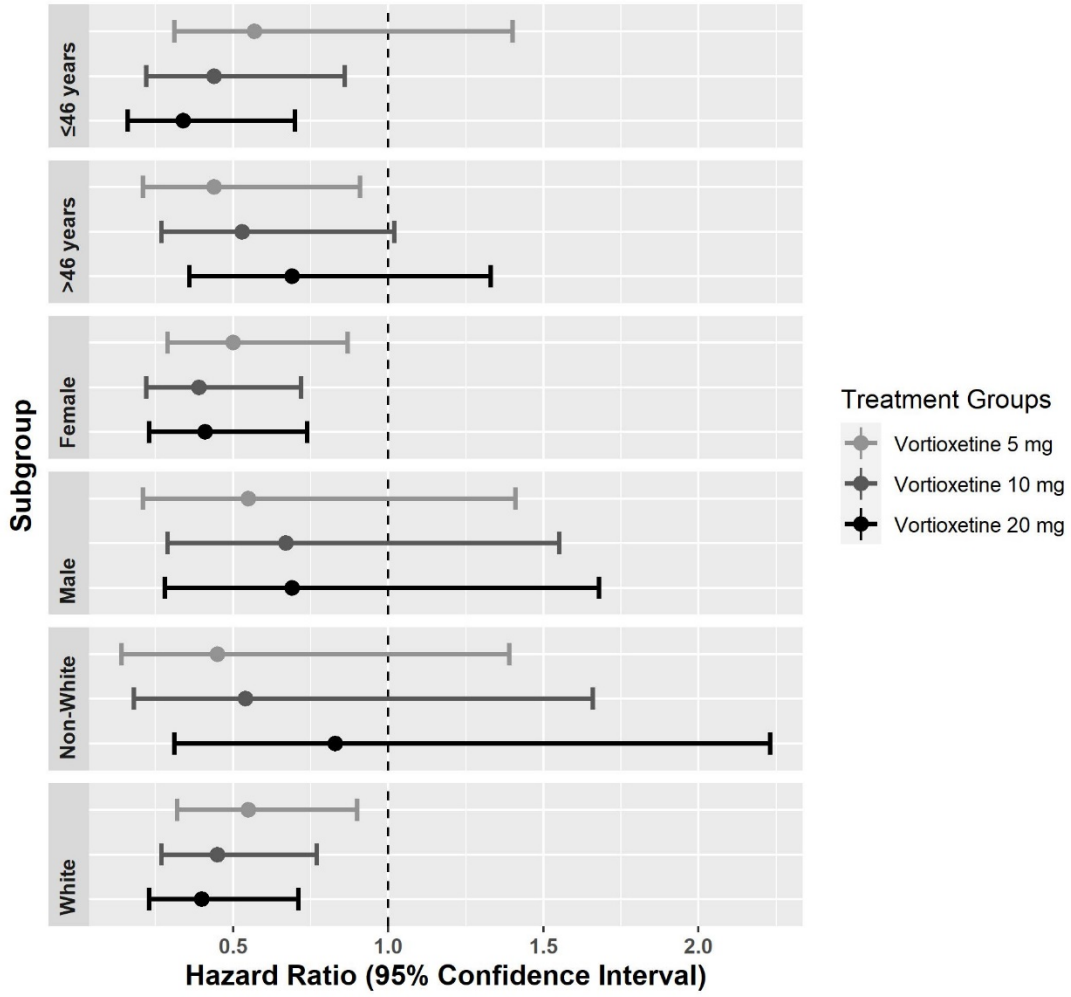
Subgroup		Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144
Sex					
Female	No. of Events/No. of Subjects (%)	38/114 (33.3)	20/103 (19.4)	15/97 (15.5)	16/106 (15.1)
	Vortioxetine/Placebo HR*		0.50	0.39	0.41
	95% CI		(0.29,0.87)	(0.22,0.72)	(0.23,0.74)
Male	No. of Events/No. of Subjects (%)	11/37 (29.7)	7/37 (18.9)	11/48 (22.9)	9/38 (23.7)
	Vortioxetine/Placebo HR*		0.55	0.67	0.69
	95% CI		(0.21,1.41)	(0.29, 1.55)	(0.28, 1.68)

Age					
≤46 years	No. of Events/No. of Subjects (%) Vortioxetine /Placebo HR* 95% CI	26/75 (34.7)	17/72 (23.6) 0.57 (0.31,1.4)	12/66 (18.2) 0.44 (0.22, 0.86)	10/79 (12.7) 0.34 (0.16, 0.70)
>46 years	No. of Events/No. of Subjects (%) Vortioxetine /Placebo HR* 95% CI	23/76 (30.3)	10/68 (14.7) 0.44 (0.21,0.91)	14/79 (17.7) 0.53 (0.27,1.02)	15/65 (23.1) 0.69 (0.36,1.33)
Race					
White	No. of Events/No. of Subjects (%) Vortioxetine /Placebo HR* 95% CI	41/117 (35.0)	22/98 (22.4) 0.55 (0.32,0.90)	21/111 (18.9) 0.45 (0.27,0.77)	17/106 (16.0) 0.40 (0.23,0.71)
Non-White	No. of Events/No. of Subjects (%) Vortioxetine /Placebo HR* 95% CI	8/34 (23.5)	5/41 (12.2) 0.45 (0.14,1.39)	5/34 (14.7) 0.54 (0.18,1.66)	8/38 (21.1) 0.83 (0.31,2.23)

Hazard Ratio and CI are estimated based on a Cox regression model with treatment, double-blind baseline MADRS as covariates.
HR = Hazard Ratio; CI = Confidence Interval
Full Analysis Set = All subjects who are randomized and take at least one dose of the double-blind trial medication.

Source: Table 11.n (cross-reference Tables 15.2.1.2.8 through Tables 15.2.1.2.11) of Applicant's CSR (Page 90-91)

Figure 6: Subgroup Forest Plot: Cox Model for Time to Relapse During the First 28 Weeks of Double-Blind Period (FAS)



Source: FDA Statistical Reviewer's Result

This was a U.S. study and it is infeasible explore treatment differences between US and non-US geographical regions.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The efficacy data provided in this submission are based on results from a single clinical trial.

8.1.4. Integrated Assessment of Effectiveness

Our analysis of data from Study LuAA21004_402 supports the Applicant's conclusion that the time to relapse of depression was longer for vortioxetine 5 mg, 10 mg, and 20 mg than for placebo. The previous maintenance study, Study 11985A, demonstrated superiority of vortioxetine 5 mg and 10 mg compared to placebo in delaying the onset of relapse of depression in a non-US population. Study LuAA21004_402 provides evidence of efficacy of vortioxetine for maintenance treatment of depression in a US-based population and provides long-term efficacy data for the 20 mg dose of vortioxetine, which was not evaluated in the previous maintenance study.

8.2. Review of Safety

8.2.1. Safety Review Approach

The focus of this safety review was to determine whether the results of Study 402 revealed any new safety signals that were not evident from the safety review of the studies that supported the original marketing approval of vortioxetine. In the original registration studies, adverse events occurring with an incidence ≥5% and at least twice the rate of placebo were nausea, constipation, and vomiting. Adverse events occurring with an incidence ≥2% and at least 2% more frequently than in placebo-treated patients were nausea, diarrhea, dry mouth, constipation, vomiting, flatulence, dizziness, abnormal dreams, and pruritis. Hyponatremia (serum sodium lower than 110 mmol/L) was reported in one patient during the registration studies. No other clinically important changes in serum chemistry, hematology, body weight, or vital signs were observed in the registration studies. For the current review, the Safety Evaluation from the Study 402 Clinical Study Report (CSR) was reviewed to identify any safety findings that were not consistent with the known safety profile of vortioxetine.

8.2.2. Review of the Safety Database

Overall Exposure

The safety set for the open-label period included all patients who received at least one dose of open-label study medication. The safety set for the double-blind period included all patients who were randomized and received at least one dose of double-blind study medication. Table 11 below extracts the rows from Table 11.a in the Applicant's CSR that are relevant to the safety analysis.

Table 11: Analysis Sets for Safety Analysis

	Number of Patients (%)				
	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Vortioxetine 20 mg	Total
All enrolled patients	1106				
Open-label safety set	1106				
All randomized patients	151	140	145	144	580
Double-blind safety set	151	140	145	144	580

Source: Adapted from Study LuAA21004_402 Clinical Study Report, Table 11.a, page 71.

Adequacy of the safety database:

Because the submitted application is a supplement and not an initial application for approval, the safety database for this study was not required to meet the ICH exposure guidelines. The size of the safety database appears adequate to support a meaningful safety analysis for this clinical trial. In the overall clinical development program for vortioxetine, 13,248 patients have been exposed to vortioxetine as of the date of submission of the NDA supplement. This exceeds the ICH guidelines recommending exposure of 1,500 patients in a clinical development program for a drug intended for chronic administration.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

As noted above, the Applicant's review of the MADRS data in the database after database lock revealed that two patients randomized to the double-blind period had protocol deviations that should have excluded them from randomization. These patients did not meet the eligibility criterion for randomization that required MADRS score ≤ 12 at the Week 14 and Week 16 visits. These two patients were removed from the per-protocol analysis set.

Clinical Reviewer's comment: These two patients were exposed to drug during both the open-label period and the double-blind period, so their inclusion in the safety set for each period was appropriate.

Categorization of Adverse Events

Adverse events were coded using MedDRA Dictionary Version 22.0.

Routine Clinical Tests

Laboratory samples were taken at the time points stipulated in the Schedule of Assessments. The maximum volume of blood at any single visit was approximately 29 milliliters (mL). The approximate total volume of blood for the study was 186 mL. Laboratory tests were performed at a central laboratory. Electrocardiograms were interpreted by a central reader.

8.2.4. Safety Results

Deaths

There was one death of a patient who completed the open-label period and was randomized to vortioxetine 10 mg/day in the double-blind period. The patient, ID# (b) (6) was a 35-year-old female who completed suicide (b) (6) on (b) (6) (Study Day 333). The patient's baseline assessment and suicide assessments over the course of the study showed no evidence of suicidal thoughts. At the patient's last study visit on (b) (6), the MADRS score was 13/60 with a score of 0 on the question about suicidal ideation and all Columbia Suicide Severity Rating Scale (C-SSRS) scores were 0. Possible contributory psychosocial stressors included loss of a relationship and loss of employment.

Clinical Reviewer's Comment: Patients with major depressive disorder are at increased risk for suicide. This event represents a very low frequency for completed suicide among the 1100 patients in the open-label safety set and the 580 patients in the double-blind safety set. The event does not appear to be related to the study drug. It is more likely related to the patient's underlying illness and recent psychosocial stressors.

Serious Adverse Events

Open-Label Period

Serious adverse events (SAEs) were reported for nine patients in the open-label period. Two patients had SAEs of suicidal ideation. One patient, ID# (b) (6), a 23-year-old female, reported active suicidal ideation 10 days after starting vortioxetine 10 mg daily. The patient had a history of passive suicidal ideation. The patient was withdrawn from the study drug. The investigator assessed this incident as related to the study drug. A second patient, ID# (b) (6) a 22-year-old female, reported passive suicidal ideation 38 days after starting vortioxetine 10 mg daily. The patient denied a suicide plan or intention. The patient was withdrawn from the study drug. The investigator assessed this incident as not related to the study drug. SAEs occurring in one patient each were upper abdominal pain, acute cholecystitis, appendicitis, hand fracture, Type 2 diabetes mellitus, missed abortion, and panic attack.

Clinical Reviewer's Comment: It is very difficult to establish causality between study drug and the onset of suicidal ideation in a study of patients diagnosed with major depressive disorder. Suicidal ideation can be related to the underlying mood disorder.

Double-Blind Period

A total of eight SAEs occurred during the double-blind period. The SAEs, which occurred in one subject each, were cardiac failure, vertigo, post-procedural cellulitis, pyelonephritis, ankle fracture, intraductal proliferative breast lesion, nephrolithiasis, and completed suicide (described above under Deaths). The number of patients with any SAE by treatment group was

one, three, four, and zero for the placebo, 5-mg, 10-mg, and 20-mg treatment groups, respectively.

Clinical Reviewer's Comment: The frequency of each SAE was low. There was no apparent dose relationship for the occurrence of SAEs.

Dropouts and/or Discontinuations Due to Adverse Effects

Open-Label Period

In the open-label period, a total of 66 patients (6%) experienced treatment-emergent adverse events (TEAEs) that led to study discontinuation. The most frequently reported TEAE leading to discontinuation was nausea (34 patients, 3.1%). Other TEAEs that led to discontinuation that were reported for more than one patient were vomiting (eight patients, 0.7%), headache (five patients, 0.5%), dizziness (four patients, 4%), and diarrhea, fatigue, anxiety, suicidal ideation, and pruritus (two patients each, 0.2% each).

Double-Blind Period

In the double-blind period, a total of 14 patients (2.4%) experienced TEAEs that led to study discontinuation, including three patients in the placebo group, three patients in the vortioxetine 5-mg group, one patient in the vortioxetine 10-mg group, and seven patients in the vortioxetine 20-mg group. The most frequently reported TEAEs leading to discontinuation were nausea, occurring in four patients (0.7%), and anxiety, occurring in three patients (0.5%). The number and percentage of patients by treatment group with discontinuations related to nausea were zero, zero, one (0.7%), and three (2.1%) for the placebo, 5-mg, 10-mg, and 20-mg treatment groups, respectively. The number and percentage of patients by treatment group with discontinuations related to anxiety were zero, one (0.7%), zero, and two (1.4%) for the placebo, 5-mg, 10-mg, and 20-mg treatment groups, respectively.

Clinical Reviewer's Comment: Although the number and percentage of discontinuations was higher for the 20-mg treatment group than for the lower-dose groups, the percentage of patients with discontinuations related to TEAEs overall was small.

Significant Adverse Events

For the vortioxetine development program, skin and allergic type reactions, liver injury, and overdose were defined as adverse events of special interest.

Skin and Allergic-Type Reactions

During the open-label period, 61 (5.5%) of patients developed skin and allergic-type reactions. The most frequently reported preferred term (PT) was pruritus in 22 patients (2.0%). Other PTs

reported in more than one patient were hyperhidrosis in nine patients (0.8%), dry skin in six patients (0.5%), night sweats in four patients (0.4%), acne and rash in three patients (0.3%) each, and contact dermatitis, maculo-papular rash, and papular rash in two patients (0.2%) each. Three patients had TEAEs that were assessed as related to study drug and led to study discontinuation: two with pruritus and one with urticaria.

During the double-blind period, 17 patients (2.9%) developed skin and allergic-type reactions: four patients (2.6%) in the placebo group, four patients (2.9%) in the vortioxetine 5-mg group, four patients (2.8%) in the vortioxetine 10-mg group, and five patients (3.5%) in the vortioxetine 20-mg group. The most frequently reported PTs were hyperhidrosis in four subjects (0.7%) and contact dermatitis, eczema, and rash in two patients (0.3%) each. Hyperhidrosis occurred in two patients (1.4%) in the vortioxetine 20-mg group. No other PT was reported in more than one patient in any treatment group. One patient in the placebo group had an event of maculo-papular rash that led to study discontinuation.

Liver Function

During the open-label period, elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase, or bilirubin occurred, with occurrences in three or fewer patients for each test. Patient (b) (6) had a TEAE of increased bilirubin that resulted in study discontinuation.

During the double-blind period, elevated GGT occurred in two patients (1.4%) in the vortioxetine 20-mg treatment group and one patient (0.7%) in the 10-mg treatment group. Elevations in ALT and AST occurred in no more than one patient in any treatment group. There were no SAEs or study discontinuations related to hepatic enzyme elevations during the double-blind period.

Further discussion of lab results is presented in the Laboratory Findings section.

Overdose

There were two patients with TEAEs of overdose, one accidental and one intentional, both during the open-label period. Neither event appears to have been related to a worsening of depressive symptoms.

The overdose by Patient (b) (6) was assessed by the investigator as mild in intensity. The patient did not report any suicidal ideation. The overdose was classified as intentional after it was discovered that the patient was simultaneously enrolled in the study at two sites from Study Day 1 to Study Day 14. The patient was withdrawn from the study on Study Day 14. The dual enrollment was recorded as a protocol deviation.

The overdose by Patient (b) (6) was assessed by the investigator as mild in intensity. It

occurred on Study Day 20, did not result in hospitalization, did not require any treatment, and was considered resolved on the same day. The patient did not report any suicidal ideation. The patient continued in the open-label period after the overdose, but ultimately did not meet the criteria for enrollment into the double-blind period.

Treatment Emergent Adverse Events and Adverse Reactions

Open-Label Period

TEAEs occurring in ≥5% of patients during the open-label period were nausea (26.4%), headache (8.2%), dry mouth (5.2%), and nasopharyngitis (5.1%). Severe TEAEs were reported in 26 patients (2.4%). Severe TEAEs were reported most frequently in the gastrointestinal disorders system organ class (12 patients, 1.1%). Severe nausea was reported in seven patients (0.6%). All other severe TEAEs were reported in one patient each.

Clinical Reviewer's Comment: Current Prescribing Information for vortioxetine indicates that headache may occur in the context of treatment discontinuation or as a symptom of low sodium levels. Headache is not listed as a commonly observed adverse reaction in Section 6. Although the incidence of headache during the open-label period was 8.2%, these events were mostly recorded as mild or moderate in severity, with severe headache reported by one patient. During the open-label period, there was no placebo group with which to compare the incidence of headache. Five patients in the open-label period discontinued the study because of headache. It should be noted that the study protocol started all patients on the 10-mg dose of vortioxetine and did not allow dose adjustment. It is possible that some patients with headache on the 10-mg dose may have experienced both better tolerability and improvement in depressive symptoms with the 5-mg dose.

Double-Blind Period

The most common TEAEs reported during the double-blind period are presented in Table 12. TEAEs occurring in ≥5% of patients in any treatment group during the double-blind period were upper respiratory tract infection, nasopharyngitis, nausea, weight increased, and back pain. The incidence of the most common TEAEs was generally higher among patients who received active treatment compared to placebo. The one exception was back pain, which occurred at a lower rate than placebo in the vortioxetine 10-mg group and at a rate comparable to placebo in the vortioxetine 20-mg group.

Table 12: TEAEs Occurring in **≥5%** of Patients in Any Treatment Group, Double-Blind Period

	Number of Patients (%)			
Preferred Term	Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144
Patients with Any of the Most Frequent TEAEs	16 (10.6)	30 (21.4)	27 (18.6)	32 (22.2)
Upper respiratory tract infection	6 (4.0)	9 (6.4)	9 (6.2)	9 (6.3)
Nasopharyngitis	4 (2.6)	7 (5.0)	7 (4.8)	8 (5.6)
Nausea	2 (1.3)	4 (2.9)	5 (3.4)	13 (9.0)
Weight increased	3 (2.0)	5 (3.6)	7 (4.8)	8 (5.6)
Back pain	2 (1.3)	8 (5.7)	0	2 (1.4)

Source: Adapted from Study 402 Clinical Study Report, Table 12e, page 105.

Severe TEAEs had a slightly higher incidence in the higher-dose vortioxetine groups (3.4% and 3.5% in the vortioxetine groups, respectively) than in the vortioxetine 5-mg (2.1%) and placebo (2.0%) groups. Severe nausea was reported in two patients (1.4%) in the 20-mg vortioxetine group. Severe nephrolithiasis was reported in one patient in each of the three vortioxetine treatment groups. All other severe TEAEs were reported in one patient each.

Incidence of Nephrolithiasis in the Open-Label and Double-Blind Periods

There were six occurrences of nephrolithiasis in vortioxetine-treated patients: three patients receiving vortioxetine 5 mg, two patients receiving vortioxetine 10 mg (one in the open-label period and one in the double-blind period), and one patient receiving vortioxetine 20 mg. The incidence of nephrolithiasis was 0.2% in the open-label period and 0.7% in the double-blind period. The incidence of nephrolithiasis was not dose-related, with the fewest occurrences in patients receiving the 20-mg dose. Nephrolithiasis is a relatively common disease, with an estimated prevalence in the United States population of 10.6% for men and 7.1% for women (Ziemba and Matlaga, 2017). The low occurrence of nephrolithiasis compared to the population prevalence and the absence of a dose relationship suggest that the TEAEs of nephrolithiasis were not related to the study drug.

Laboratory Findings: Serum Chemistry (Excluding Liver Function Tests)

Open-Label Period

Table 13 shows the serum chemistry tests for which ≥2% of patients had at least one potentially clinically significant (PCS) laboratory test result during the open-label period.

Table 13: Chemistry Tests for which ≥ 2% of Patients Had ≥ 1 PCS Result, Excluding Liver Function Tests, Open-Label Period

Laboratory Test	PCS Criteria (SI Units)	Patients (%) N=1106
Creatine kinase	≥2 x ULN	58/1002 (5.8)
HDL cholesterol	<0.9 mmol/L	60/1002 (6.0)
LDL cholesterol	≥5.0 mmol/L	28/995 (2.8)
Potassium	≥5.5 mmol/L	25/996 (2.5)
Triglycerides	≥3.40 mmol/L	55/1002 (5.5)

Source: adapted from Study 402 Clinical Study Report, Table 12.n, page 121.
SI Units=International System of Units

Double-Blind Period

Table 14 shows the serum chemistry tests for which ≥2% of the total randomized population had at least one PCS laboratory test result during the double-blind period.

Table 14: Chemistry Tests for which 2% of Randomized Patients Had 1 PCS Result, Excluding Liver Function Tests, Double-Blind Period

		Number of Patients (%)			
Laboratory Test	PCS Criteria (SI Units)	Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144
Creatine kinase	≥2 x ULN	12/147 (8.2)	11/139 (7.9)	14/144 (9.7)	7/140 (5.0)
HDL cholesterol	<0.9 mmol/L	13/147 (8.8)	7/139 (5.0)	10/144 (6.9)	10/140 (7.1)
LDL cholesterol	≥5.0 mmol/L	1/147 (0.7)	3/139 (2.2)	6/144 (4.2)	4/140 (2.9)
Potassium	≥5.5 mmol/L	4/148 (2.7)	1/139 (0.7)	4/144 (2.8)	4/140 (2.9)
Triglycerides	≥3.4 mmol/L	11/147 (7.5)	4/139 (2.9)	6/144 (4.2)	10/140 (7.1)

Souce: adapted from Study 402 Clinical Study Report, Table 12.o, page 122.
SI Units=International System of Units

Clinical Reviewer's Comment: Although abnormalities in HDL cholesterol and triglycerides showed a dose relationship for patients who received active treatment, the percentage of patients with at least one PCS value was lower in each of the vortioxetine treatment groups than in the placebo group for both laboratory tests. Elevation of potassium levels showed a dose relationship for patients who received active treatment, but the percentage of patients with at least one PCS value was lower than placebo in the vortioxetine 5-mg group and comparable to placebo in the vortioxetine 10-mg and 20-mg groups.

Laboratory Findings: Liver Function Tests (LFTs)

Open-Label Period

Table 15 shows the liver function tests for which any patient had at least one potentially clinically significant (PCS) laboratory test result during the open-label period.

Table 15: Liver Function Tests For Which Any Patient Had **≥1** PCS Result, Open-Label Period

Laboratory Test	PCS Criteria (SI Units)	Patients (%) N=1106
ALT	≥3 x ULN	4/1002 (0.4)
AST	≥3 x ULN	3/1002 (0.3)
Bilirubin	≥34.2 µmol/L	5/1002 (0.5)
GGT	>3 x ULN	23/1002 (2.3)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; ULN = upper limit of normal.
Source: adapted from Study 402 Clinical Study Report, Table 12.p, page 123.

The most frequently reported PCS LFT result was elevated GGT (23 patients, 2.3%). One patient had a TEAE of increased bilirubin that led to study discontinuation. The number and percentage of patients with shifts from normal to high at the end of the open-label period were 30/644 (4.7%) for ALT, 18/644 (2.8%) for AST, 10/644 (1.6%) for bilirubin, and 31/644 (4.8%) for GGT. There were no SAEs related to LFT results during the open-label period.

Double-Blind Period

Table 16 shows the liver function tests for which any patient in the total randomized population had at least one PCS laboratory test result during the double-blind period.

Table 16: Liver Function Tests For Which Any of the Randomized Patients Had **≥1** PCS Result, Double-Blind Period

		Number of Patients (%)			
Laboratory Test	PCS Criteria (SI Units)	Placebo N=151	Vortioxetine 5 mg N=140	Vortioxetine 10 mg N=145	Vortioxetine 20 mg N=144
ALT	≥3 x ULN	2/147 (1.4)	1/139 (0.7)	1/144 (0.7)	0/140
AST	≥3 x ULN	3/147 (2.0)	0.139	0/144	1/140 (0.7)
GGT	≥3 x ULN	2/148 (1.4)	6/139 (4.3)	3/144 (2.1)	4/140 (2.9)

Souce: adapted from Study 402 Clinical Study Report, Table 12.q, page 124.

As in the open-label study, the most frequent PCS elevation in liver function tests was in GGT, which occurred in 2.6% of the total randomized population. PCS elevations in GGT occurred more frequently in each of the vortioxetine treatment groups than in the placebo group, but PCS elevations in ALT and AST occurred more frequently in the placebo group than in any of the vortioxetine treatment groups. There was no clear dose relationship for PCS elevations in ALT, AST, or GGT. There were no reported PCS bilirubin test results for any patient in the double-blind period. There were no SAEs or Hy's Law cases related to LFT values during the double-blind period. No patient discontinued from the study due to a TEAE related to LFT values.

Laboratory Findings: Hematology

Open-Label Period

The most common PCS hematology changes in the open-label period were decrease in hemoglobin (19/998 patients, 1.9%) and increase in eosinophils (22/996 patients, 2.2%). Iron deficiency anemia was reported as a TEAE in one patient (<0.1%), and neutropenia was reported as a TEAE in one patient (<0.1%). Overall, there was no notable pattern of change from baseline in any hematology parameter during the open-label period.

Double-Blind Period

The most common PCS changes during the double-blind period, across treatment groups, were increased eosinophils (17/570, 3.0%) and decreased neutrophils (17/570, 3.0%). There were no dose-related PCS changes in any hematology parameter during the double-blind period. There was no notable pattern of shift from baseline in any hematology parameter during the double-blind period and no notable differences in shifts from baseline among the treatment groups.

Laboratory Findings: Urinalysis

Open-Label Period

Proteinuria was reported as a TEAE in two patients. Chromaturia and glycosuria were reported as TEAEs in one patient each. Overall, there were no clinically notable changes in any urinalysis laboratory parameter during the open-label period. No patient had any PCS urinalysis result during the open-label period.

Double-Blind Period

Glycosuria was reported as a TEAE in one patient in the vortioxetine 5-mg group. Overall, there were no meaningful differences between the vortioxetine and placebo treatment groups during the double-blind period. No patient had any PCS urinalysis result during the double-blind period.

Vital Signs

For both the open-label and double-blind periods, PCS changes in blood pressure and pulse rate were defined as follows:

- Systolic blood pressure:
  - ≤90 mmHg and a decrease of ≥ 20 mmHg
  - ≥180 mmHg and an increase of ≥20 mmHg

- Diastolic blood pressure:
  - ≤50 mmHg and a decrease of ≥15 mmHg
  - ≥105 mmHg and an increase of ≥15 mmHg

- Pulse rate:
  - ≤50 bpm and a decrease of ≥15 bpm
  - ≥120 bpm and an increase of ≥15 bpm

Open-Label Period

During the open-label period, PCS changes in systolic blood pressure, changes in diastolic blood pressure, and changes in pulse rate each occurred in fewer than 1% of patients. Decrease in body weight ≤ -7% occurred in 14/1005 (1.4%) of patients, while increase in body weight ≥ +7% occurred in 32/1005 (3.2%) of patients. Data on changes in body weight during the double-blind period was analyzed to assess whether there might be a drug-related effect on body weight (see below).

Double-Blind Period

During the double-blind period, a dose response was noted for the occurrence of PCS values for decreases in systolic blood pressure, which occurred in none of the patients taking placebo, 1/139 (0.7%) of patients in the vortioxetine 5-mg group, 2/144 (1.4%) of patients in the vortioxetine 10-mg group, and 3/141 (2.1%) of patients in the vortioxetine 20-mg group. However, the percentage of patients with decreases in systolic blood pressure was small in all treatment groups. There was no dose response noted for any other vital sign changes.

Both increases and decreases in weight were observed more frequently in the vortioxetine 10-mg group than in the other treatment groups. However, the percentage of patients with PCS weight loss and the percentage of patients with PCS weight gain were comparable in all treatment groups. Changes in body weight are presented in Table 17.

Table 17: PCS Changes in Body Weight for Patients in the Double-Blind Period

Parameter	PCS Criteria	Number of Patients (%)			
		Placebo N=151	Vortiox 5 mg N=140	Vortiox 10 mg N=145	Vortiox 20 mg N=144
Weight	Change ≤ -7%	8/148 (5.4%)	4/139 (2.9%)	12/144 (8.3%)	9/141 (6.4%)
	Change ≥ +7%	6/148 (4.1%)	4/139 (2.9%)	11/144 (7.6%)	10/141 (7.1%)

Souce: adapted from Study 402 Clinical Study Report, Table 12.v, page 129.

Clinical Reviewer's Comment: No clinically meaningful pattern was noted for changes in systolic blood pressure, diastolic blood pressure, or puse rate. For each treatment group, the percentage of patients who gained weight was comparable to the percentage of patients who lost weight, suggesting that the study drug had no clinically meaningful effect on body weight during the open-label period.

Electrocardiograms (ECGs) and QTc

For both the open-label and double-blind periods, PCS changes in 12-lead ECG parameters were defined as follows:

- Heart rate:
  - ≤ 50 beats per minute (bpm) and change ≤ -15 bpm
  - ≥ 120 bpm and change ≥ 15 bpm
- PR interval:
  - ≤ 120 msec
  - ≥ 250 msec
- QRS duration:
  - < 40 msec
  - > 150 msec
- QT interval:
  - < 280 msec
  - > 500 msec
- QTcB interval:
  - < 340 msec or change < -60 msec
  - > 500 msec or change > 60 msec

- QTcF interval:
  - < 340 msec or change < -60 msec
  - > 500 msec or change > 60 msec

- RR interval:
  - < 500 msec and change ≤ -200 msec
  - > 1200 msec and change ≥ 200 msec

Open-Label Period

The most common PCS ECG result was PR interval abnormality, which was reported for 1.5% of patients. All other ECG abnormalities were reported for ≤0.4% of patients. There were no TEAEs related to ECG abnormalities. Overall, there was no clinically meaningful pattern of shifts from baseline in ECGs during the open-label period.

Double-Blind Period

The most common PCS ECG results among all patients in the double-blind period were PR interval abnormality (11 patients, 2.1%) and RR interval abnormality (six patients, 1.1%). All other ECG abnormalities were reported for ≤3 patients. There was no clear dose relationship for any ECG abnormality. Bradycardia was reported as a TEAE in one patient in the vortioxetine 20-mg group. Left bundle branch block was reported as a TEAE in one patient in the vortioxetine 20-mg group. Right bundle branch block was reported as a TEAE in one patient in the vortioxetine 10-mg group. Overall, there was no clinically meaningful pattern of shifts from baseline in ECGs and no clinically meaningful differences across treatment groups in shifts from baseline.

Immunogenicity

Immunogenicity was not assessed during this study.

8.2.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses related to safety were performed.

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were not conducted.

8.2.8. Specific Safety Studies/Clinical Trials

The application did not include any studies specifically designed for evaluation of safety.

8.2.9. Additional Safety Explorations

No additional safety explorations were conducted.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

On November 25, 2019, the Applicant submitted a Periodic Safety Update Report to NDA 204447. In the report, the Applicant documented their evaluation of a potential safety signal for hostility/aggression. The evaluation noted several post-marketing cases with a positive de-challenge and re-challenge for aggressive behavior, as well as research literature suggesting higher patient self-reports of agitation, aggression, and increased anger for vortioxetine compared to other SSRIs. The Applicant felt that a causal relationship between vortioxetine and hostility/aggression could not be definitively confirmed, but that the post-marketing cases suggested the possibility of a causal relationship. The Applicant proposed to add the following text to the European Union Summary of Product Characteristics (SmPC):

Aggression/Agitation

(b) (4) *of aggression, agitation, anger and irritability* (b) (4)

(b) (4) *Patient's condition and disease status should be closely monitored.*

The Applicant did not propose any changes to the United States product label.

The Agency's Division of Pharmacovigilance (DPV) conducted a review to evaluate the potential safety signal. DPV's review suggested a possible relationship between vortioxetine and aggression. Review of the labels for similar SSRIs showed that other labels include a warning for aggression, but the vortioxetine label does not.

As part of the review of the draft labeling submitted with the supplemental NDA, the Agency recommends the addition of text to the Postmarketing Experience section of the label to document that incidents of aggression and agitation have been reported in the postmarketing setting. Specific changes to the label will be described in Section 11, Labeling Recommendations.

Expectations on Safety in the Postmarket Setting

Continued monitoring of the possible safety signal for aggression and agitation will be

accomplished through routine pharmacovigilance.

8.2.11. Integrated Assessment of Safety

Review of the safety data from Study LuAA21004_402 did not reveal any new safety signal for vortioxetine. The most commonly observed adverse events in the study mirrored adverse events that are already listed in labeling. No new or clinically signifcant findings on laboratory assessments, vital signs, or electrocardiograms were noted.

8.3. Statistical Issues

None.

8.4. Conclusions and Recommendations

Our review of the efficacy data from Study LuAA21004_402 indicates that vortioxetine 5 mg, vortioxetine 10 mg, and vortioxetine 20 mg all were superior to placebo in prolonging the time to relapse of major depression in patients who demonstrated response to vortioxetine 10 mg during the open-label period of the study. Our review of the safety data from the study did not reveal any new safety signal for vortioxetine. The safety profile for vortioxetine remains favorable. The efficacy and safety data support the approval of this NDA supplemental application.

9 Advisory Committee Meeting and Other External Consultations

No Advistory Committee meeting was convened in the course of the review of this application.
No other external consultations were requested by the Division.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

No pediatric data was submitted with this supplement.

APPEARS THIS WAY
ON ORIGINAL

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

[1] Changes to Section 2, Dosage and Administration

Section 2.2, Maintenance/Continuation/Extended Treatment, will be removed for consistency with more recent antidepressant labels. Results of the second maintenance study will be added to Section 14, Clinical Studies.

[2] Changes to Section 6, Adverse Reactions

The exploration of a possible safety signal for aggression and agitation was discussed in Chapter 3, Regulatory History. Section 6.2, Postmarketing Experience, will be updated to include the following adverse reactions that have been identified during postapproval use of vortioxetine:

Psychiatric disorders – aggression, agitation, anger, hostility, irritability

[3] Changes to Section 14, Clinical Studies

Section 14 will be updated to include a discussion of the design and results from Study LuAA21004-402. A Kaplan-Meier curve showing differences in time to relapse between the three vortioxetine treatment groups and the placebo group will be included.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

The completion of Study LuAA21004-402 fulfills Postmarketing Commitment 2084-6, described above in Chapter 3, Regulatory History. No new postmarketing requirements or commitments will be issued in association with this supplement.

APPEARS THIS WAY
ON ORIGINAL

14 Division Director (Signatory Authority) Comments

I have personally reviewed and edited this document and concur with the findings presented herein.

APPEARS THIS WAY ON ORIGINAL

15 Appendices

15.1. References

1. Ziemba, J and BR Matlaga, 2017, Epidemiology and economics of nephrolithiasis, Investigative and Clinical Urology 58(5): 299-306.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): LuAA21004-402

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80 principal investigators; 539 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in S Sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ n/a	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ n/a	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ n/a	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted with this supplement.

15.1. OCP Appendices (Technical documents supporting OCP recommendations)

No new clinical pharmacology data was submitted with this supplement.

15.2. Additional Clinical Outcome Assessment Analyses

No additional clinical outcome assessment analyses were conducted.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
11/13/2020 03:55:42 PM

TIFFANY R FARCHIONE
11/13/2020 03:57:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s020

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

RE: NDA 20447 S-020 Multidisciplinary Review

The Clinical review is complete and has been added to the multidisciplinary review and evaluation document. Our review is based on the information currently in the administrative record. If we must review information that is subsequently added to the administrative record, we will update our part of the multidisciplinary review and evaluation document accordingly.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID H MILLIS
11/13/2020 02:26:31 PM

MARTINE M SOLAGES
11/13/2020 02:29:33 PM

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/BLA #:	204447/S-020
Drug Name:	Trintellix (vortioxetine)
Indication:	Treatment of Major Depressive Disorder (MDD)
Applicant:	Takeda
Date(s):	Submission Date: 1/14/2020 PDUFA Date: 11/14/2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Semhar Ogbagaber, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., HM James Hung, Ph.D.
Medical Division:	Division of Psychiatry
Clinical Team:	David Millis, M.D.
Project Manager:	Keith Kiedrow, Pharm. D.

The statistical review was completed prior to PDUFA Goal Date and it has been incorporated into the uni-review.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SEMHAR B OGBAGABER
11/13/2020 03:00:58 PM

PEILING YANG
11/13/2020 03:04:54 PM

HSIEN MING J HUNG
11/13/2020 03:42:10 PM

EXCLUSIVITY SUMMARY

NDA # 204447 SUPPL # S-020 HFD # 130

Trade Name Trintellix

Generic Name vortioxetine

Applicant Name Takeda

Approval Date, If Known 11/13/2020

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

SE8

b) 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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) 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# 204447

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:

Investigation 1: Study Lu AA21004-402 – "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder"

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"):

Study Lu AA21004-402

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 # 76307	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	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: Keith Kiedrow
Title: Chief, Project Management Staff
Date: 11/30/2020

Name of Division Director signing form: Tiffany Farchione, MD
Title: Director, Division of Psychiatry

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
11/30/2020 06:05:28 PM

TIFFANY R FARCHIONE
11/30/2020 06:43:44 PM

NDA 204447 S-020

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Takeda Pharmaceuticals, USA, Inc.
Attention: Kinnari Shaw
Senior Manager, Global Regulatory Affairs, Marketed Products
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Shaw:

Please refer to your supplemental new drug application (sNDA) dated and received January 14, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trintellix (vortioxetine) Tablets.

This Prior Approval supplemental new drug application provides for updates to labeling to reflect efficacy and safety results from study Lu AA21004-402: A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder.

APPROVAL & LABELING

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

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

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

Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

Your January 20, 2020, submission contains the final report for the following postmarketing commitment listed in the September 30, 2013 approval letter.

2084-6 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vortioxetine in the treatment of adults with major depressive disorder in the US. This trial must include a placebo group and several fixed doses and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of vortioxetine. Because the short-term trials appear to show that higher doses have demonstrated better treatment effects in the US population compared to the rest of the

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

world, it is important to establish the dose-response for maintenance in the US. This trial should randomize patients on stable doses of vortioxetine to several different doses (e.g., 5 mg, 10 mg, and 20 mg) of vortioxetine (and to placebo) during the maintenance phase.

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

We remind you that there are postmarketing requirements listed in the September 30, 2013, approval letter that are still open.

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, email Jasmeet (Mona) Kalsi, Senior Regulatory Project Manager, at Jasmeet.Kalsi@FDA.HHS.GOV.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
11/13/2020 03:58:55 PM

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:

CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Kim Updegraff, ADL, Division of Psychiatry
Office: 301-796-2201
Kimberly.updegraff@fda.hhs.gov

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
10/15/2020		204447 S-020	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Trintellix (vortioxetine) Tablets	Standard	Indication – treatment of major depressive disorder (MDD)	10/27/20 PDUFA date: November 14, 2020

NAME OF FIRM:

Takeda

PDUFA Date: 11-14-2020

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (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

For OSE USE ONLY
☐ REMS

EDR link to submission: \\Cdsesub1\evsprod\NDA204447\0249

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.
OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Takeda has submitted a new sNDA to include data from completed study in response to PMC 2084-6 – a maintenance study that was requested in the 9/30/2013 AP action. Study Lu AA21004-402 – "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults with Major Depressive Disorder". This is a labeling supplement with clinical data (SE8).

NOTE: DP previously consulted OPDP for this supplement (PI and MG) on February 7, 2020. We request that this consult request replace the former. For purposes of S-020, DP is requesting a targeted review of the affected sections under S-020 which include sections 7, 8.6, 12.3, and 14. DP has another pending supplement for Trintellix, S-021, with a PDUFA of 1/22/2021 (OPDP consulted on August 3, 2020). We will incorporate class revisions and additional changes into supplement 021 and request OPDP (and DMPP) input on both the PI and MG during that review cycle.**

Labeling Meeting (final): October 28, 2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIMBERLY S UPDEGRAFF
10/15/2020 10:48:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**	FROM: (Name/Title, Office/Division/Phone number of requestor) Keith Kiedrow, Regulatory Project Manager Division of Psychiatry (DP) 301-796-1924

REQUEST DATE: 10/5/2020	NDA/BLA NO.: NDA 204447 S-020	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)

NAME OF DRUG: Trintellix (vortioxetine) tablets	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: SE8 labeling supplement with clinical data	DESIRED COMPLETION DATE 2 weeks from receiving substantially complete labeling from DP

SPONSOR: Takeda	PDUFA Date: 11/14/2020

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
\\Cdsesub1\evsprod\NDA204447\0249

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:
Takeda has submitted a new sNDA to include data from completed study in response to PMC 2084-6 – a maintenance study that was requested in the 9/30/2013 AP action. Study Lu AA21004-402 – "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder". This is a labeling supplement with clinical data (SE8).

DPP requests DMPP to review the proposed labeling for this application. Please email Keith Kiedrow at Keith.Kiedrow@fda.hhs.gov the names of the DMPP staff who should receive meeting invitations/correspondences.

Remaining scheduled meetings -
Wrap-Up Meeting: October 14, 2020
Labeling Meetings: October 28, 2020

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

Version: 06/06/2016

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
10/05/2020 04:25:17 PM

Memo To File

Date	7/27/2020
From	Christian Shenouda, MD Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	David Millis, M.D., Division Psychiatry (DP) Mike Davis, M.D., Team Leader, DP Keith Kiedrow, RPM, DP
NDA	NDA 204447 S020
Applicant	Takeda Pharmaceuticals, Inc.
Drug	Vortioxetine (Trintellix)
NME	No
Proposed Indication	(b) (4)
Consultation Request Date	2/25/2020
Summary Goal Date	11/7/2020
PDUFA Date	11/14/2020

A consult to conduct inspections was received from the Division of Psychiatry on 2/25/2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections: Drs. Ethan Kass (Site #7005) and James Knutson (Site #7071).

An inspection assignment was issued on 3/24/2020, and the request to conduct GCP inspections was coordinated via the Office of Regulatory Affairs (ORA). However, the COVID-19 global pandemic has significantly limited our ability to conduct on-site Good Clinical Practice (GCP) inspections. This application was designated as non-mission critical based on OND and ORA criteria, and after two extensions were granted to complete the inspections, it was determined that the sNDA review could continue without the requested inspections. DP agreed to cancel the inspections on 7/22/2020. As a result, at this time, OSI will be unable to provide a review to determine if Protocol LuAA21004_402 was conducted adequately and whether the study data are reliable in support of the proposed indication.

{See appended electronic signature page}

Christian Shenouda
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. NDA 204447 S020
DP Review Division /Division Director/Tiffany Farchione
DP Review Division /Medical Team Leader/ Michael Davis
DP Review Division /Project Manager/ Keith Kiedrow
DP Review Division/MO/ David Millis
OSI/Office Director/ Ni Khin
OSI/DCCE/ Division Director/ David Burrow
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/ Phillip Kronstein
OSI/DCCE/GCP Reviewer/ Christian Shenouda
OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTIAN N SHENOUDA
07/27/2020 02:47:14 PM

PHILLIP D KRONSTEIN
07/27/2020 02:49:40 PM

KASSA AYALEW
07/28/2020 11:53:32 AM

MEMORANDUM

OSI/DCCE CONSULT: CLINICAL INSPECTIONS REQUEST

CDER's Clinical Investigator Site Selection Tool Generated

Date: 2/25/2020

To: Ni Khin, M.D., Division Director, DCCE
Kassa Ayalew, M.D., Branch Chief, GCPAB
Phillip Kronstein, M.D., Team Leader, GCPAB

Christian Shenouda, M.D.
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance/CDER

Through: David Millis, M.D., Division Psychiatry (DP)
Mike Davis, M.D., Team Leader, DP

From: Keith Kiedrow, DP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA 204447 S020
IND#:76307
Applicant: Takeda Pharmaceuticals, USA, Inc..
Phone:
Email:
Regulatory Point of Contact: (b) (4), Global Regulatory Affairs-Neuroscience
Regulatory Point of Contact Phone: (b) (4)
Regulatory Point of Contact Email: (b) (4)@takeda.com

Drug Proprietary Name: Trintellix
Generic Drug Name: Vortioxetine
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
FDA.GOV

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): PMC 2084-6 Study for Major Depressive Disorder

Submission Date: 14Jan2020
PDUFA: 11/14/2020
Action Goal Date: 11/13/20
Inspection Summary Goal Date: 9/23/20

II. Protocol/Site Identification

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects (SAFPOP)	Study Title
Kass, Ethan CNS Clinical Research Group, 5491 N. University Drive, Suite 201 Coral Springs, FL 33067 USA United States phone:(954)796-8222 fax:(954)796-5016 email (b) (6)	7005	2. Randomized Period LuAA21004_402	35	A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating The Efficacy And Safety Of Vortioxetine (5, 10 And 20 Mg) In Adults With Major Depressive Disorder
Knutson, James Eastside Therapeutic Resource, 2918 Colby Avenue, Suite 101 Everett, WA 98201 USA United States phone:(425)443-9551 fax:(425)827-7288 email:drjames.knutson@ccrtrial.com	7071	2. Randomized Period LuAA21004_402	34	A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating The Efficacy And Safety Of Vortioxetine (5, 10 And 20 Mg) In Adults With Major Depressive Disorder

III. Site Selection/Rationale

Site Information

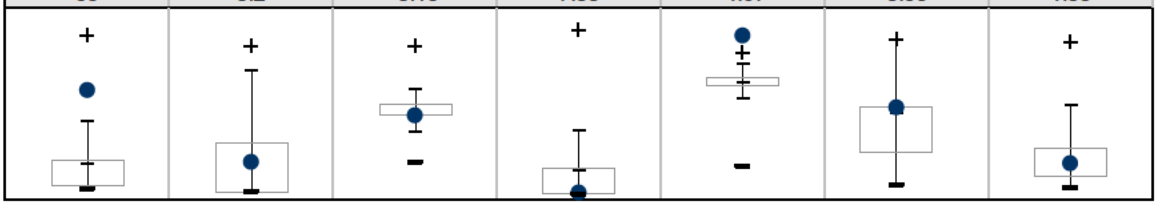
STUDY:	2. Randomized Period LuAA21004_402	**SITEID:**	7005

NAME	Kass, Ethan
LOCATION	CNS Clinical Research Group, 5491 N. University Drive, Suite 201 Coral Springs, FL, USA 33067
PHONE/FAX	(954)796-8222 / (954)796-5016
EMAIL	(b) (6)

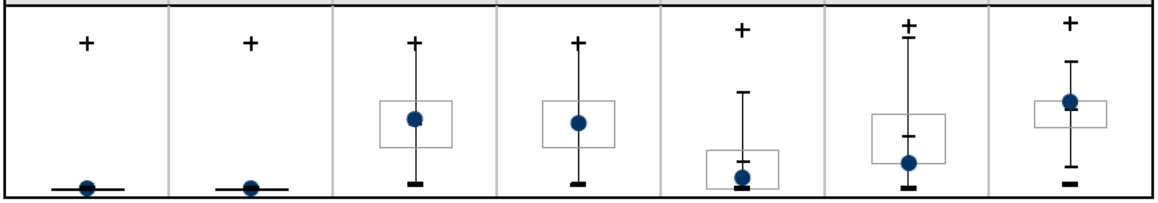
RANK	6	**FINLDISC**	<25k	**COMPLAINT**	No
SITE RISK	10.8	**OAI**	No	**TSLI**	3

Site Values vs. Overall Study Results

	SAFPOP	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN	NSAE
Max	54	1.0	1.0	13.00	4.00	0.70	6.00
Study Rate	9	0.22	-0.14	1.87	-0.84	0.36	1
Min	1	0.0	-1.0	0.00	-15.00	0.03	0.00
Site	35	0.2	-0.18	7.00	-4.67	0.38	1.00



	SAE	DEATH	DISCSTUD	DISCTRT	PROTVIOL	INDS	EXPERIENCE
Max	0.50	0.50	1.00	1.00	0.82	13.22	38.00
Study Rate	0.02	0.00	0.42	0.42	0.14	4.40	18
Min	0.00	0.00	0.00	0.00	0.00	0.20	1
Site	0.00	0.00	0.46	0.43	0.06	2.25	20



Site Memo

Site 7005 is noted to be a high enroller with a high number of discontinuations and adverse events. The study also showed a high weighted efficacy.

Site Information

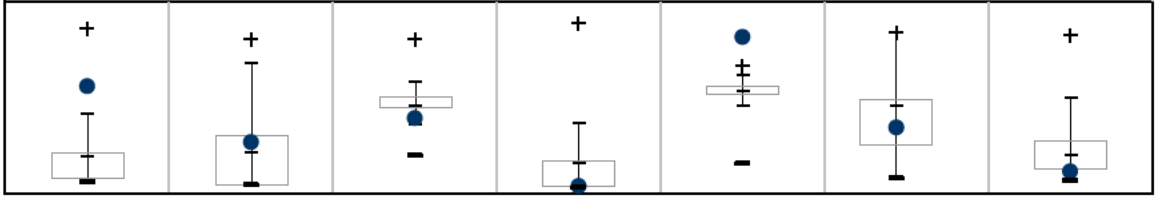
STUDY:	2. Randomized Period LuAA21004_402	**SITEID:**	7071

NAME	Knutson, James
LOCATION	Eastside Therapeutic Resource, 2918 Colby Avenue, Suite 101 Everett, WA, USA 98201
PHONE/FAX	(425)443-9551 / (425)827-7288
EMAIL	drjames.knutson@ccrtrial.com

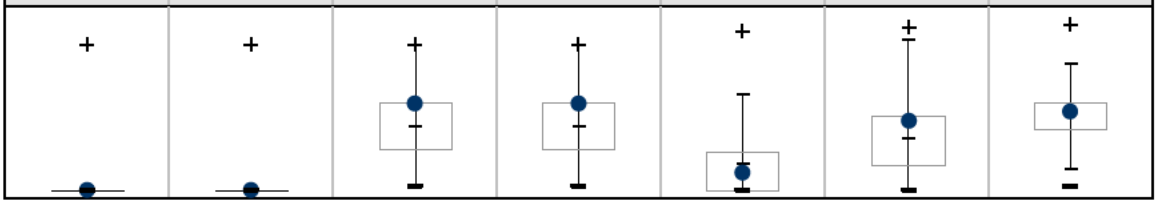
RANK	1	**FINLDISC**	<25k	**COMPLAINT**	Yes
SITE RISK	16.3	**OAI**	No	**TSLI**	3

Site Values vs. Overall Study Results

	SAFPOP	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN	NSAE
Max	54	1.0	1.0	13.00	4.00	0.70	6.00
Study Rate	9	0.22	-0.14	1.87	-0.84	0.36	1
Min	1	0.0	-1.0	0.00	-15.00	0.03	0.00
Site	34	0.29	-0.36	10.00	-8.89	0.27	0.38



	SAE	DEATH	DISCSTUD	DISCTRT	PROTVIOL	INDS	EXPERIENCE
Max	0.50	0.50	1.00	1.00	0.82	13.22	38.00
Study Rate	0.02	0.00	0.42	0.42	0.14	4.40	18
Min	0.00	0.00	0.00	0.00	0.00	0.20	1
Site	0.00	0.00	0.59	0.59	0.09	5.78	18



Site Memo

Site 7071 is noted to be a high enroller with a high number of discontinuations. The study also showed a high weighted efficacy.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ✓ 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:

Reasons for inspections (please check all that apply):

- _ 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 OSI inspections to verify the quality of conduct of the study).

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 Keith Kiedrow, RPM at 301-796-1924.

Concurrence: (as needed)

See electronic signature Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
02/28/2020 01:18:53 PM

MICHAEL C DAVIS
02/28/2020 02:46:09 PM

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:

CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Keith Kiedrow, RPM, Division of Psychiatry
Office: 301-796-1924
Keith.Kiedrow@fda.hhs.gov

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
February 7, 2020		204447 S-020	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Trintellix (vortioxetine) Tablets	Standard	Indication – treatment of major depressive disorder (MDD)	10/7/20 PDUFA date: November 14, 2020

NAME OF FIRM:

Takeda

PDUFA Date: 11-14-2020

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (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

For OSE USE ONLY
☐ REMS

EDR link to submission: \\Cdsesub1\evsprod\NDA204447\0249

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.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Takeda has submitted a new sNDA to include data from completed study in response to PMC 2084-6 – a maintenance study that was requested in the 9/30/2013 AP action. Study Lu AA21004-402 – "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder". This is a labeling supplement with clinical data (SE8). DP would appreciate OPDP assistance in the review of this supplement.

Mid-Cycle Meeting: Mid-June 2020
Labeling Meetings: TBD
Wrap-Up Meeting: End of September, 2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
02/07/2020 09:05:32 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Keith Kiedrow, RPM, Division of Psychiatry Office: 301-796-1924	
DATE: February 6, 2020	IND NO.	NDA NO. 204447 S-020	TYPE OF DOCUMENT Efficacy Supplement (SE-8)	DATE OF DOCUMENT January 14, 2020
NAME OF DRUG Trintellix (vortioxetine) Tablets	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Indication – treatment of major depressive disorder (MDD)	DESIRED COMPLETION DATE 10/7/20 PDUFA date: November 14, 2020

NAME OF FIRM: Forest Laboratories, LLC

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
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☒ 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:

Takeda has submitted a new sNDA to include data from completed study in response to PMC 2084-6 – a maintenance study that was requested in the 9/30/2013 AP action. Study Lu AA21004-402 – "A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder". This is a labeling supplement with clinical data (SE8). DP would appreciate OSE assistance in the review of this supplement.

Clinical reviewer: David Millis
Clinical TL: Mike Davis

Please let me know if there are any questions related to the supplement. Thanks, Keith – Keith.Kiedrow@FDA.HHS.GOV

Materials:

SharePoint	204447 S-020 Sharepoint Link
EDR	\\Cdsesub1\evsprod\NDA204447\0249

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
02/06/2020 04:46:48 PM

NDA 204447 S-020

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Takeda Pharmaceuticals, USA, Inc.
Attention: (b) (4)
Global Regulatory Affairs - Neuroscience
40 Landsdowne St.
Cambridge, MA 02139

Dear Dr. (b) (4):[1]

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 204447

SUPPLEMENT NUMBER: S-020

PRODUCT NAME: Trintellix (vortioxetine) Tablets

DATE OF SUBMISSION: January 14, 2020

DATE OF RECEIPT: January 14, 2020

This supplemental application proposes to update product labeling with data from the completed Post Marketing Commitment (PMC) 2084-6, Study Lu AA21004-402: A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults with Major Depressive Disorder.

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 March 14, 2020, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be November 14, 2020.

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 FDA.gov.[2] Failure to submit the content of labeling in SPL format may result in a refusal-

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

to-file action. 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).

If you have questions, call me at 301-796-1924.

Sincerely,

{See appended electronic signature page}

CAPT Keith Kiedrow, Pharm.D., M.S., RAC
Team Leader, Regulatory Project Management
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEITH J KIEDROW
02/06/2020 04:23:48 PM