# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 204447Orig1s017

| | |
|---|---|
| ***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

## 204447Orig1s017

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204447/S-017

**SUPPLEMENT APPROVAL**

Takeda Pharmaceuticals, USA, Inc.
Attention: Joanna Sambor, MS
Senior Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your Supplemental New Drug Application (sNDA) dated December 21, 2017, received December 21, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trintellix (vortioxetine) 5mg, 10mg, and 20mg tablets.

This Prior Approval supplemental new drug application provides for an update to the Prescribing Information for Trintellix (vortioxetine) and includes clinically relevant information on treatment-emergent sexual dysfunction.

## APPROVAL & LABELING

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

## WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that 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, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

## PROMOTIONAL MATERIALS

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

**REPORTING REQUIREMENTS**

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

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE(S):
Content of Labeling
Prescribing Information

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

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/s/

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MITCHELL V Mathis
10/19/2018

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# 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----------**
Indications and Usage (1) 10/2018

**----------INDICATIONS AND USAGE----------**
TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults (1, 14).

**----------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 (2.3).
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers (2.6).

**----------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 a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is coadministered (2.6, 7.3).
- Strong CYP Inducers: Consider increasing TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose (2.7, 7.3).

**----------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: 10/2018**

**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

### 1.1 Major Depressive Disorder

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults *[see Clinical Studies (14)]*.

## 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 *[see Clinical Studies (14)]*.

### 2.2 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression should be followed by several months or longer of sustained pharmacologic therapy. A maintenance study of TRINTELLIX demonstrated that TRINTELLIX decreased the risk of recurrence of depressive episodes compared to placebo.

### 2.3 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 Adverse Reactions (6)]*.

### 2.4 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)]*.

### 2.5 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)]*.

### 2.6 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 (7.3)]*.

### 2.7 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 (7.3)]*.

## 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 components of the formulation. Angioedema has been reported in patients treated with TRINTELLIX.

- 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 (2.4), 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 Dosage and Administration (2.5), 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 (2.4)]*.

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 (7.2)]*.

### 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

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 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in premarketing 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 and 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. 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.

*Metabolic disorders* — weight gain

*Nervous system disorders* — seizure

*Skin and subcutaneous tissue disorders* — rash, generalized rash

*Gastrointestinal System* — acute pancreatitis

## 7 DRUG INTERACTIONS

### 7.1 CNS Active Agents

**Monoamine Oxidase Inhibitors**
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2)]*.

**Serotonergic Drugs**
Based on the mechanism of action of TRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when TRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if TRINTELLIX is coadministered with other serotonergic drugs. Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions (5.2)]*.

**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. 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). Details on the potential pharmacokinetic interactions between TRINTELLIX and bupropion can be found in Section 7.3.

### 7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

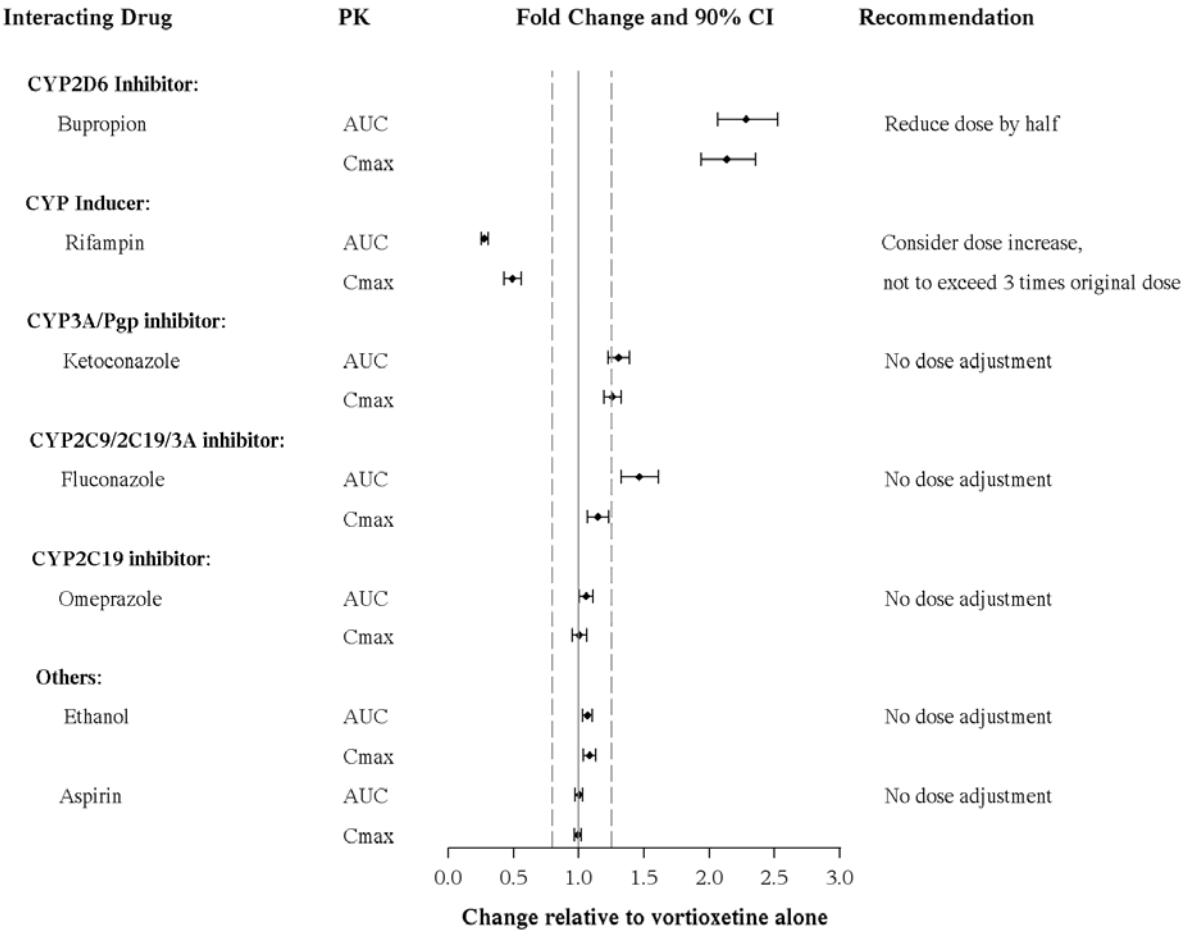
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

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 *[see Drug Interactions (7.4)]*. 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 Drug Interactions (7.4)]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions (5.3)]*.

### 7.3 Potential for Other Drugs to Affect TRINTELLIX

Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose *[see Dosage and Administration (2.5, 2.6)] (Figure 1)*.

**Figure 1. Impact of Other Drugs on Vortioxetine PK**




## 7.4 Potential for TRINTELLIX to Affect Other Drugs

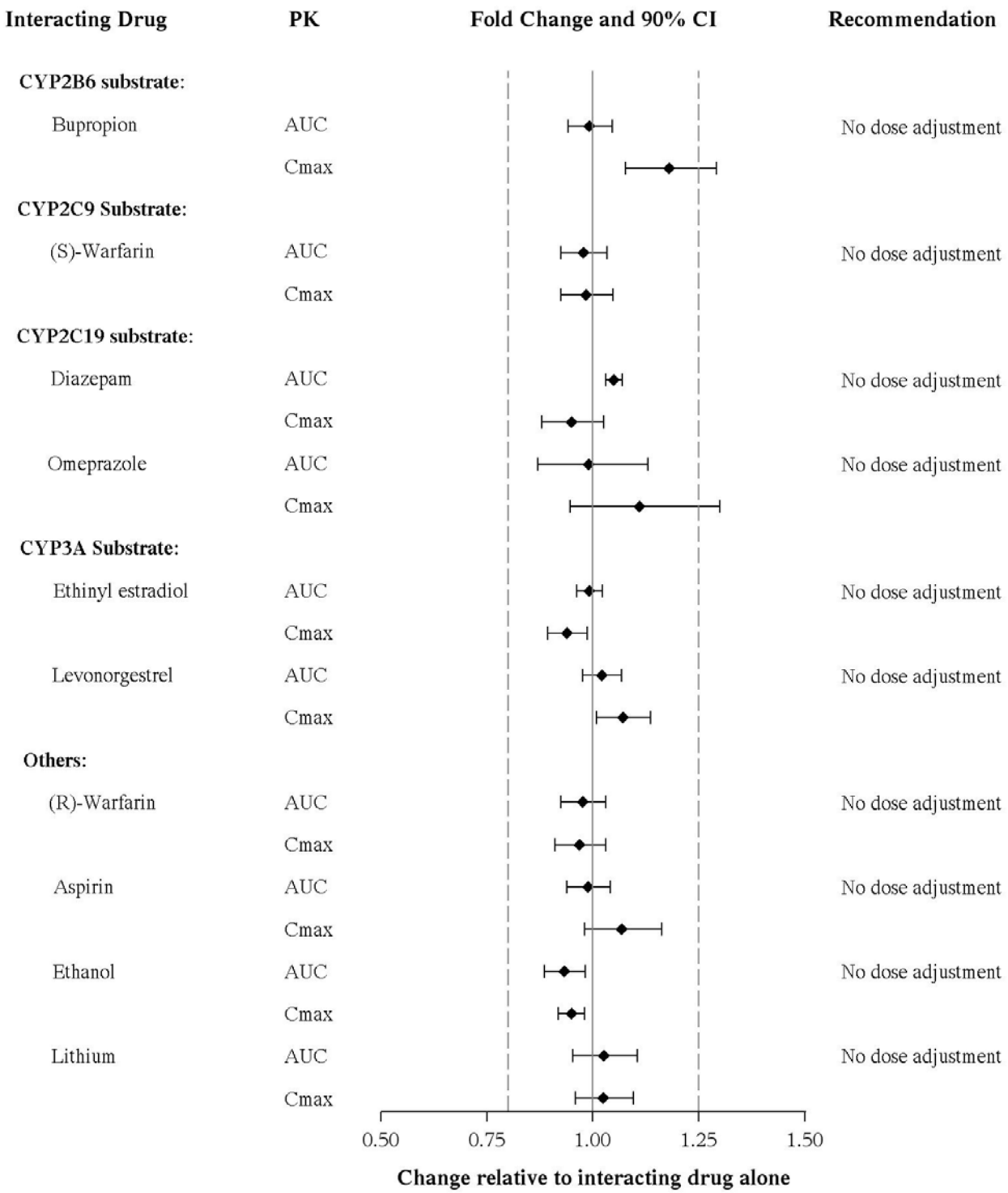
No dose adjustment for the comedications is needed when TRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine, caffeine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinide), CYP2C9 (e.g., S-warfarin, tolbutamide), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine, dextromethorphan), CYP3A4/5 (e.g., budesonide, midazolam), P-gp (e.g., digoxin), BCRP (e.g., methotrexate), OATP1B1/3 (e.g., rosuvastatin) and OCT2 (e.g., metformin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

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 *(Figure 2)*.

Because vortioxetine is highly bound to plasma protein, coadministration of TRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, 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 (7.2)]*.

**Figure 2. Impact of Vortioxetine on PK of Other Drugs**



# 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 3)*. 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.

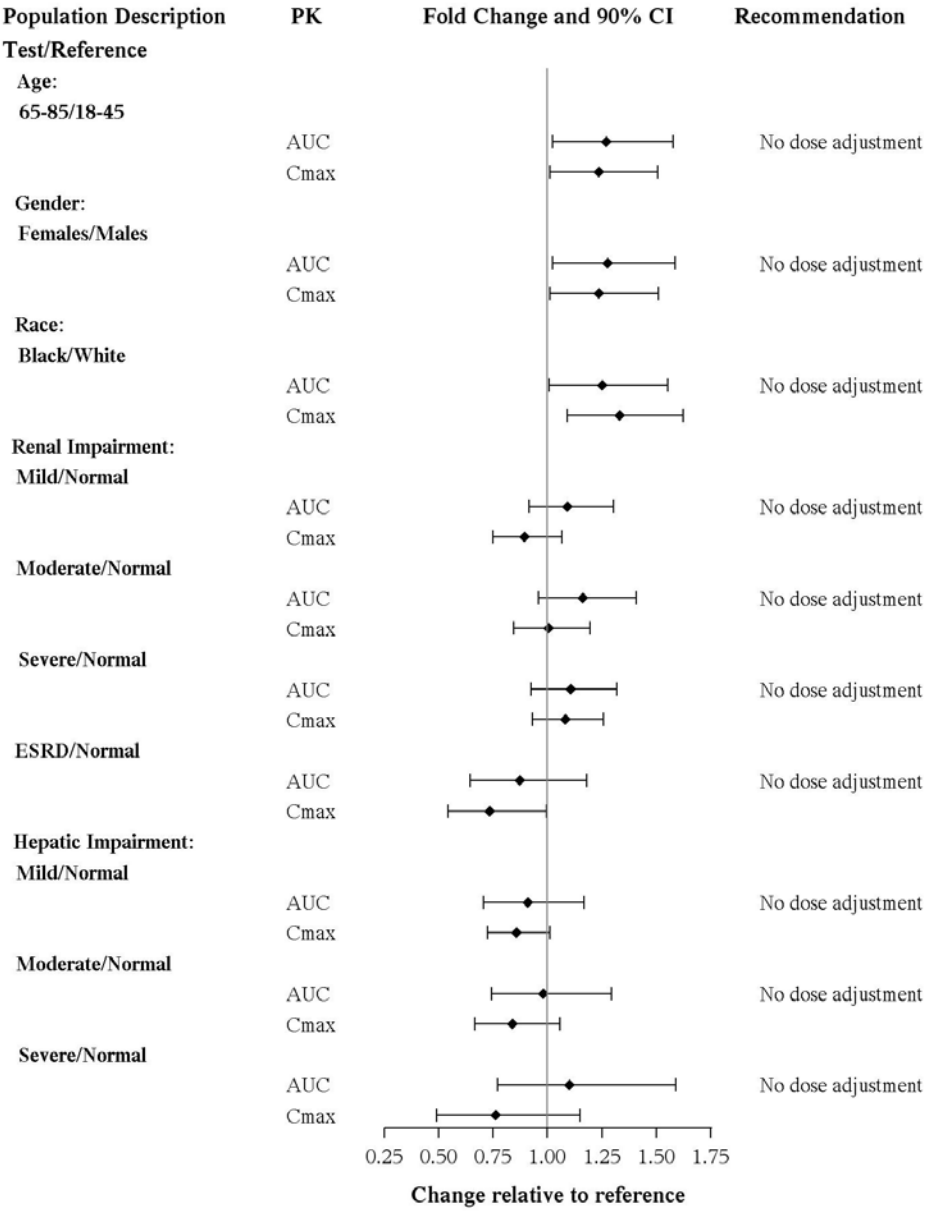
Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger 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 Use in Other Patient Populations

No dose adjustment of TRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to severe hepatic impairment *(Figure 3) [see Clinical Pharmacology (12.3)]*.

**Figure 3. Impact of Intrinsic Factors on Vortioxetine PK**



## 9 DRUG ABUSE AND DEPENDENCE

TRINTELLIX is not a controlled substance.

## 10 OVERDOSAGE

### 10.1 Human Experience

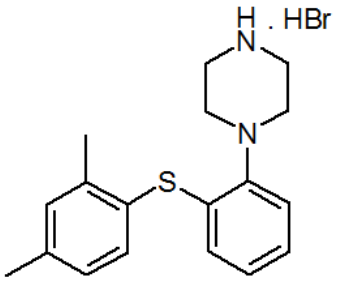
There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In premarketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. 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.

### 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%. 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.

### Metabolism and Elimination

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.

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.

## 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 4*). 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 4)*. 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 4*) 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 4*). 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 4. 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**

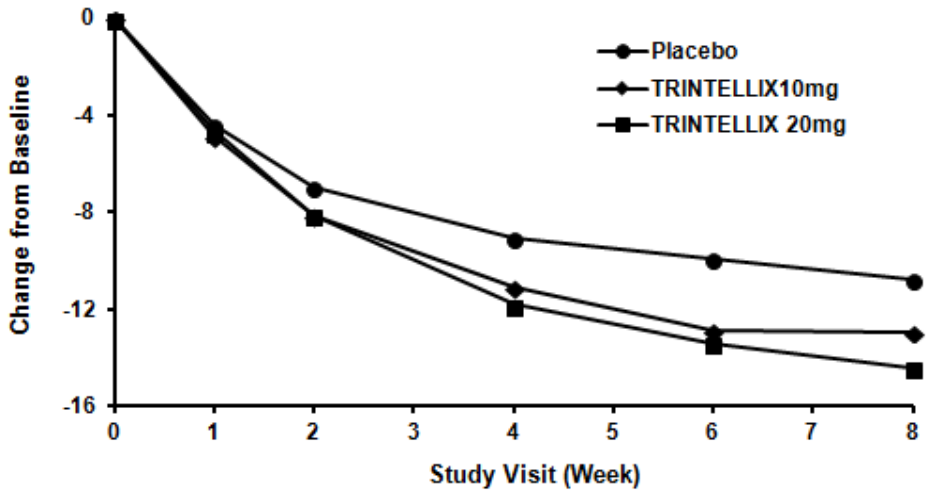
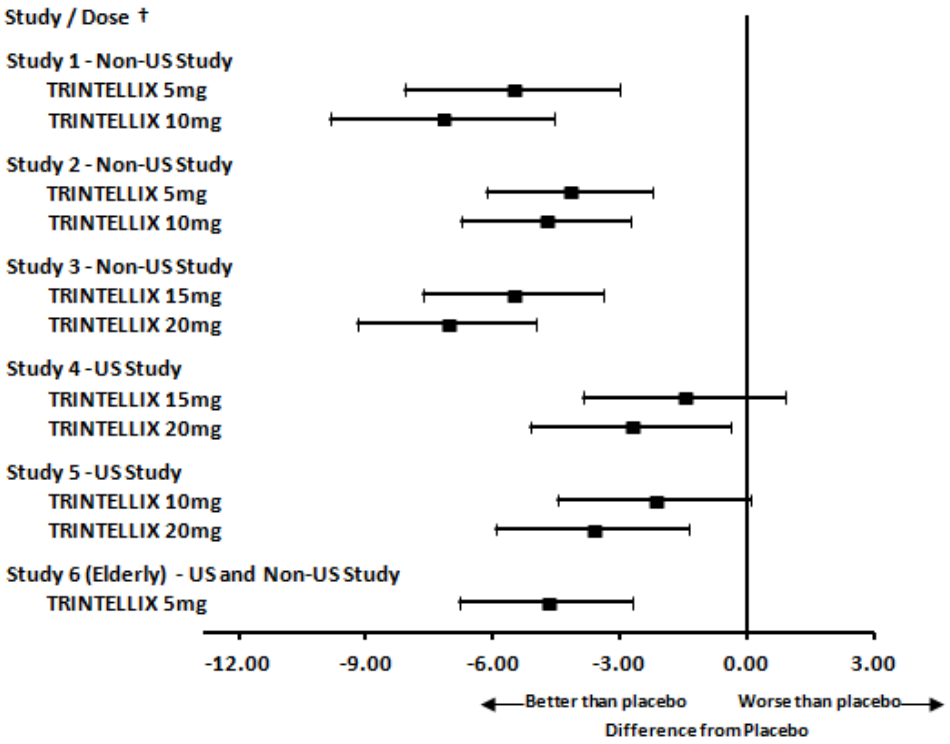



**Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8**




† 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 5)*; depressed mood as assessed by change from baseline in MADRS total score also improved in both studies.

**Table 5. 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.

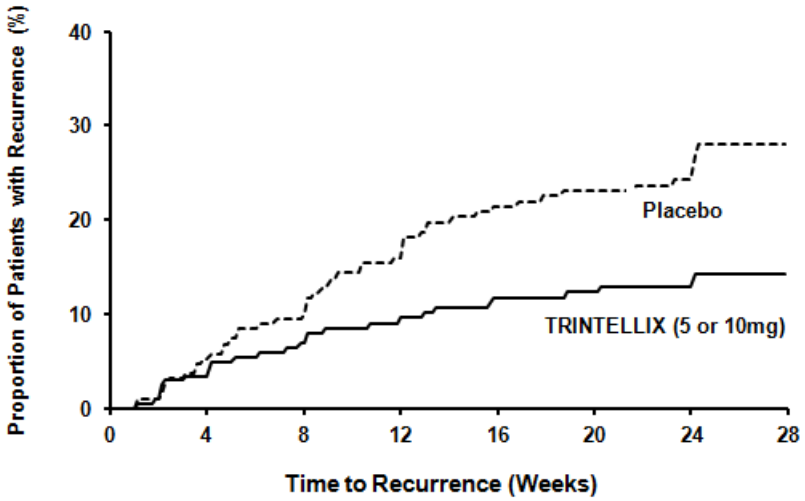
[‡] Doses are statistically significantly superior to placebo.

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 Study

In a non-US 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)**




**Prospective Evaluation of Treatment Emergent Sexual Dysfunction (TESD)**

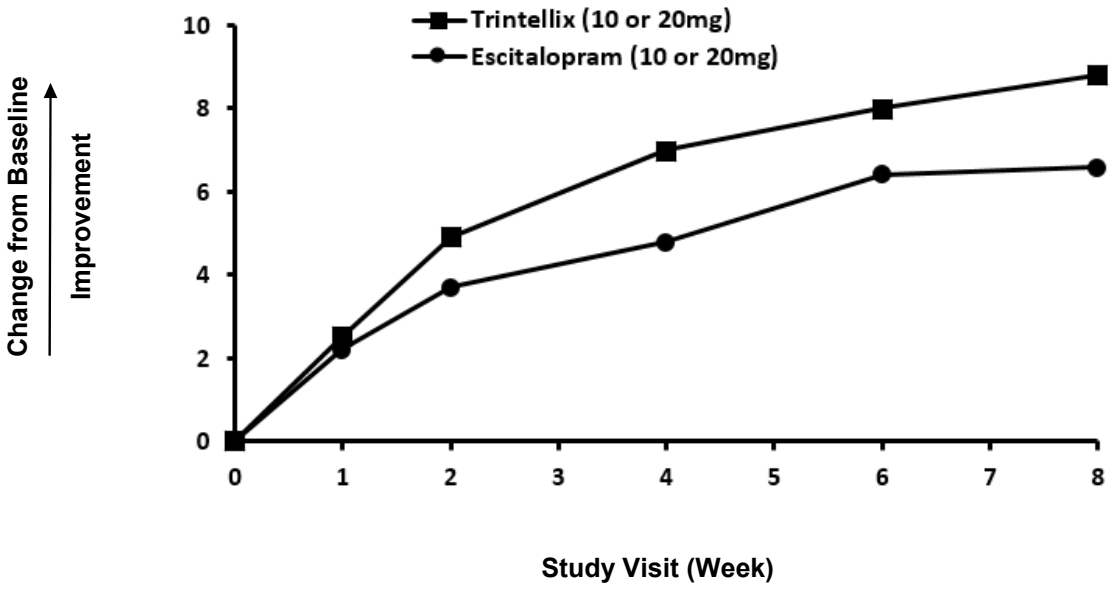
Two, randomized, double-blind, active-controlled studies were conducted to prospectively compare the incidence of TESD between TRINTELLIX and SSRIs via a validated self-rated measure of sexual function, the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). The CSFQ-14 is designed to measure 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 10). 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 7*.

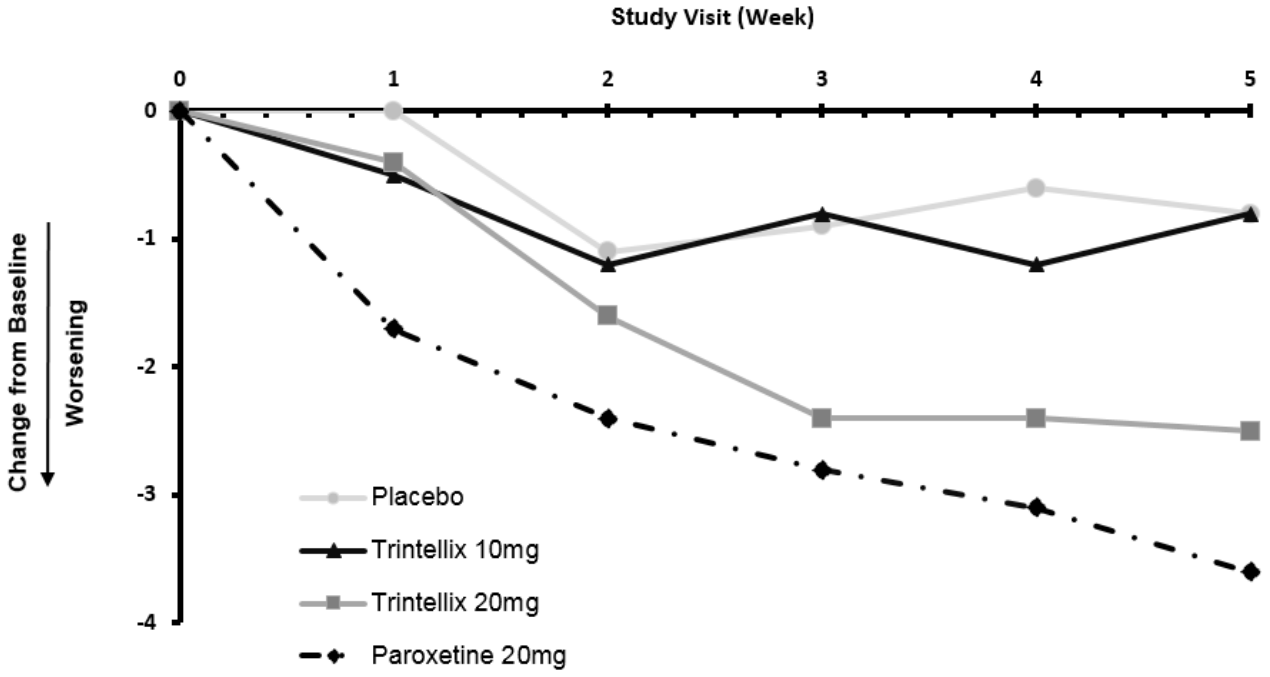
**Figure 7. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Study 10**




*Effects in Healthy Volunteers with Normal Sexual Functioning at Baseline*

In a randomized Healthy Volunteer study (Study 11) 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 8*.

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




## 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<br>"TL" on other side of tablet | "10" on one side of tablet<br>"TL" on other side of tablet | "20" on one side of tablet<br>"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 (2.4), 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)]*.

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**Takeda Pharmaceuticals America, Inc.**
Deerfield, IL 60015

Marketed by:
**Lundbeck**
Deerfield, IL 60015



LUN205 R18

**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:
- agitation, hallucinations, coma or other changes in mental status
- problems controlling your movements or muscle twitching
- fast heartbeat
- high or low blood pressure
- sweating or fever
- nausea or vomiting
- 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:

| | | | |
|---|---|---|---|
| o greatly increased energy | o racing thoughts | o unusually grand ideas | o reckless behavior |
| o severe problems sleeping | o talking more or faster than usual | o 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 R18 Revised: April 2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | October 18, 2018 |
| **From** | CDR Javier A. Muniz |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #**<br>**Supplement#** | 204447<br>S-017 |
| **Applicant** | Takeda |
| **Date of Submission** | December 21, 2017 |
| **PDUFA Goal Date** | October 21, 2018 |
| **Proprietary Name /**<br>**Established (USAN) names** | Trintellix<br>vortioxetine |
| **Dosage forms / Strength** | 5mg, 10mg, 20mg tablets |
| **Proposed Indication(s)** | Treatment of Major Depressive Disorder in adults with treatment-emergent sexual dysfunction |
| **Recommended:** | Approval |

## 1. Introduction

Trintellix (vortioxetine) was approved for the treatment of Major Depressive Disorder (MDD) on September 30, 2013 (NDA 204447). The exact mechanism of action is not entirely understood but it is thought to work primarily as a serotonin (5-HT) reuptake inhibitor. Additionally, vortioxetine has multiple effects on various 5-HT receptors (i.e., antagonism, agonism, and partial agonism), which may or may not explain subtle differences in the observed adverse event profile when compared to other serotonin reuptake inhibiting drugs (e.g., paroxetine, citalopram, escitalopram, etc.). According to the most recent product label, its most commonly reported adverse events during registration clinical trials were nausea, constipation, and vomiting. Vortioxetine is orally administered once daily as a 5mg, 10mg, or 20mg tablet. The recommended dose for most adult patients is 20mg per day.

It is well known that untreated patients with MDD can experience sexual dysfunction: loss of libido has been reported in various studies, affecting 25-75% of these patients and its prevalence appears to be correlated with the severity of the condition. Most currently available antidepressants, particularly those with serotonergic properties, can cause or exacerbate sexual dysfunction, making it a common cause of medication discontinuation. Importantly, poor treatment compliance can lead to relapse or deterioration of the illness. Currently, there are no approved treatments for antidepressant-induced sexual dysfunction. Most clinicians resort to a variety of unproven mitigation strategies to deal with treatment-emergent sexual dysfunction (TESD): reduce the dose, use a combination of antidepressant drugs, switching to a different antidepressant drug, combine the antidepressant drug with off-label supplements or non-antidepressant drugs, use of a temporary “drug holiday”, etc.

The Applicant (Takeda) submitted two pivotal studies (Study 318 and 4001) under this supplement (S-017). These prospective studies were designed to investigate vortioxetine’s effects on TESD. The primary outcome for these studies was the CSFQ-14 (Changes in Sexual

Functioning Questionnaire), which is a 14-item structured self-report questionnaire designed to measure illness- and medication-related changes in sexual dysfunction.

The purpose of this supplemental New Drug Application (sNDA) is to update the text in the United States Prescribing Information (USPI) to include the results studies 318 and 4001, describing vortioxetine's comparative effect on TESD.

## 2. CMC/Device

No new CMC information was submitted with this application.

## 3. Nonclinical Pharmacology/Toxicology

No new non-clinical information was submitted with this application.

Clinical inspections were conducted by the Office of Scientific Investigations (OSI) at four clinical sites. The sites were selected based on high enrollment numbers, large treatment effects, and previous history. Two of the sites were found to have some regulatory violations. However, the OSI reviewer, Jenn Seller, MD, PhD, concluded that "these violations do not appear to impact the overall efficacy or safety outcomes of the studies". Overall, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable.

## 4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted with this application.

## 5. Clinical Microbiology

Not applicable.

## 6. Clinical/Statistical- Efficacy

As previously discussed, the Applicant has submitted two clinical trials in support of this supplement. Anisa Cott, MD, was the clinical reviewer for this sNDA; she recommends approval. Semhar Ogbagaber, PhD, was the biostatistical reviewer; he also recommends approval.

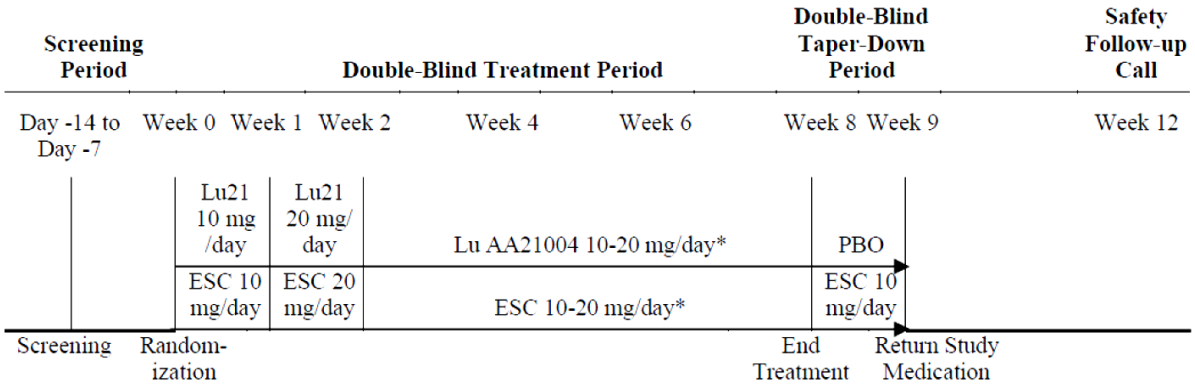
**Study 318**

This was a Phase 3, multicenter, randomized, double-blind, active-controlled (escitalopram), parallel group, flexible-dose study comparing vortioxetine (10 and 20mg daily) and escitalopram (10 and 20mg daily) in subjects with adequately-treated MDD [i.e., as judged by the investigator, and with a Clinical Global Impression Scale-Severity of Illness Scale (CGI-S) total score ≤3] who were experiencing sexual dysfunction due to SSRI use. SSRI-inducted sexual dysfunction was established per investigator judgment and must have met the threshold criterion for sexual dysfunction as measured by the CSFQ-14 total score (≤41 women; ≤47 men).

Subjects who were screened for the study were on SSRI monotherapy (i.e., citalopram, paroxetine, or sertraline; escitalopram was not allowed) to treat an MDD episode and were experiencing sexual dysfunction for at least eight weeks. Subjects were to stop all disallowed medication with the exception of their current SSRI treatment. This trial enrolled subjects at 57 sites in the US and nine sites in Canada.

Subjects who fulfilled the inclusion and exclusion criteria were randomized (on a 1:1 ratio to either escitalopram or vortioxetine) and enrolled in an 8-week double-blind treatment period. Randomized patients received 10mg of either escitalopram or vortioxetine for the first week. The dose was increased to 20 mg/day for both drugs at the end of Week 1. Investigators were able to monitor and adjust doses (range:10 -20mg/day) during the treatment period at Week 2, 4, and 6, based on individual response and tolerability. Subjects who completed the treatment period entered a 1-week drug-tapering period. During this tapering period, subjects who were on vortioxetine received placebo; subjects receiving any dose of escitalopram received escitalopram 10mg daily. There was safety follow-up 4 weeks after completion of the 8-week treatment period. The overall study period was 12 weeks.

**Figure 1: Study 318 Schematics**




*Both arms flexible dosing at Weeks 2, 4, and 6 based on investigator judgment

ESC=esctitalopram, Lu21/Lu AA21004=vortioxetine, PBO=placebo
[Source: Figure 6a, Trial 318's Clinical Study Report, page 26]

The primary efficacy outcome was the mean change from baseline to Week 8 in CSFQ-14 total score between vortioxetine and escitalopram. The mixed model repeated measure (MMRM) with unstructured covariance structure was used to evaluate the change from baseline to week 8 in CSFQ-14 total score. The model included terms: treatment, center, week, treatment-by-week interaction, and baseline CSFQ-14 total score-by-week. To evaluate robustness of the main results from MMRM, the Sponsor conducted sensitivity analyses using pattern mixture models (PMM).

Of 711 subjects who were screened, 447 subjects (62.9%) were randomized (222 subjects in the escitalopram group and 225 subjects in vortioxetine group). A total of 348 (77.9%) subjects completed the study; 179 (80.6%) subjects in the escitalopram arm and 169 (75.1%) subjects in vortioxetine arm. Ninety-nine (99) subjects (22.1%) prematurely discontinued the study; 43 (19.4%) subjects in the escitalopram arm and 56 (24.9%) subjects in vortioxetine arm. The most common reason for study discontinuation was due to adverse events or AEs (7.6%), followed by lost to follow-up (5.6%), consent withdrawal (3.6%), protocol deviation (2.7%), and lack of efficacy (1.3%). All of the subjects who withdrew due to lack of efficacy were in the vortioxetine group (2.7%).

The average age of patients was 39.8 years, ranging from 19 to 55 years. Overall, treatment groups were balanced with respect to age, sex, weight, BMI and race. Many of the participants were Caucasian (80.3%), including Hispanics. This was followed by Black or African American (17.0%).

The full analysis set FAS population consisted of 424 subjects: escitalopram (207), vortioxetine (217). Ten subjects (all male, six randomized to escitalopram and four randomized to vortioxetine) were excluded from the FAS because they did not have a valid CSFQ-14 at baseline, as per the pre-specified Statistical Analysis Plan. The Applicant clarified that these excluded subjects were given an incorrect CSFQ-14 at baseline that did not match all the authorized CSFQ-14 questions correctly.

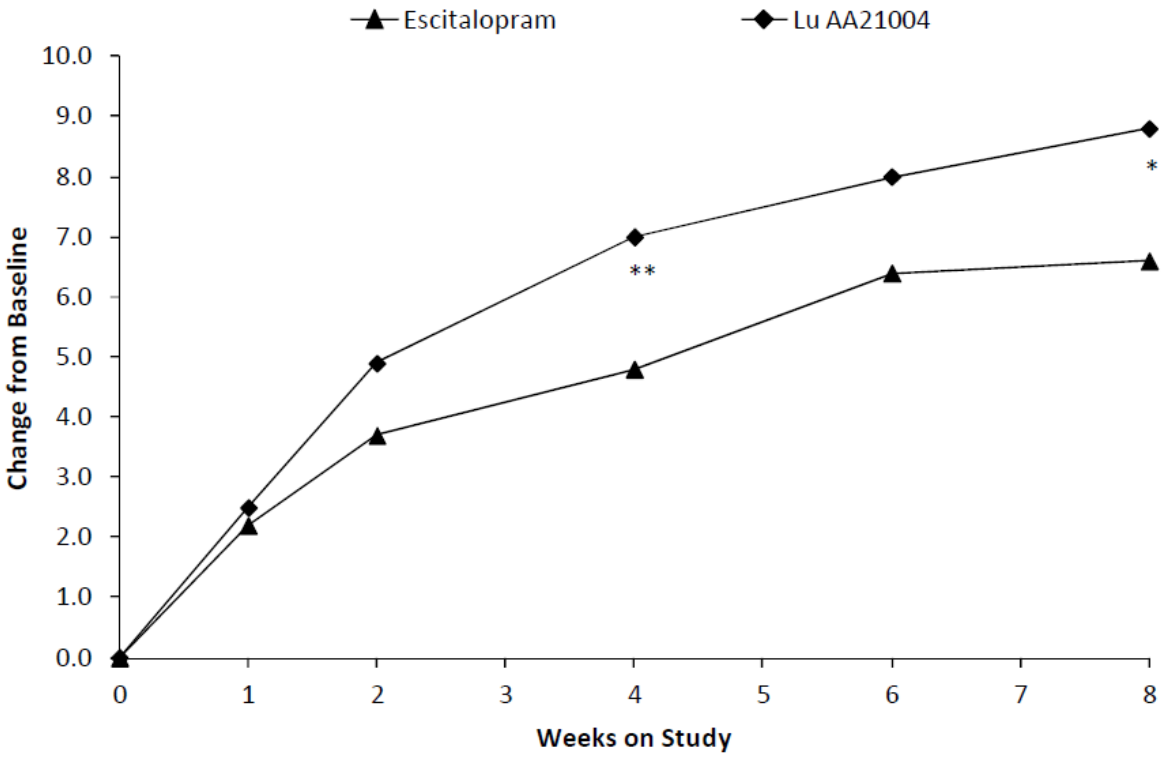
Dr. Ogbagaber confirmed the Applicant's efficacy findings (see table below). Vortioxetine was statistically significantly superior to escitalopram in the mean change from baseline in CSFQ-14 total score at week 8 (FAS, MMRM), with a least square mean treatment difference from placebo of 2.2 (p-value = 0.013).

**Table 1: Change from Baseline in CSFQ-14 Total Score at Week 8; Study 318**

| Visit | Escitalopram N=207 | Vortioxetine N=217 |
|---|---|---|
| Baseline | | |
| N | 207 | 217 |
| LS Mean ± SE (a) | 36.0 ±0.40 | 36.1 ±0.39 |
| Change from Baseline at Week 8 | | |
| N | 173 | 165 |
| Change from Baseline LS Mean ± SE | 6.6±0.40 | 8.8 ±0.64 |
| p-value, Lu AA21004 vs Escitalopram (b) | | 0.013 |
| LS mean differences ± SE from Escitalopram (b) | | 2.2 ±0.90 |
| 95% CI for differences | | (0.48-4.02) |

Lu AA21004=vortioxetine, CI=confidence interval, LS=least-squares, MMRM=mixed model repeated measures, SE=standard error, FAS=Full Analysis Set, SD=standard deviation
[Source: Table 11.f, Trial 318's Clinical Study Report, page 73]
Note: Increase in CSFQ-14 total score indicates improvement.
Note: Baseline value was defined as the last observation prior to the first dose of double-blind medication.
(a) Baseline LS means and p-values were from an ANOVA model with terms for treatment and pooled center.
(b) Postbaseline LS means and p-values were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

**Figure 2: Changes from Baseline in CSFQ-14 Total Score by Visit; Study 318**




[Source: Figure 11.b, Trial 318's Clinical Study Report, page 75]
*p<0.05 vs escitalopram, **p<0.01 vs escitalopram.
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

Supportive analyses using ANCOVA with LOCF [LS Mean (SE) = 1.8 (0.84); p = 0.037] and OC [LS Mean (SE) = 2.5 (0.96), p = 0.011] yielded the same conclusions as the primary efficacy analysis results. Also, pattern mixture model sensitivity results [LS Mean (SE) = 2.0 (0.95); 95% CI: (0.15, 3.88)] were consistent with the main efficacy conclusions.

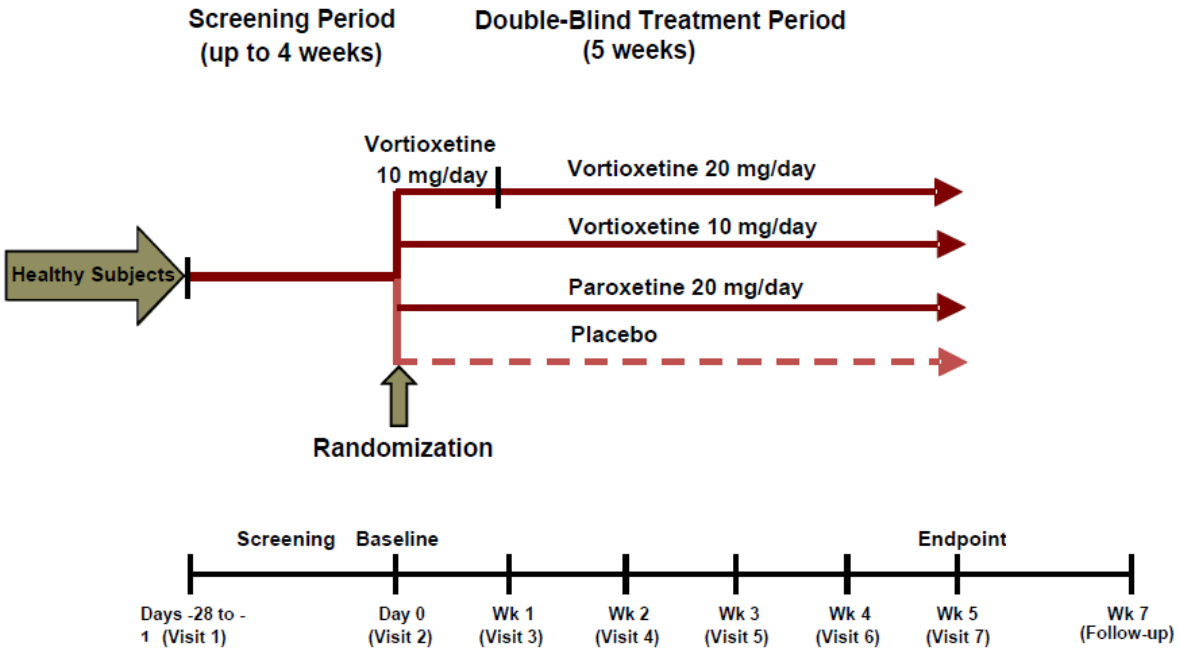
**Study 4001**

This was a Phase 4, multicenter, double-blind, placebo- and active-controlled (paroxetine), 4-arm, parallel-group, fixed-dose study to assess the effect of vortioxetine (10 and 20mg daily) vs. paroxetine (20mg daily) on sexual function in healthy adult subjects. The use of healthy subjects in lieu of patients with MDD theoretically removes the confounding sexual dysfunction symptoms that often accompany the illness.

The study consisted of screening period up to 4 weeks. At baseline eligible patients were randomized (1:1:1:1) to double-blind vortioxetine 10mg, vortioxetine 20mg, paroxetine 20mg, or placebo. Subjects were treated for 5 weeks. Randomization was stratified by sex. Subjects who were randomized to the vortioxetine 20mg arm were on a 10mg dose for 1 week prior to starting their assigned dose. Those who were randomized to the 10mg dose arm remained at the same dose throughout the study. Subjects were observed every week during the double-blind treatment period and were contacted 2 weeks after the completion of treatment for a safety follow-up.

This study enrolled men and women aged 18-40, who were currently sexually active (≥2 times per week), had no sexual dysfunction, had been in steady sexual relationship for ≥3 months, and planned to remain in that relationship for the duration of the study.

**Figure 3: Study 4001 Schematics**




[Source: Figure 6.a, Trial 4001's Clinical Study Report, page 75]

The primary efficacy outcome was the change from baseline to Week 5 in CSFQ-14 total score difference between each vortioxetine arm and paroxetine. The primary endpoint was assessed using analysis of covariance (ANCOVA) which uses last observation carried forward (LOCF) technique. The model terms were treatment group, center, sex, and baseline CSFQ-14 total score. No key secondary endpoints were specified. It should be noted that because the recommended dose of vortioxetine for the treatment of MDD is 20mg/day, (b) (4)

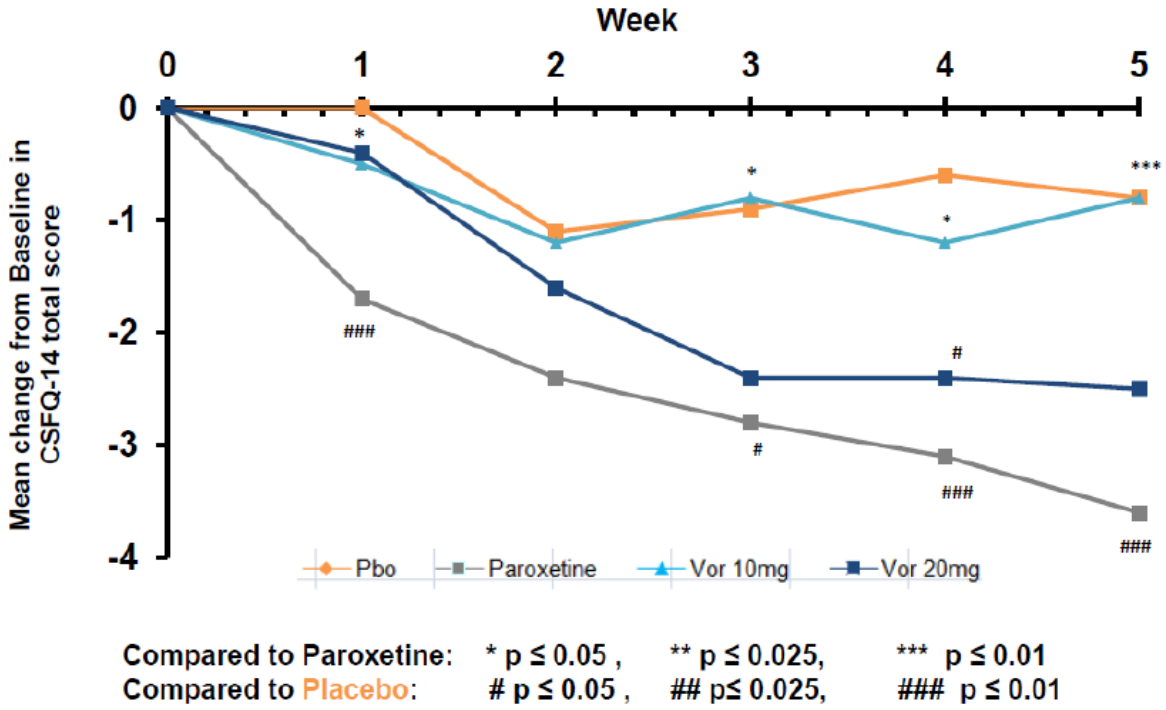
The study involved 16 sites in United States. A total of 361 subjects were randomized to the 5-week treatment period; four did not receive study medication; 290 subjects (80.3%) completed study drug; 288 (79.8%) completed all study visits. The percentage of study discontinuation was 20.2% and was similar between all four treatment groups. The most frequent discontinuation reasons included loss to follow-up (5.8%), voluntary withdrawal (3.9%), significant protocol deviation (3.3%), AEs (2.8%), and non-compliance with study drug (3.3%).

The FAS population included 348 subjects who met the eligibility criteria and were randomized placebo (89), paroxetine 20mg/day (83), vortioxetine 10mg/day (85), or vortioxetine 20mg/day (91).

The average subject age was 28.4 years, ranging from 18 to 40 years. In general, treatment groups were comparable in baseline characteristics. However, most participants were White (57.3%), and most of them were of non-Hispanic or Latino origin (76.7%).

Dr. Ogbagaber confirmed the Applicant's efficacy findings. Using ANCOVA (LOCF), vortioxetine 10mg/day was shown to be associated with statistically significantly less TESD than paroxetine 20mg/day in the mean change from baseline in CSFQ-14 at Week 5 ($p=0.009$). The least square mean treatment difference was 2.74 points. The change from baseline in CSFQ-14 total score vortioxetine 20mg/day group did not separate statistically significantly from paroxetine 20mg/day whether adjusting for multiplicity or not (LS Mean = 1.05; nominal $p = 0.303$). The figure below presents the mean profile plot for each treatment group by visit along with the least-square mean change from baseline.

**Figure 4: Mean Change from Baseline in CSFQ-14 Total Score at Each Visit; Study 4001**




[Source: Figure 6.a, Trial 4001's Clinical Study Report, page 75]
Holm-Bonferroni method; the smallest p-value < 0.025, other p-values are compared against 0.05.

Supportive analyses using observed data and MMRM confirmed the primary efficacy analysis (vortioxetine 10mg/day compared to paroxetine 20mg/day was statistically significant across the methods).

## 7. Safety

There were no deaths in either study. There were five serious adverse events (SAEs) in three patients during Study 318. However, these SAEs do not appear to be directly related to the study drug(s) and Dr. Cott notes in her review that "none of these SAEs gave me cause for concern." No SAEs occurred during Study 4001.

In Study 318, discontinuations due to a treatment-emergent adverse events (TEAE) occurred in 14/222 (6.3%) escitalopram subjects and 20/225 (8.9%) vortioxetine subjects. The TEAE that caused the greatest number of discontinuations was nausea, which resulted in discontinuation for 4.0% of subjects in the vortioxetine group. One subject in the escitalopram group withdrew due to the sexual dysfunction TEAE, ejaculation failure. Discontinuations primarily due to lack of efficacy were low (2.7% in vortioxetine and none in escitalopram subjects).

In Study 4001, discontinuations primarily due to a TEAE were low, 10 subjects total: two in placebo; four in paroxetine; one in vortioxetine 10mg; and three in vortioxetine 20mg. The TEAEs that caused discontinuation for more than one subject overall were nausea (two

subjects in the paroxetine group) and dysphoria (one subject each in the paroxetine and vortioxetine 20mg groups).

In addition to conducting traditional safety analyses with the data submitted, Dr. Cott specifically targeted sexual dysfunction TEAEs. In Study 318, there were nine subjects who reported sexual dysfunction TEAEs, all in the escitalopram group (4.1%). In Study 4001, a total of 87 subjects (24.4%) had at least one reported sexual dysfunction TEAE. The incidence was highest in the paroxetine group (35.7%) and lowest in the placebo group (17.6%). The incidence was 19.8% in the vortioxetine 20mg group and 25.3% in the vortioxetine 10mg group. The most frequent sexual dysfunction TEAEs were decreased libido (21.4% in the paroxetine group, 15.4% in the vortioxetine 10mg group, 12.1% in the placebo group, and 11.0% in the vortioxetine 20mg group) and abnormal orgasm (16.7% in the paroxetine group, 7.7% in the vortioxetine 10mg group, 3.3% in the vortioxetine 20mg group, and 2.2% in the placebo group). The vortioxetine 20mg group had the lowest rates of decreased libido compared with the placebo group and the other active-treatment groups, and the lowest rate of abnormal orgasm and erectile disorder among the active-treatment groups. The vortioxetine 20mg group had no occurrences of anorgasmia, disturbance in sexual arousal, decreased orgasmic sensation, sexual dysfunction, and inadequate lubrication.

In general, the safety data submitted with this NDA are consistent with the known safety profile of vortioxetine. Dr. Cott's review revealed no safety findings that would require a labeling revision, preclude approval of this supplement, or necessitate other regulatory action.

## 8. Advisory Committee Meeting

No advisory committee meeting was held for this supplemental application. The evaluation of the safety data did not reveal safety issues that were unexpected for this drug and class. The design and results of the submitted trials did not pose concerns.

## 9. Pediatrics

TESD is not considered a new indication for vortioxetine; thus, it does not trigger new PREA requirements.

During the review of this supplement, the Applicant requested an extension for the outstanding pediatric postmarketing requirements (PMRs) listed below. We agreed to partially extend these PMRs, in addition to other requested changes. The PMR descriptions listed below reflect the newly agreed dates and additional changes.

> **PMR 2084-7:** Deferred pediatric study under PREA for the treatment of major depressive disorder in children aged 7 to 11 years. Conduct a study to obtain data on the efficacy and safety of vortioxetine in the relevant pediatric population. This must be a placebo-controlled study. This study must be a fixed-dose study.

Final Protocol Submission: 08/2015
Trial Completion: 09/2019
Final Report Submission: 03/2020

**PMR 2084-8:** Deferred pediatric study under PREA for the treatment of major depressive disorder in adolescents aged 12 to17 years. Conduct a study to obtain data on the efficacy and safety of vortioxetine in the relevant pediatric population. This must be a placebo-controlled study. This study must be a fixed-dose study.

Final Protocol Submission: 08/2015
Trial Completion: 09/2019
Final Report Submission: 03/2020

## 10. Other Relevant Regulatory Issues

None.

## 11. Labeling

The initial label submitted with this supplement contained existing sexual dysfunction information (derived from reported AEs occurring during registration clinical trials) and the sexual dysfunction data from the new clinical trials (Study 318 and 4001) in Section 6. Labeling was updated to include a description of Study 318 and Study 4001, along with all the sexual dysfunction data obtained in these prospective trials, in the Clinical Studies section. Specific language modification recommendations by the Office of Prescription Drug Promotion (OPDP) were incorporated as necessary. In addition, modifications were made throughout the label for consistency with recent class labeling changes. The Applicant agreed to these changes.

## 12. Recommendations/Risk Benefit Assessment

The Applicant has provided sufficient evidence to demonstrate potential benefit for patients experiencing antidepressant-induced sexual dysfunction, a common cause of medication noncompliance, with two prospective clinical trials.

Both trials used the CSFQ-14 as a primary endpoint, a validated self-rated measure of sexual functioning. SSRIs were chosen as the active comparator in both studies. The data from Study 318 indicate that, while maintaining antidepressant efficacy, vortioxetine is superior to escitalopram in relieving the symptoms of SSRI-induced sexual dysfunction. Data from Study 4001 demonstrate that in healthy volunteers with no sexual dysfunction, vortioxetine 10mg caused less TESD than paroxetine 20mg. The results of these two studies is useful information for clinicians treating patients with MDD with TESD and these findings should be described in

labeling. It should also be noted in labeling that vortioxetine 20 mg, the recommended dose for treatment of MDD, does not have the same advantage as 10 mg with regard to sexual dysfunction.

No new safety signals were identified in these trials that would require a regulatory action or labeling revision. The benefits of vortioxetine continue to outweigh the risks in treating patients with MDD. The label has been negotiated to current Division standards. This application should be approved by the PDUFA date.

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

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/s/
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JAVIER A MUNIZ
10/19/2018

MITCHELL V Mathis
10/19/2018

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | sNDA |
| **Application Number(s)** | 204447/S-017 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | December 21, 2017 |
| **Received Date(s)** | December 21, 2017 |
| **PDUFA Goal Date** | October 21, 2018 |
| **Division/Office** | Division of Psychiatry Products |
| **Reviewer Name(s)** | Anisa Cott, MD |
| **Review Completion Date** | September 14, 2018 |
| **Established/Proper Name** | Vortioxetine |
| **(Proposed) Trade Name** | Trintellix |
| **Applicant** | Takeda Pharmaceuticals, USA, Inc. |
| **Dosage Form(s)** | 5mg, 10mg, 20mg tablet |
| **Applicant Proposed Dosing Regimen(s)** | once daily |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment Emergent Sexual Dysfunction in Adult Patients with Major Depressive Disorder |
| **Recommendation on Regulatory Action** | Approve |
| **Recommended Indication(s)/Population(s)** (if applicable) | Adult Patients with Major Depressive Disorder and Treatment Emergent Sexual Dysfunction |

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| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MDD | Major Depressive Disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |

| | |
|---|---|
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SGE | special government employee |
| SOC | standard of care |
| SSRI | selective serotonin reuptake inhibitor |
| TEAE | treatment emergent adverse event |
| TESD | treatment emergent sexual dysfunction |

# 1. Executive Summary

## 1.1. Product Introduction

Trintellix (vortioxetine) is a serotonin reuptake inhibitor approved in 2013 for the treatment of Major Depressive Disorder (MDD). Trintellix is orally administered once daily as a 5mg, 10mg, or 20mg tablet. The purpose of this supplemental New Drug Application (sNDA) is to update the text in the United States Prescribing Information (USPI) to include the results of two prospective clinical studies describing vortioxetine's comparative effect on treatment-emergent sexual dysfunction (TESD).

The Applicant has submitted sufficient evidence to support approval recommendation. Labeling will be updated to describe clinical trial data related to TESD but with some changes to the Applicant's proposed language.

## 1.2. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

MDD is a serious and debilitating illness. Antidepressant drug therapy is the preferred treatment for moderate to severe depression. Untreated patients with MDD can experience sexual dysfunction: loss of libido has been reported in various studies, affecting 25-75% of these patients and its prevalence appears to be correlated with the severity of the condition. Most currently available antidepressants, particularly those with serotonergic properties, can cause or exacerbate sexual dysfunction, making it a common cause of medication discontinuation. Importantly, poor treatment compliance can lead to relapse or deterioration of the illness. Currently, there are no approved treatments for antidepressant-induced sexual dysfunction.

Vortioxetine is an approved antidepressant indicated for the treatment of MDD. The Applicant has provided sufficient evidence to demonstrate potential benefit for patients experiencing antidepressant-induced sexual dysfunction with two prospective clinical trials. Both trials used the primary endpoint, Changes in Sexual Functioning Questionnaire (CSFQ-14), a validated self-rated measure of sexual functioning. SSRIs were chosen as the active comparator in both studies. The data from Study 318 indicate that, while maintaining antidepressant efficacy, vortioxetine is superior to escitalopram in improving sexual functioning in MDD subjects with SSRI-induced sexual dysfunction. Data from Study 4001 demonstrates that in healthy volunteers, with no sexual dysfunction, vortioxetine 10 mg caused significantly less TESD than paroxetine 20 mg. This supports the strategy to use a lower dose of vortioxetine to address treatment-emergent sexual dysfunction.

Vortioxetine has been on the market since 2013. No new safety signals were identified in these trials that would require a regulatory action or labeling revision. The benefits of vortioxetine continue to outweigh the risks in treating patients with MDD.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • MDD is a serious illness and antidepressant drug therapy is the preferred treatment for moderate to severe depression.<br>• MDD often requires months or years of daily antidepressant medication.<br>• Most currently available antidepressants produce sexual dysfunction. | • Although successful treatment of depression may alleviate sexual dysfunction in some patients, the available evidence suggests that many patients |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • TESD can affect one or multiple phases of sexual activity by decreasing desire, arousal, orgasm, and ejaculation.<br>• Sexual dysfunction is a common cause of medication discontinuation.<br>• Poor treatment compliance can cause a relapse or deterioration of the illness. | treated with SSRIs or SNRIs develop TESD during treatment and continue to experience sexual dysfunction for prolonged periods.<br>• A safe and effective drug for MDD that minimizes treatment-emergent sexual dysfunction would potentially improve treatment compliance. |
| **Current Treatment Options** | • There are no FDA-approved treatments for TESD.<br>• Many clinicians will lower the dose or discontinue the antidepressant.<br>• Switching to another antidepressant is a common strategy.<br>• Some clinicians will add another agent to treat sexual dysfunction off-label. | • No drug has been approved to treat antidepressant induced sexual dysfunction.<br>• Off-label use of agents is not known to be safe or effective.<br>• Drug discontinuation and switching could lead to relapse of MDD. |
| **Benefit** | • Vortioxetine is already approved for the treatment of MDD.<br>• Minimizing an antidepressant adverse effect such as sexual dysfunction would potentially improve treatment compliance.<br>• Study 318 represents a “real world” scenario where patients with stable depressive symptoms are experiencing sexual dysfunction symptoms as a result of antidepressant treatment. This study demonstrated that the switch to vortioxetine resulted in greater improvements in sexual functioning over escitalopram with no loss of antidepressant efficacy.<br>• Study 4001 demonstrates that in healthy volunteers, with no sexual dysfunction, vortioxetine 10mg caused significantly less TESD than paroxetine 20 mg. This study supports a strategy of dose reduction for managing TESD. | • Patients with MDD would benefit from safe and effective treatments that don’t induce or exacerbate sexual dysfunction.<br>• Based on the presenting studies, reasonable approaches to addressing TESD while maintaining therapeutic benefit include switching from another SSRI to vortioxetine or reducing the vortioxetine dose from 20 mg to 10 mg. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Risk and Risk Management** | • The safety profile of vortioxetine with respect to adverse events in the studies supporting this supplemental application does not substantively differ from that in the USPI. No new safety signals were identified.<br>• The postmarket safety data are consistent with clinical data and do not highlight any new safety findings. | • No new safety concerns regarding the use of vortioxetine were identified in this review.<br>• The benefits of vortioxetine continue to outweigh the risks in treating patients with MDD. |

### 1.3. Patient Experience Data

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

| | | | | |
|---|---|---|---|---|
| □ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | X | Clinical outcome assessment (COA) data, such as | | Sec 6.1 and 6.2 |
| | | X | Patient reported outcome (PRO) | |
| | | □ | Observer reported outcome (ObsRO) | |
| | | □ | Clinician reported outcome (ClinRO) | |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | □ | Input informed from participation in meetings with patient stakeholders | |
| | | □ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | □ | Observational survey studies designed to capture patient experience data | |
| | | □ | Other: (Please specify) | |
| □ | Patient experience data was not submitted as part of this application. | | | |

## 2. Therapeutic Context

### 2.1. Analysis of Condition

MDD is estimated to affect about 16.6% of people in the United States at some time during their lives, and to affect 8.6% of people during a typical year. Sexual dysfunction is a frequently

reported symptom of depression with studies reporting loss of libido between 25% and 75% of depressed patients. Antidepressant drug therapy is the preferred treatment for moderate to severe depression. Unfortunately, most of the currently available antidepressants produce sexual dysfunction in men and women and affect all phases of sexual activity by decreasing desire, arousal, orgasm, and ejaculation. Such side effects affect the patient's quality of life, can lead to therapeutic noncompliance, and often interfere with recovery from a depressive episode.

Estimates of the percentage of patients on SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs), or other antidepressant agents who experience treatment-related sexual dysfunction have varied widely but range from 25% to 80% depending on the method of assessment and number of sexual phases assessed. In addition, data extracted from a review of 200 published articles suggested that between 30% and 60% of SSRI-treated patients may experience some form of treatment-induced sexual dysfunction. Assessing the prevalence of sexual dysfunction in antidepressant-treated MDD population may be confounded by several factors: (1) most studies have relied on spontaneous reporting of sexual side effects; (2) sexual dysfunction is often underreported because patients may be reluctant to discuss this with the investigator; and (3) since patients with mood disorders already have an elevated risk of sexual dysfunction, accurate assessment of prevalence is better obtained within the context of randomized trials, which include baseline assessments.

The goals of treatment of MDD are that the symptoms are effectively alleviated and that the treatment is safe and tolerable. Although successful treatment of depression may alleviate sexual dysfunction in some patients, the available evidence suggests that many patients treated with SSRIs or SNRIs develop TESD during treatment and continue to experience sexual dysfunction for prolonged periods. Sexual dysfunction is also frequently cited as leading to treatment discontinuation and/or medication noncompliance.

## 2.2. Analysis of Current Treatment Options

There are no FDA-approved treatments for this indication.

There is limited evidence to support the treatment of antidepressant related sexual dysfunction and in clinical practice treatment approaches vary widely. Switching antidepressants because of sexual side effects is common and appears to be supported by indirect comparisons of clinical trial data, which have concluded that different antidepressants are associated with different rates of sexual dysfunction. Furthermore, few randomized trials have explored the effectiveness of switching antidepressants to alleviate treatment-associated sexual dysfunction while maintaining effective treatment of depressive symptoms.

Switching therapy or augmentation with bupropion or nefazodone have been tried, however, these methods have not shown clear efficacy in controlled trials. Avoidance of antidepressants has been reported, which can have negative consequences on depression management.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Vortioxetine was approved in the United States for the treatment of MDD on September 30, 2013. Vortioxetine is available as an immediate-release tablet for oral administration in strengths of 5 mg, 10 mg, and 20 mg. H. Lundbeck A/S was the initial developer of vortioxetine. In 2008, Lundbeck transferred sponsorship to Takeda Global Research & Development Center, Inc., but continued to co-develop vortioxetine.

Since initial approval, new safety information regarding angle-closure glaucoma, weight gain, and acute pancreatitis has been added to this product's labeling. Supplement 9 added Clinical Global Impression-Improvement (CGI) scale data to the Clinical Studies section of the package label and was approved in March 2017. Supplement 6 sought to add data regarding improvement in cognitive dysfunction to the package label and was issued a complete response letter for lack of clinical meaningfulness in March 2016, and again in June 2017, after a resubmission. The Applicant submitted a formal dispute resolution request (FDRR) and the appeal was granted in March 2018, allowing the addition of Digit Symbol Substitution Test (DSST) results to be added to Section 14 of the package label.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant discussed the potential claim related to TESD with the Division in a face-to-face meeting on February 18, 2015. At that time, they presented the results from a completed 8-week, double-blind, flexible-dose study (Study 318) of sexual functioning in men and women with well-treated MDD who had been randomized to receive vortioxetine (10 to 20 mg/day) or escitalopram (10 to 20mg/day). Vortioxetine-treated patients demonstrated a statistically greater improvement in sexual functioning as measured by the change from baseline in the CSFQ-14 (Changes in Sexual Functioning Questionnaire Short-Form) total score. The Division stated that the design of Study 318 was reasonable but added that two positive trials or a strong justification for reliance on a single trial was necessary to support the claim of a superior effect of vortioxetine with respect to TESD.

The Applicant subsequently proposed a new trial (Study 4001). This was a 5-week, double-blind study in 160 healthy male volunteers with normal sexual functioning who were to be randomized to vortioxetine 10 mg/day, vortioxetine 20 mg/day, paroxetine 20 mg/day, or placebo. The primary endpoint was the change from baseline in the CSFQ-14 total score. The Division advised to include both men and women in the trial (b) (4) The protocol for this trial was submitted on September 28, 2016. The sample size was

increased to 352 healthy men and women ages 18 to 40 years (88 per arm) and randomization was to be stratified by gender.

At a pre-NDA meeting on November 28, 2017, the Division stated that no significant review issues had been identified and that the proposed content appeared to be acceptable for filing the application. Study 318 was conducted in patients with treated MDD and closely reflects use in a typical clinical setting. The Division stated that Study 4001 is also useful in that it evaluated sexual functioning without confounding by depressive illness and examined the dose-response for sexual symptoms. The Division recommended that the proposed labeling address the findings from both studies. (b) (4) The Division expressed that the dose-response observed in Study 4001 would be useful to prescribers and could be described in labeling.

### 3.3. Foreign Regulatory Actions and Marketing History

As of September 29, 2017, vortioxetine is authorized in 74 countries and available in 59 countries. There have been no known adverse regulatory actions or marketing withdrawals.

During the period September 30, 2016, to September 29, 2017, covered by the most recent Periodic Safety Update Report, the estimated exposure from postmarketing sources of vortioxetine was (b) (4) patient-years, and the estimated cumulative exposure was (b) (4) patient-years. Assuming an average treatment period of 3 months, this corresponds to an exposure of (b) (4) patients. The cumulative world-wide available postmarketing data to date is in line with the known safety profile of vortioxetine. No new safety concerns have been identified from the post marketing experience.

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

### 4.1. Office of Scientific Investigations (OSI)

Two sites from each of the two clinical studies were selected for audits. The basis for the selection included enrollment of large numbers of study subjects and high treatment responders. OSI concluded that no inspection findings were likely to have affected the study efficacy or safety results. The data generated by these sites appear acceptable to support this submission.

**Table 1**: **OSI Results (by site):**

| Site #/Name of CI/Address | Protocol #/ # of Subjects Enrolled | Inspection Dates | Classification |
|---|---|---|---|
| Site # 5003<br>**Sarah D. Atkinson, M.D.**<br>885 Winton Road South<br>Rochester, NY 14618 | T21004-318<br>Subjects: 19 | 24-27 April 2018 | VAI |
| Site # 58001<br>**James H. Bergthold, M.D.**<br>2701 NW Vaughn Street<br>Suite 350<br>Portland, OR 97210 | Vortioxetine-4001<br>Subjects: 41 | 17-24 May 2018 | NAI |
| Site # 5006<br>**Mark DiBuono, M.D.**<br>4349 Hylan Boulevard<br>Staten Island, NY 10312 | T21004-318<br>Subjects: 18 | 11-14 June 2018 | NAI |
| Site # 58005<br>**Michael J. Downing, M.D.**<br>5445 La Sierra Drive,<br>Suite 101<br>Dallas, TX 75231 | Vortioxetine-4001<br>Subjects: 30 | 23-27, 29-30 May 2018 | VAI |

Key to Compliance Classifications:

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable

## 4.2. Product Quality

No new CMC information was included with this submission.

## 4.3. Clinical Microbiology

No new clinical microbiology information was included with this submission.

## 4.4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was included with this submission.

## 4.5. Clinical Pharmacology

No new clinical pharmacology information was included with this submission.

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

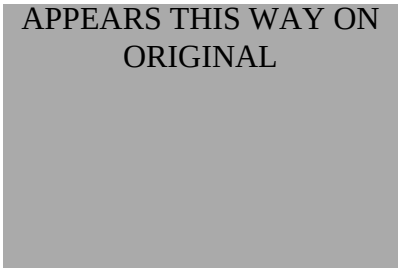


**Table 2: Listing of Clinical Trials Relevant to this sNDA**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| ***Controlled Studies to Support Efficacy and Safety*** | | | | | | | |
| 318 | Phase 3, multicenter, randomized, double-blind, 2-arm, active-controlled, parallel-group, flexible-dose study | Vortioxetine: 10, 20 mg/day<br>Escitalopram: 10, 20 mg/day<br>Orally | Change from baseline in CSFQ-14 total score Vortioxetine vs Escitalopram at Week 8 | 8 weeks<br>Vortioxetine: 10 mg in Week 1, increased to 20 mg if needed, and later tapered back to 10 mg, if needed.<br>Escitalopram: 10 mg in Week 1, increased to 20 mg if needed, and later back to 10mg, if needed. | 447 treated<br>225 with Vortioxetine<br>222 with Escitalopram | Well treated and stable patients with MDD, CGI-S $\leq$3, with SSRI induced sexual dysfunction (defined by CSFQ-14), sexually active | 57 sites in US and 9 sites in Canada |
| 4001 | Phase 4, multicenter, randomized, double-blind, parallel group, 4-arm, placebo- and active-controlled, fixed-dose study | Vortioxetine: 10 mg/day<br>Vortioxetine: 20 mg/day<br>Paroxetine: 20 mg/day<br>Placebo<br>Orally | Change from baseline in CSFQ-14 total score Vortioxetine vs Paroxetine at Week 5 | 5 weeks<br>(Vortioxetine 20 mg group received 10 mg in Week 1) | 357 treated<br>91 with Vortioxetine 10mg<br>91 with Vortioxetine 20 mg<br>84 with Paroxetine 20mg<br>91 with Placebo | Healthy, normal sexual functioning (defined by CSFQ-14), sexually active, 18 to 40 years old | 16 sites in US |

### 5.2. Review Strategy

This review is focused on the efficacy and safety results from Study 318 and Study 4001. These studies evaluated safety on the basis of AEs, clinical safety laboratory tests, vital signs, weight, and physical examinations. However, the safety data from these studies is consistent with the known safety profile of vortioxetine. In this review, I will only focus on the top-level safety data (e.g., deaths, SAEs, AEs leading to discontinuation, etc.). Adverse events of interest were the sexual dysfunction AEs in both studies. A pooled analysis of the data was not performed for Studies 318 and 4001 in this sNDA due to the differences in populations and study designs.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Study 318

#### 6.1.1. Study Design

**Overview and Objective**

Study 318 is formally entitled "A Randomized, Double-Blind, Parallel-Group, Active-Controlled, Flexible-Dose Study Evaluating the Effect of Lu AA21004 vs Escitalopram on Sexual Functioning in Adults With Well-Treated Major Depressive Disorder Experiencing Selective Serotonin Reuptake Inhibitor Induced Sexual Dysfunction." The primary objective of this study was to evaluate the effects of flexible doses of vortioxetine (10 and 20 mg once daily) vs flexible doses of escitalopram (10 and 20 mg once daily) after 8 weeks of treatment on sexual functioning in subjects with well-treated MDD who were experiencing SSRI-induced sexual dysfunction.

**Trial Design**

Study 318 was a phase 3b, multicenter, randomized, double-blind, active-controlled (escitalopram), parallel-group, flexible-dose study comparing vortioxetine (10 and 20 mg QD) with escitalopram (10 and 20 mg QD) in subjects with well-treated MDD who were experiencing SSRI-induced sexual dysfunction. This study enrolled men and women, ages 18 through 55 years, who were sexually active at least once every two weeks.

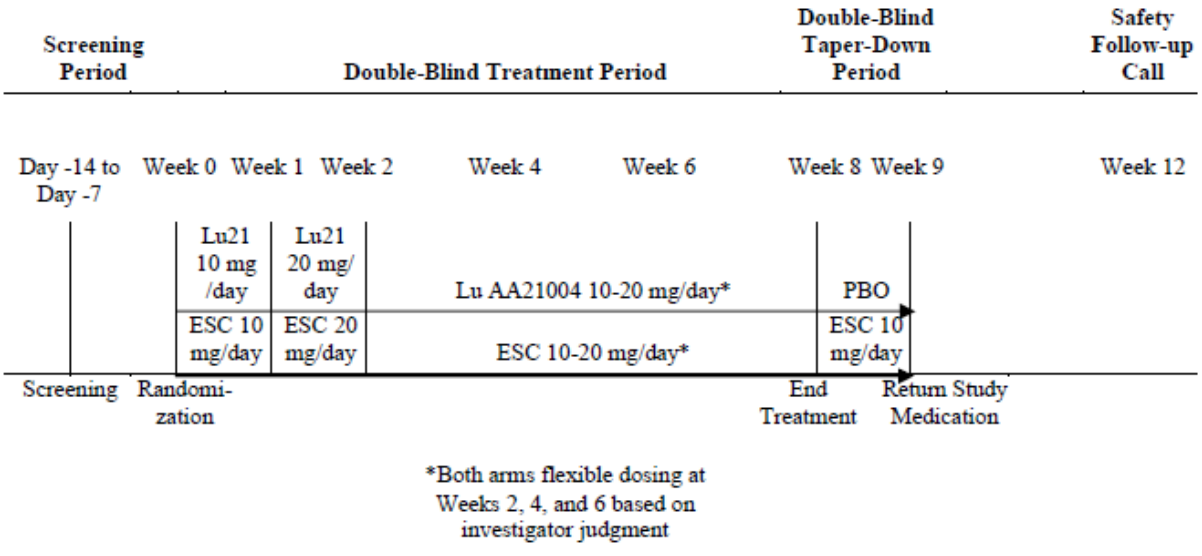
Subjects with a diagnosis of major depressive episode (MDE) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for which they had been receiving SSRI monotherapy (only citalopram, paroxetine, or sertraline were allowed; escitalopram was not allowed) for at least 8 weeks prior to the Screening Visit, and who were experiencing sexual dysfunction were screened for eligibility. The MDE should have been well-treated, that is, currently stable as judged by the investigator, and with a Clinical Global

Impression Scale-Severity of Illness Scale (CGI-S) total score ≤3. Additionally, patients must have been experiencing SSRI-induced sexual dysfunction per investigator judgment and must have met the threshold criterion for sexual dysfunction as measured by the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score (≤41 women; ≤47 men).

At Baseline, subjects who continued to fulfill all the inclusion criteria and none of the exclusion criteria were randomized equally (1:1) to one of two treatment arms for an 8 week, double-blind Treatment Period. Subjects were randomized to flexible doses of either vortioxetine 10/20 mg QD or escitalopram 10/20 mg QD. Subjects must have discontinued their current SSRI monotherapy treatment at Baseline. Randomized subjects received either vortioxetine 10 mg or escitalopram 10 mg for the first week. Subjects initiated investigational drug the day after the Baseline Visit. At the Week 1 visit all subjects had their dose increased to 20 mg/day of either vortioxetine or escitalopram. At the Week 2, 4, or 6 visits, investigators may have adjusted dose based on subject response and tolerability as judged by the investigator. The dose was not to be increased above 20 mg/day vortioxetine or escitalopram.

Subjects who completed the 8-week Treatment Period entered a 1-week, Double-Blind, Taper-Down Period. Subjects treated with vortioxetine (10/20 mg QD) received placebo; and subjects treated with escitalopram (10/20 mg QD) received 10 mg QD escitalopram, during the Taper-Down Period.

**Figure 1: Schematic of Study 318 Design**




ESC=escitalopram, Lu21=Lu AA21004, PBO=placebo.

An SSRI was chosen as the active comparator because SSRIs are the most commonly prescribed antidepressants, despite having some tolerability issues, including TESD. In Study 318, escitalopram in the approved dose range of 10 to 20 mg was chosen for its favorable efficacy

profile and because it is commonly prescribed for MDD.

**Study Endpoints**

The primary endpoint for assessment of TESD was the CSFQ-14 total score change from Baseline, vortioxetine vs the active comparator. Secondary sexual function endpoints included the CSFQ-14 total score at each visit, change from Baseline in CSFQ subscales 5 dimensions and three phases of sexual functioning, the number of subjects with a shift in CSFQ-14 from abnormal to normal (no sexual dysfunction), percentage of responders at each visit (CSFQ-14 total score increase from Baseline $\geq$3), and change from Baseline in CSFQ-14 total score in subjects in remission of depressive symptoms at study start (defined as a CGI-S score $\leq$2) and in CGI-S non-remitters.

Per the Applicant, the self-reported 14-item CSFQ scale was implemented because (a) it is a validated questionnaire designed to assess and detect changes in sexual functioning, (b) it is recognized by regulatory authorities as an accepted tool to assess sexual functioning in clinical studies, (c) it is more comprehensive than the ASEX scale, and (d) can be analyzed as a continuous variable using total score (i.e., including all patients) or as a categorical value via shift analysis, and (e) can be analyzed by subscales of sexual functioning.

Determination of a clinically meaningful difference in the CSFQ-14 total score of 2 to 3 points seen between antidepressant agents was established by the Applicant in consultation with the scale developer and expert in TESD, Anita Clayton, MD. Further, a distribution-based method was used to estimate a clinically important difference for the CSFQ-14 based on data from Study 318. The distribution approach evaluates meaningful change in relation to statistical parameters of group variability such as the baseline standard deviation (SD). Research supports that the threshold for discrimination of a meaningful change is one-half the SD of the Baseline score. The distribution-based method of half the baseline SD yielded results of 2.9 points, given the baseline SD was 5.7 in Study 318, further supporting the meaningfulness of a 2 to 3 point difference.

Study 318 also included assessments of depressive symptoms to determine whether clinical improvement was maintained with the switch in antidepressants: the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S, and the CGI-I.

**Statistical Analysis Plan**

The full analysis set (FAS) (the primary analysis population) included all subjects who were randomized, received at least one dose of double-blind study drug, and had at least one valid postbaseline value for assessment of the primary efficacy endpoint.

Change from Baseline in CSFQ-14 total score after 8 weeks of treatment was the primary endpoint. The primary analysis was based on a mixed model for repeated measurements

(MMRM) analysis of covariance with treatment, center, week, treatment-by-week interaction as fixed effects, Baseline CSFQ-14 total score-by-week as covariate, and a completely unstructured covariance matrix. Comparisons between vortioxetine and escitalopram were performed on Week 8. The primary analysis was performed using observed case data only. The statistical tests were 2-sided comparing vortioxetine to escitalopram. Ninety-five percent confidence intervals (CIs) were presented together with the estimated p-values.

As supportive analyses, the change from Baseline in CSFQ-14 total score after 8 weeks of treatment was also analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors, Baseline CSFQ-14 total score as covariate, and using last observation carried forward (LOCF) and observed case (OC) methods.

For the primary efficacy variable, subgroup analyses by age (≤41, >41, sex (female, male), Baseline CSFQ-14 (≤ median, > median), and CGI-S remitter (yes, no), and other variables, if necessary, was performed if each of the subgroups contained at least 20% of the total subjects in the study. The treatment groups were compared within each subgroup.

**Protocol Amendments**

A Protocol Amendment on September 12, 2011, excluded more concomitant medications during the study and made minor text revisions including providing clarification on the lack of SSRI taper and the need for a direct switch at randomization.

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**

This study was conducted in compliance with the institutional review board (IRB) regulations stated in Title 21 of the United States (US) Code of Federal Regulations (CFR), Part 56, Good Clinical Practice (GCP) regulations and guidelines, and all applicable local regulations.

**Financial Disclosure**

The Applicant provided a table of clinical investigators and all the investigators were marked as Yes for Certification and No for disclosure. This was a randomized, blinded trial with objective endpoints and I have no reason to be concerned that financial interests affected the integrity of the data in this study.

**Patient Disposition**

Of 711 subjects who were screened, 447 subjects (62.9%) were randomized in North America (222 subjects in escitalopram group and 225 subjects in vortioxetine). The FAS population

contains a total of 424 subjects: escitalopram (207), vortioxetine (217). Ninety-nine (99) subjects (22.1%) prematurely discontinued the study (43 (19.4%) subjects in the escitalopram arm; 56 (24.9%) subjects in vortioxetine arm). The most common reason for study discontinuation was due to AE (7.6%), followed by lost to follow-up (5.6%), consent withdrawal (3.6%), protocol deviation (2.7%), and lack of efficacy (1.3%). All the subjects that withdrew due to lack of efficacy were in the vortioxetine group (2.7%).

**Protocol Violations/Deviations**

Twelve subjects (2.7%) had protocol deviations as the primary reason leading to study discontinuation: eight subjects (3.6%) in the escitalopram group and four subjects (1.8%) in the vortioxetine group.

Ten subjects (all male, six randomized to escitalopram and four randomized to vortioxetine) were given an unauthorized version of the male CSFQ-14, which did not contain the same questions. The individual scores to the questions could not be entered into the database as the response options did not match. Consequently, these subjects did not have valid Baseline CSFQ-14 total scores and could not be included in efficacy analyses. The SAS code and dataset submitted with the sNDA for the FAS excludes these 10 subjects because the assessment of the primary efficacy endpoint (change from Baseline) could not be calculated. The Applicant considers that the exclusion of these subjects is already covered in the description of the FAS in the SAP, as Baseline CSFQ-14 scores are required for calculation of the primary endpoint. In addition, these subjects were identified prior to database lock and documented as excluded from the FAS per Sponsor SOP.

The biostatistics reviewer incorporated this information into their review and found the handling of it by the Applicant to be acceptable.

**Table 3: Summary of Demographics and Baseline Characteristics (All Randomized Set; N=447)**

| | Escitalopram (N=222) | Lu AA21004 (N=225) | Total (N=447) |
|---|---|---|---|
| Age (years) (a) | | | |
| Mean | 40.2 | 39.3 | 39.8 |
| SD | 10.01 | 9.96 | 9.98 |
| Median | 41.0 | 40.0 | 40.0 |
| Minimum/Maximum | 19/55 | 19/55 | 19/55 |
| Age category [n(%)] | | | |
| ≤41 years | 112 (50.5) | 122 (54.2) | 234 (52.3) |
| >41 years | 110 (49.5) | 103 (45.8) | 213 (47.7) |
| Sex n (%) | | | |
| Male | 87 (39.2) | 97 (43.1) | 184 (41.2) |
| Female | 135 (60.8) | 128 (56.9) | 263 (58.8) |
| Ethnicity [n(%)] | | | |
| Hispanic or Latino | 36 (16.2) | 14 (6.2) | 50 (11.2) |
| Non-Hispanic and non- Latino | 186 (83.8) | 211 (93.8) | 397 (88.8) |
| Race n [n(%)] | | | |
| Caucasian (or White, including Hispanic) | 181 (81.5) | 178 (79.1) | 359 (80.3) |
| Black of African American | 35 (15.8) | 41 (18.2) | 76 (17.0) |
| Asian | 3 (1.4) | 4 (1.8) | 7 (1.6) |
| American Indian or Alaska Native | 3 (1.4) | 1 (0.4) | 4 (0.9) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.4) | 1 (0.2) |
| Height (cm) | | | |
| Mean | 170.3 | 169.6 | 169.9 |
| SD | 8.81 | 9.73 | 9.28 |
| Median | 170.0 | 169.0 | 170.0 |
| Minimum/Maximum | 150/204 | 146/198 | 146/204 |
| Weight (kg) | | | |
| Mean | 81.22 | 79.62 | 80.41 |
| SD | 16.012 | 16.202 | 16.110 |
| Median | 80.95 | 79.40 | 80.00 |
| Minimum/Maximum | 47.5/135.0 | 42.2/121.8 | 42.2/135.0 |
| BMI ($kg/m^2$) (b) | | | |
| Mean | 27.90 | 27.54 | 27.72 |
| SD | 4.440 | 4.352 | 4.395 |
| Median | 27.75 | 27.50 | 27.70 |
| Minimum/Maximum | 16.6/35.0 | 18.2/34.9 | 16.6/35.0 |
| Waist Circumference (cm) | | | |
| Mean | 93.31 | 90.85 | 92.07 |
| SD | 13.074 | 13.274 | 13.218 |
| Median | 93.65 | 92.00 | 92.40 |
| Minimum/Maximum | 58.0/129.2 | 38.0/121.0 | 38.0/129.2 |
| Smoking classification [n(%)] | | | |
| Never smoked | 126 (56.8) | 112 (49.8) | 238 (53.2) |
| Current smoker | 55 (24.8) | 69 (30.7) | 124 (27.7) |
| Ex-smoker | 41 (18.5) | 44 (19.6) | 85 (19.0) |
| Alcohol consumption [n(%)] | | | |
| Never | 65 (29.3) | 65 (28.9) | 130 (29.1) |
| Once monthly or less often | 82 (36.9) | 86 (38.2) | 168 (37.6) |
| Once a week | 37 (16.7) | 40 (17.8) | 77 (17.2) |
| 2 to 6 times per week | 36 (16.2) | 33 (14.7) | 69 (15.4) |
| Daily | 2 (0.9) | 1 (0.4) | 3 (0.7) |

Source: Summary of Demographics of Sponsor's CSR (Table 11.b, Page 67-68)
SD=standard deviation

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

In Study 318, demographics and baseline characteristics were similar between the escitalopram and vortioxetine groups. The mean age of the subjects was 39.8 years, ranging from 19 to 55 years of age. The majority of subjects were women (58.8%) and Caucasian (80.3%). Mean body mass index (BMI) was similar between treatment groups (27.90 versus 27.54 kg/m2, escitalopram and vortioxetine, respectively).

Consistent with eligibility requirements of sexual dysfunction and depressive symptoms, the mean Baseline CSFQ-14 score was 36.4, the mean MADRS total score was 8.1, and mean CGI-S score was 2.0, indicative of a population in partial/full remission at study start.

The incidence of concomitant medications that were started prior to and were ongoing at Baseline, was comparable between treatment groups (66.7% escitalopram vs 66.2% vortioxetine). The therapeutic classes with the greatest incidence overall were anti-inflammatory and antirheumatic products (16.8%), vitamins (16.3%), sex hormones and modulators of the genital system (13.6%) and lipid modifying agents (10.3%).

For concomitant medications that were started after Baseline, the therapeutic classes with the greatest incidence in the escitalopram group were analgesics (7.2%) and anti-inflammatory and antirheumatic products (5.9%) and in the vortioxetine group were analgesics (8.4%), anti-inflammatory and antirheumatic products (7.6%), and antihistamines for systemic use (5.3%).

**Efficacy Results – Primary Endpoint**

The FDA statistician, Semhar Ogbagaber, PhD, confirmed the Applicant's analyses of efficacy data. The primary endpoint was change from Baseline in the CSFQ-14 total score after 8 weeks of treatment. At Baseline, there was no difference in the CSFQ-14 total score between the escitalopram and vortioxetine groups. In the primary analysis based on MMRM, the LS mean change from Baseline in CSFQ-14 total score was 6.6 points in the escitalopram group and 8.8 points in the vortioxetine groups at Week 8. The LS mean difference of 2.2 points was statistically significant (p=0.013), demonstrating the improvement in sexual functioning for the vortioxetine group.

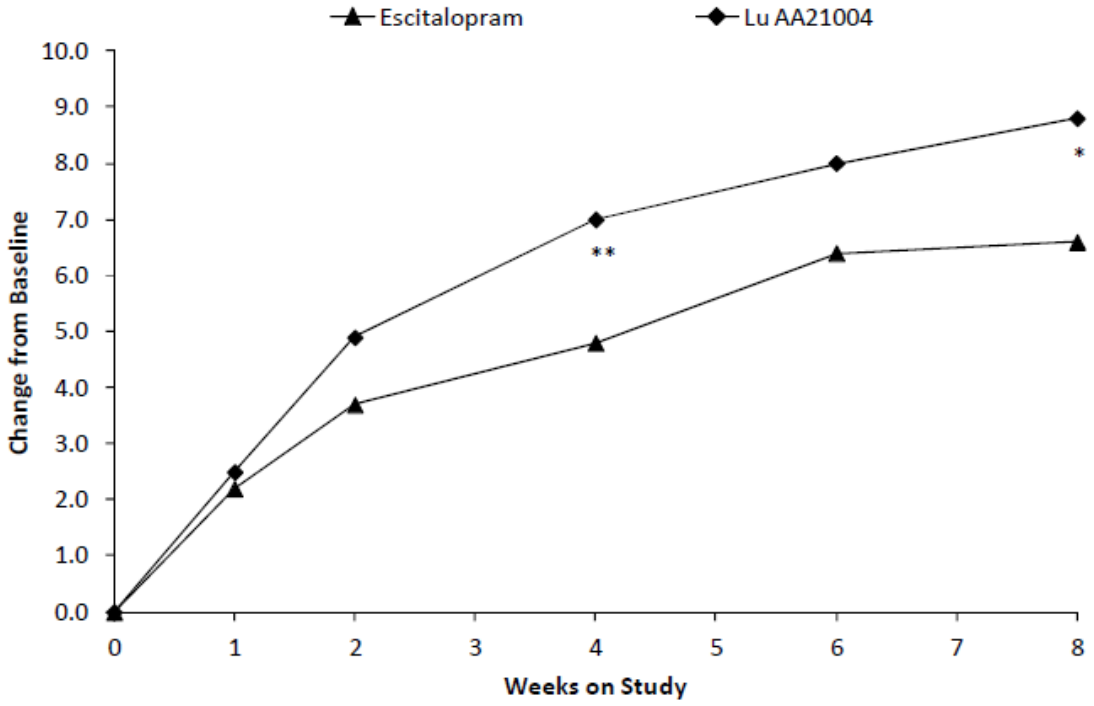
**Table 4: Change From Baseline in CSFQ-14 Total Score at Week 8 (FAS, MMRM)**

| | Escitalopram (N=207) | Lu AA21004 (N=217) |
|---|---|---|
| Baseline | | |
| N | 207 | 217 |
| LS mean ± SE (a) | 36.0 ±0.40 | 36.1 ±0.39 |
| Change from Baseline at Week 8 | | |
| N | 173 | 165 |
| Change from Baseline LS mean ± SE | 6.6 ±0.64 | 8.8 ±0.64 |
| p-value, Lu AA21004 vs Escitalopram (b) | | 0.013 |
| LS mean differences ± SE from Escitalopram (b) | | 2.2 ±0.90 |
| 95% CI for differences | | (0.48-4.02) |

Source: Table 15.2.1.1.5.
Note: Increase in CSFQ-14 total score indicates improvement.
Note: Baseline value was defined as the last observation prior to the first dose of double-blind medication.
(a) Baseline LS means and p-values were from an ANOVA model with terms for treatment and pooled center.
(b) Postbaseline LS means and p-values were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

The change from Baseline in the CSFQ-14 total score was also analyzed by study visit as a secondary endpoint. CSFQ-14 total scores increased (improved) over time in both treatment groups, with the difference between the vortioxetine and escitalopram groups reaching statistical significance favoring vortioxetine at Week 4 (p=0.004) and Week 8 (p=0.013). The LS mean difference at Week 6 (1.6 points) was close to the threshold for significance (p=0.057).

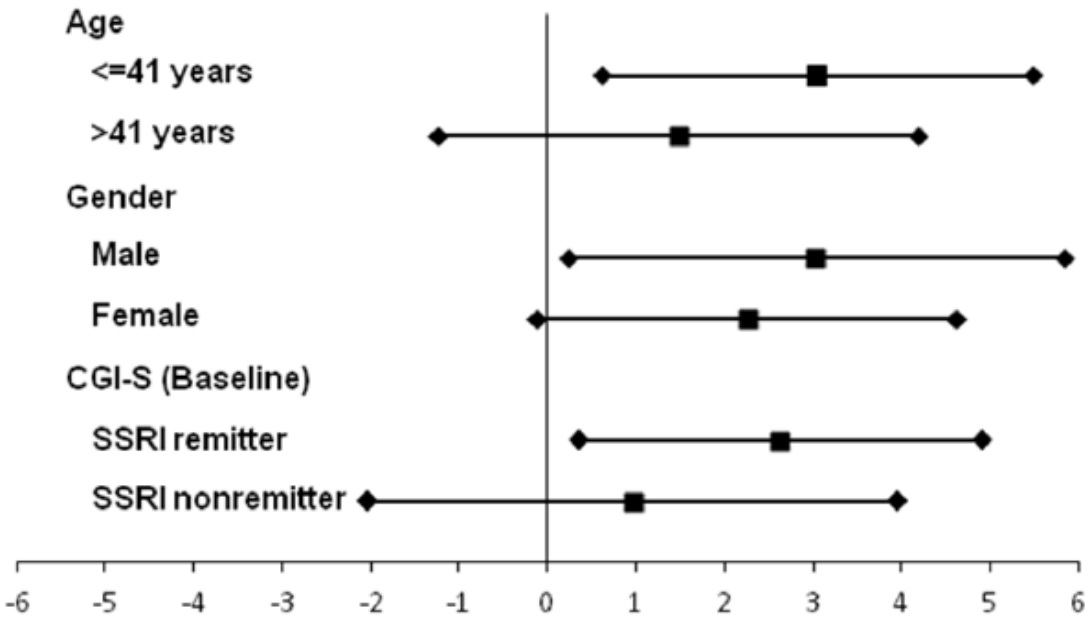
**Figure 2: Changes From Baseline in CsFQ-14 Total Score by Visit (FAS, MMRM)**




Source: Table 15.2.1.1.5.
*p<0.05 vs escitalopram, **p<0.01 vs escitalopram.
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

Subgroup analyses were conducted to examine changes from Baseline in CSFQ-14 at Week 8 by age (≤41 years or >41 years), gender (male or female) and SSRI CGI-S remitter (yes or no). The LS mean difference in CSFQ-14 at Week 8 was numerically in favor of vortioxetine vs escitalopram, reaching statically significance for subjects that were ≤41 years of age (p=0.014), male (p=0.034), and a CGI-S remitter at Baseline (p=0.024).

**Figure 3: Subgroup Analyses of Change From Baseline in CSFQ-14 Total Score At Week 8: Age, Gender, and CGI-S-Remitter (FAS, MMRM)**




Source: Table 15.2.1.4.5, 15.2.1.5.5, 15.2.1.6.5, and 15.2.1.7.5.
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.
Note: Number of subjects in each subgroup (escitalopram and Lu AA21004): ≤41 years (107 and 117); ≤41 years (100 and 100); female (129 and 126); male (78 and 91); nonremitter (77 and 74); remitter (130 and 143).

The other secondary endpoint was the number (percentage) of subjects with a shift in the CSFQ-14 total score from abnormal at Baseline to normal at each visit. While the percentage of subjects that shifted from abnormal at Baseline to normal was numerically greater in the vortioxetine group at every visit, the difference between the treatment groups did not reach the threshold for statistical significance. When the analysis was conducted using observed cases, the percentage of subjects that shifted from abnormal at Baseline to normal was significantly greater in the vortioxetine group at Week 6 (p=0.013) and Week 8 (p=0.018) vs escitalopram.

**Table 5**: **Number of Subjects With Shifts in the CSFQ-14 from Abnormal to Normal by Visit (FAS, LOCF)**

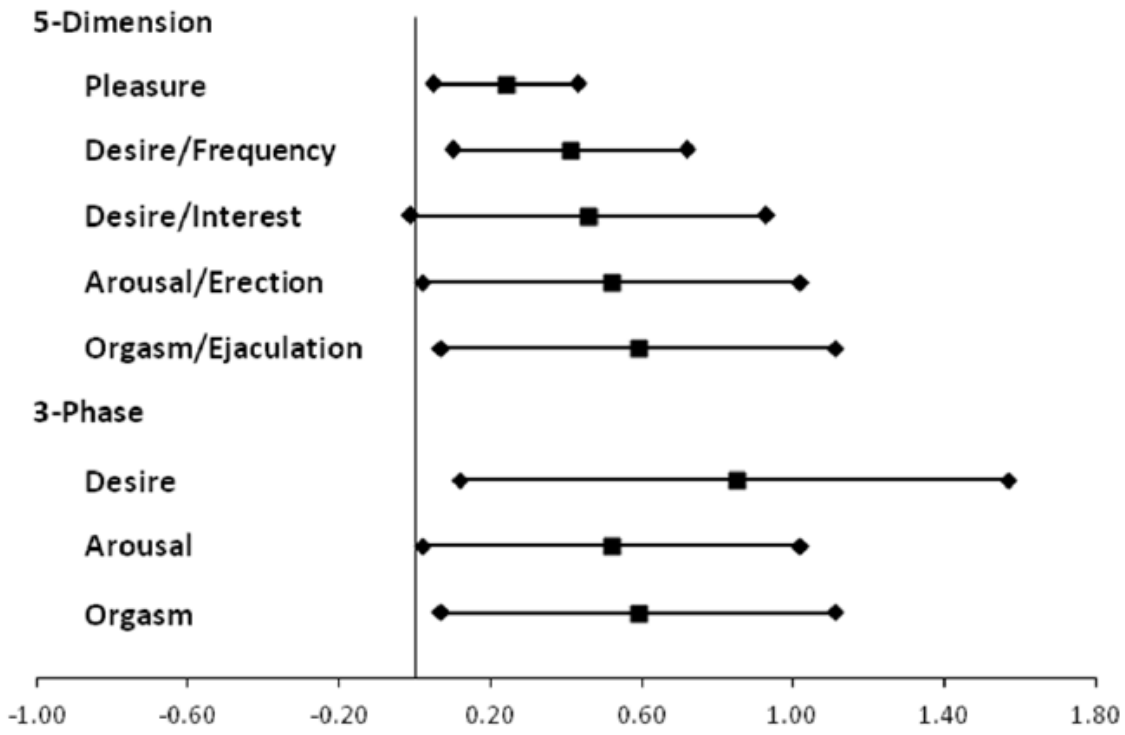
| | Escitalopram (N=207) | Lu AA21004 (N=217) |
|---|---|---|
| Week 1 | N=205 | N=213 |
| Normal at Week 1 (N [%]) | 36 (17.6) | 48 (22.5) |
| OR (a) | | 1.3445 |
| 95% CI for OR (a) | | (0.8126, 2.2244) |
| p-value (a) | | 0.249 |
| Week 2 | N=206 | N=217 |
| Normal at Week 2 (N [%]) | 63 (30.6) | 81 (37.3) |
| OR (a) | | 1.3535 |
| 95% CI for OR (a) | | (0.8887, 2.0614) |
| p-value (a) | | 0.158 |
| Week 4 | N=206 | N=217 |
| Normal at Week 4 (N [%]) | 84 (40.8) | 93 (42.9) |
| OR (a) | | 1.0753 |
| 95% CI for OR (a) | | (0.7212, 1.6033) |
| p-value (a) | | 0.722 |
| Week 6 | N=206 | N=217 |
| Normal at Week 6 (N [%]) | 93 (45.1) | 112 (51.6) |
| OR (a) | | 1.2979 |
| 95% CI for OR (a) | | (0.8728, 1.9301) |
| p-value (a) | | 0.198 |
| Week 8 | N=206 | N=217 |
| Normal at Week 8 (N [%]) | 91 (44.2) | 113 (52.1) |
| OR (a) | | 1.3735 |
| 95% CI for OR (a) | | (0.9283, 2.0322) |
| p-value (a) | | 0.112 |

Source: Table 15.2.1.15.1.
Note: Abnormal was defined as CSFQ-14 total score ≤41 for female and ≤47 for male subjects and normal was defined as CSFQ-14 total score > 41 for female and >47 for male subjects.
(a) Odds ratio, 95% confidence intervals and p-values are from logistic regression with explanatory variables for treatment and Baseline CSFQ-14 total score.

An additional endpoint was to examine the change from Baseline in CSFQ-14 subscales: 5-dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) and 3-phases of sexual functioning (desire, arousal, and orgasm/completion). The LS mean differences at Week 8 demonstrated statistically significant improvement for vortioxetine vs escitalopram for the 5-dimension subscale measures of pleasure (p=0.015), desire/frequency (p=0.010), arousal/erection (p=0.042), and orgasm (p=0.026). The LS mean difference at Week 8 for desire/interest was close to the threshold for statistical significance (p=0.058). For the 3-phases of sexual functioning, the LS mean

differences at Week 8 demonstrated statistically significant improvement in vortioxetine over escitalopram for the measures of desire (p=0.022), arousal (p=0.042), and orgasm (p=0.026).

**Figure 4**: **Changes from Baseline in CSFQ-14 Subscales: 5-Dimension and 3 Phases of Sexual Functioning at Week 8 (FAS, MMRM)**




Source: Table 15.2.1.8.5, 15.2.1.9.5, 15.2.1.10.5, 15.2.1.11.5, 15.2.1.12.5, and 15.2.1.13.5.
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.
Note: Measures of arousal/erection and orgasm on the 5-dimension subscale are the same as measures of arousal and orgasm on the 3-phases of sexual functioning.

Another additional endpoint was assessment of the percentage of responders according to the CSFQ-14 (defined as CSFQ-14 total score increase from Baseline $\geq$3) at each visit. The percentage of responders increased at each study visit in the vortioxetine group, but improvements were not significantly better than escitalopram at any of the visits, although the difference was close to the threshold of significance at Week 8 (p=0.057). When the analysis was conducted using observed cases, the percentage of responders was significantly greater in the vortioxetine vs escitalopram group at Week 8 (p=0.030).

**Table 6**: **Number of CSFQ-14 Responders by Study Visit (FAS, LOCF)**

| | Escitalopram (N=207) | Lu AA21004 (N=217) |
|---|---|---|
| Week 1 | N=206 | N=213 |
| CSFQ-14 Responders at Week 1 (N[%]) | 85 (41.3) | 95 (44.6) |
| OR (a) | | 1.1445 |
| 95% CI for OR (a) | | (0.7770, 1.6860) |
| p-value (a) | | 0.495 |
| Week 2 | N=207 | N=217 |
| CSFQ-14 Responders at Week 2 (N[%]) | 116 (56.0) | 136 (62.7) |
| OR (a) | | 1.3203 |
| 95% CI for OR (a) | | (0.8949, 1.9479) |
| p-value (a) | | 0.161 |
| Week 4 | N=207 | N=217 |
| CSFQ-14 Responders at Week 4 (N[%]) | 133 (64.3) | 150 (69.1) |
| OR (a) | | 1.2462 |
| 95% CI for OR (a) | | (0.8314, 1.8678) |
| p-value (a) | | 0.287 |
| Week 6 | N=207 | N=217 |
| CSFQ-14 Responders at Week 6 (N[%]) | 146 (70.5) | 157 (72.4) |
| OR (a) | | 1.0920 |
| 95% CI for OR (a) | | (0.7162, 1.6649) |
| p-value (a) | | 0.683 |
| Week 8 | N=207 | N=217 |
| CSFQ-14 Responders at Week 8 (N[%]) | 137 (66.2) | 162 (74.7) |
| OR (a) | | 1.5048 |
| 95% CI for OR (a) | | (0.9886, 2.2905) |
| p-value (a) | | 0.057 |

Source: Table 15.2.1.16.1.
Note: Responder is defined as a subject with CSFQ-14 total score increased from Baseline>=3.
(a) Odds ratio, 95% confidence intervals and p-values are from logistic regression with explanatory variables for treatment and Baseline CSFQ-14 total score.

The changes from Baseline in the MADRS, CGI-S, CGI-I, and POMS at each visit were additional endpoints. The MADRS total score, CGI-S, CGI-I, and POMS total score were maintained or improved slightly over the course of treatment, with similar responses observed between the escitalopram and vortioxetine treatment groups at Week 8.

*Dropouts*

Missing values for postbaseline assessments were imputed by the last observed value immediately prior to the LOCF. This rule did not apply to individual items in a multiple item assessment. LOCF was used after imputation, i.e., LOCF values were not used for calculations of

subscale/scale scores. If >20% of items were missing the total score was set to missing. Worsening in sexual functioning associated with the treatment therapy may potentially cause some subjects to dropout from the study. Therefore, the primary analysis was based on a Missing at Random assumption. As a sensible sensitivity analysis, the pattern mixture models were performed using standard SAS STAT procedures. This method used sequential regression and multiple imputation methodology to impute missing values after subjects' discontinuation from the study.

**Data Quality and Integrity**

The statistical reviewer found the quality and integrity of the submitted data satisfactory and acceptable for the review analysis.

**Efficacy Results – Secondary and other relevant endpoints**

The statistical reviewer confirmed analysis of the CSFQ-14 subscales. The secondary endpoint—CSFQ-14 changes at each visit assessed—was nominally significantly different favoring vortioxetine at Weeks 4 and Week 8. The mean difference at Week 6 (1.6 points) was close to the threshold for significance (p=0.057).] The number of subjects in Study 318 with a shift in the CSFQ-14 from abnormal at Baseline (mean 36.4; range 21, 47) to normal (defined as >41 for women and >47 for men) was numerically greater in the vortioxetine group at every visit, although the difference did not reach significance. In Study 318, nominally significantly more vortioxetine subjects showed a clinically relevant improvement (responder) in CSFQ-14 total scores (increase of $\geq$3 points) favoring vortioxetine versus escitalopram.

The significantly favorable results for vortioxetine versus escitalopram on 4 of 5 dimensions and on all 3 phases of sexual functioning assessed by the CSFQ-14 support the clinical relevance of the primary analysis. Furthermore, TEAEs of sexual dysfunction were spontaneously reported only by subjects in the escitalopram group. These differential effects on TESD were demonstrated while maintaining the antidepressant efficacy. Both vortioxetine and escitalopram had similar clinical antidepressant efficacy profiles in this study.

**Dose/Dose Response**

Study 318 was conducted in the relevant patient population and assessed flexible doses of 10 and 20 mg vortioxetine versus flexible doses of 10 and 20 mg escitalopram. The majority of subjects received the 20 mg dose of escitalopram (71.9%) or the 20 mg dose of vortioxetine (65.6%) and vortioxetine was superior to escitalopram in improving the TESD caused by the prior antidepressant.

## 6.2. Study 4001

### 6.2.1. Study Design

**Overview and Objective**

Study 4001 was conducted with healthy volunteers, with no sexual dysfunction, and eliminated the confounding effects on sexual function that would be expected in a study with acutely depressed patients. The effect on sexual functioning of vortioxetine 10 mg and 20 mg was compared with paroxetine 20 mg and placebo. The SSRI paroxetine was chosen as the active comparator in Study 4001 as it is still prescribed and is known to cause sexual dysfunction, thereby allowing for validation of the study (i.e., the level of sexual dysfunction with paroxetine is worse than that of placebo). Per the Applicant, the dose of 20 mg paroxetine was selected for Study 4001 as it is the recommended starting dose, is considered to have the lowest incidence of TESD, and would provide a conservative comparison versus vortioxetine.

**Trial Design**

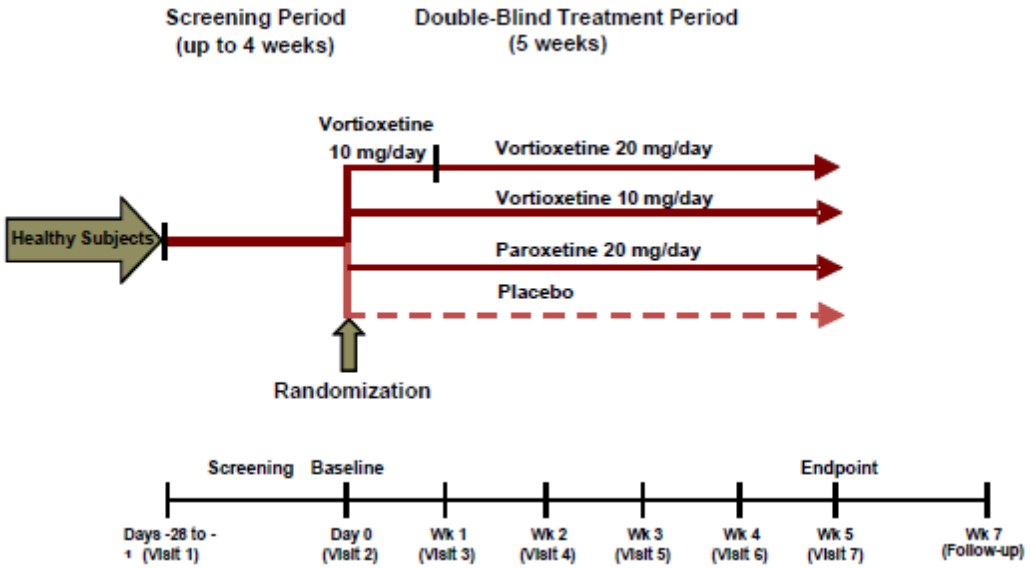
Study 4001 was a phase 4, fixed-dose, double-blind study in 16 US sites comparing vortioxetine vs paroxetine on sexual function in healthy men and women, aged between 18 and 55 years, after five weeks of treatment. Subjects had no sexual dysfunction at study start (defined as a CSFQ-14 total score >41 for women or >47 for men), were in a steady relationship for $\geq$3 months, and were currently sexually active $\geq$2 times per week. Subjects were stratified by gender and enrolled in approximately equal proportions. Subjects were randomized equally to 4 arms: vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, placebo.

Subjects allocated to vortioxetine 20 mg, initiated treatment at 10 mg/day for the first week. Subsequently, the dose was increased to 20 mg/day and remained at 20 mg/day until study completion. Subjects allocated to vortioxetine 10 mg, initiated treatment at 10 mg/day and remained at 10 mg/day until study completion. Subjects allocated to paroxetine 20 mg, initiated treatment at 20 mg/day and remained at 20 mg/day until study completion. Subjects were instructed to take their first dose of study drug the day after Baseline on Day 1, preferably in the morning. After randomization, subjects were seen for weekly visits and received a follow-up safety contact by telephone two weeks after the end of double-blind treatment.

Sexual functioning was assessed at each study visit using the CSFQ-14 (primary variable). The PGI-I scale was administered at each study visit except at Screening and Baseline. Signs of suicidal risk were assessed at each study visit using the Columbia-Suicide Severity Rating Scale (C-SSRS). A total of six sparse pharmacokinetic (PK) samples (trough samples) were collected to measure plasma vortioxetine or paroxetine concentrations at Weeks 3, 4, and 5/ET (two samples at each time point). A pharmacogenomic (PGx) blood sample for deoxyribonucleic acid (DNA) isolation was collected predose at Baseline (Day 0), and two PGx blood samples for

ribonucleic acid (RNA) isolation were collected predose at Baseline (Day 0) and also at Week 5/ET.

**Figure 5: Schematic of Study Design 4001**




**Study Endpoints**

In Study 4001, the mean change from Baseline in the CSFQ-14 total score after five weeks of treatment was the primary endpoint with the difference for vortioxetine vs paroxetine as the primary comparison.

Secondary endpoints included the change from Baseline in CSFQ-14 total score difference for vortioxetine vs paroxetine, paroxetine vs placebo, and vortioxetine vs placebo at each visit assessed; change from Baseline in CSFQ subscales 5-dimensions and 3-phases of sexual functioning; and percentage of subjects meeting criteria for sexual dysfunction at any visit.

Additional endpoint analyses using the CSFQ-14 in Study 4001 included: percentage of subjects meeting criteria for sexual dysfunction at any two consecutive visits; time to sexual dysfunction; percentage of subjects with a shift from normal at Baseline to abnormal (sexual dysfunction); percentage of subjects showing decreased sexual function (i.e., negative responders with CSFQ-14 total score decrease from Baseline $\geq$3), and the self-reported PGI-I.

**Statistical Analysis Plan**

Mean change from Baseline in the CSFQ-14 total score difference for vortioxetine versus

paroxetine after five weeks of treatment was the primary endpoint. The primary analysis was based on analysis of covariance (ANCOVA) using the last observation carried forward technique, with treatment, pooled center, and sex as fixed factors, and baseline CSFQ-14 total score as covariate. The comparisons were between each vortioxetine dose (10 or 20 mg) and paroxetine, and both statistical tests were 2-sided.

The primary efficacy was conducted on the FAS population. The FAS includes subjects who were randomized, received at least one dose of study drug, and had at least one valid post-baseline value for assessment of primary efficacy. The FAS population included 348 subjects who met the eligibility criteria and were randomized to placebo (89), paroxetine 20 mg/day (83), vortioxetine 10 mg/day (85), or vortioxetine 20 mg/day (91).

The Holm-Bonferroni was used to adjust for multiplicity and control type I error. If the *smaller of the two p-values* is < 0.025, significance is obtained for the associated dose and the other dose is subsequently evaluated at 0.05 significance level. Paroxetine is compared to placebo for assay sensitivity purposes.

**Protocol Amendments**

The original protocol was issued on July 12, 2016, and was amended once with minor changes on January 10, 2017.

### 6.2.2. Study Results

**Compliance with Good Clinical Practices**

This study was conducted in compliance with the institutional review board (IRB) regulations stated in Title 21 of the United States (US) Code of Federal Regulations (CFR), Part 56, Good Clinical Practice (GCP) regulations and guidelines, and all applicable local regulations.

**Financial Disclosure**

The Applicant provided a table of clinical investigators and all the investigators were marked as Yes for Certification and No for disclosure. This was a randomized, blinded trial with objective endpoints and I have no reason to be concerned that financial interests affected the integrity of the data in this study.

**Patient Disposition**

A total of 361 subjects were randomized to the 5-week treatment period; four did not receive study medication; 290 subjects (80.3%) completed study drug; 288 (79.8%) completed all study visits.

A total of 348 subjects (96.4% of those randomized) were included in the FAS, which included 89 subjects in the placebo group, 83 subjects in the paroxetine group, 85 subjects in the vortioxetine 10 mg group, and 91 subjects in the vortioxetine 20 mg group. Thirteen randomized subjects (3.6%) were excluded from the FAS: three in the placebo group, two in the paroxetine group, six in the vortioxetine 10 mg group, and two in the vortioxetine 20 mg group, because they did not have at least one postbaseline CSFQ-14 assessment or were not treated. The study drug blind was broken for two subjects. For one subject in the paroxetine group, the blind was broken on Day 8 because of pregnancy. For one subject in the vortioxetine 10 mg group, the blind was broken on Day 36 because of a positive HCG test result.

**Protocol Violations/Deviations**

At least one significant protocol deviation was reported for 41 subjects (11.4%) overall, including 16.5% in the vortioxetine 10 mg group and 8.6% to 10.6% in the other groups.
At least one major protocol violation was reported for 37 subjects (10.2%) overall, including 14.3% in the vortioxetine 10 mg group and 7.6% to 9.7% in the other groups. Notable violations related to the interpretation of results were as follows:

- Six subjects (6.6%) in the vortioxetine 10 mg group, two subjects (2.2%) in the placebo group, and one subject (1.2%) in the paroxetine group had no evaluable postbaseline assessment of CSFQ-14.
- Ten subjects (2.8%) overall had study drug exposure <7 days (2-3 subjects in each group).
- Eight subjects (2.2%) overall had behaviors consistent with noncompliance per (b) (4) (including four subjects [4.3%] in the vortioxetine 20 mg group)
- Nine subjects (2.5%) overall had low study drug compliance per the major protocol deviation page.

Significant protocol deviations recorded by sites were reviewed, and any subjects with major violations that might impact the analysis were identified for removal from the FAS as part of the definition of the PPS before database lock. Analysis of the PPS population did not alter the conclusions of the primary analysis. Identification of protocol deviations due to noncompliance did not include results of the PK assessments, as this was evaluated post database lock, in accordance with the SAP.

**Table of Demographic Characteristics**

The average age of patients was 28.4 years, ranging from 18 to 40 years. Overall, treatment groups were comparable in baseline characteristics. The majority of participants were whites (57.3%), and the overwhelming majority were of Non-Hispanic or Latino origin (76.7%).

**Table 7: Demographic and Baseline Characteristics (All Randomized Subjects)**

| | Placebo (N=92) | Paroxetine (N=85) | Vortioxetine 10 mg (N=91) | Vortioxetine 20 mg (N=93) | Total (N=361) |
|---|---|---|---|---|---|
| Age (years) (a) | | | | | |
| Mean (SD) | 27.8 (5.45) | 28.9 (5.96) | 28.1 (5.56) | 28.8 (5.91) | 28.4 (5.72) |
| Median | 27.0 | 28.0 | 28.0 | 28.0 | 28.0 |
| Minimum, maximum | 18, 40 | 18, 40 | 18, 40 | 18, 40 | 18, 40 |
| p-value | | | | | 0.469 |
| Median age categories (N [%]) | | | | | |
| ≤28 years | 51 (55.4) | 43 (50.6) | 52 (57.1) | 47 (50.5) | 193 (53.5) |
| >28 years | 41 (44.6) | 42 (49.4) | 39 (42.9) | 46 (49.5) | 168 (46.5) |
| p-value | | | | | 0.774 |
| Gender (n [%]) | | | | | |
| Male | 46 (50.0) | 43 (50.6) | 47 (51.6) | 49 (52.7) | 185 (51.2) |
| Female | 46 (50.0) | 42 (49.4) | 44 (48.4) | 44 (47.3) | 176 (48.8) |
| p-value | | | | | 0.947 |
| Ethnicity (n [%]) | | | | | |
| Hispanic or Latino | 21 (22.8) | 20 (23.5) | 25 (27.5) | 18 (19.4) | 84 (23.3) |
| Non-Hispanic and Latino | 71 (77.2) | 65 (76.5) | 66 (72.5) | 75 (80.6) | 277 (76.7) |
| p-value | | | | | 0.539 |
| Race (n [%]) | | | | | |
| American Indian or Alaska Native | 0 | 0 | 3 (3.3) | 0 | 3 (0.8) |
| Asian | 7 (7.6) | 3 (3.5) | 2 (2.2) | 3 (3.2) | 15 (4.2) |
| Black or African American | 30 (32.6) | 29 (34.1) | 31 (34.1) | 34 (36.6) | 124 (34.3) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (1.2) | 0 | 0 | 1 (0.3) |
| White | 51 (55.4) | 49 (57.6) | 52 (57.1) | 55 (59.1) | 207 (57.3) |
| Multiracial (b) | 4 (4.3) | 3 (3.5) | 3 (3.3) | 1 (1.1) | 11 (3.0) |
| p-value | | | | | 0.237 |
| Race categories (n [%]) | | | | | |
| White | 51 (55.4) | 49 (57.6) | 52 (57.1) | 55 (59.1) | 207 (57.3) |
| Non-White | 41 (44.6) | 36 (42.4) | 39 (42.9) | 38 (40.9) | 154 (42.7) |
| p-value | | | | | 0.920 |

| | | | | | |
|---|---|---|---|---|---|
| Height (cm) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 172.0 (10.75) | 172.1 (10.59) | 171.3 (9.14) | 170.8 (10.04) | 171.5 (10.12) |
| Median | 173.0 | 173.0 | 173.0 | 170.0 | 172.0 |
| Minimum, maximum | 151, 201 | 152, 195 | 152, 193 | 149, 199 | 149, 201 |
| p-value | | | | | 0.827 |
| Weight (kg) (c) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 76.49 (15.523) | 80.19 (16.808) | 78.67 (14.850) | 75.12 (13.282) | 77.56 (15.19 |
| Median | 76.55 | 79.30 | 78.00 | 76.00 | 77.30 |
| Minimum, maximum | 51.9, 112.5 | 42.2, 125.0 | 49.9, 118.8 | 47.3, 108.4 | 42.2, 125.0 |
| p-value | | | | | 0.131 |
| BMI ($kg/m^2$) (d) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 25.72 (3.925) | 26.91 (4.245) | 26.77 (4.306) | 25.70 (3.668) | 26.26 (4.062 |
| Median | 24.59 | 26.62 | 26.53 | 25.34 | 25.86 |
| Minimum, maximum | 18.4, 34.0 | 18.3, 35.0 | 18.3, 34.9 | 18.2, 34.8 | 18.2, 35.0 |
| p-value | | | | | 0.075 |
| Smoking classification (n [%]) | | | | | |
| Subject has never smoked | 73 (79.3) | 70 (82.4) | 70 (76.9) | 77 (82.8) | 290 (80.3) |
| Subject is a current smoker | 7 (7.6) | 2 (2.4) | 4 (4.4) | 7 (7.5) | 20 (5.5) |
| Subject is an ex-smoker | 12 (13.0) | 13 (15.3) | 17 (18.7) | 9 (9.7) | 51 (14.1) |
| p-value | | | | | 0.383 |
| Female reproductive status (n [%]) | | | | | |
| Postmenopausal | 0 | 0 | 0 | 0 | 0 |
| Surgically sterile | 3 (3.3) | 4 (4.7) | 2 (2.2) | 3 (3.2) | 12 (3.3) |
| Female of childbearing potential | 43 (46.7) | 38 (44.7) | 42 (46.2) | 41 (44.1) | 164 (45.4) |
| NA/subject is male | 46 (50.0) | 43 (50.6) | 47 (51.6) | 49 (52.7) | 185 (51.2) |
| p-value | | | | | 0.986 |
| Duration of menstruation (days) | | | | | |
| N | 45 | 42 | 44 | 43 | 174 |
| Mean (SD) | 4.9 (1.36) | 4.4 (1.27) | 4.2 (1.27) | 4.6 (1.37) | 4.5 (1.33) |
| Median | 5.0 | 4.0 | 4.0 | 5.0 | 4.0 |
| Minimum, maximum | 3, 7 | 2, 7 | 0, 7 | 0, 7 | 0, 7 |
| p-value | | | | | 0.087 |
| Duration of menstrual cycle (days) | | | | | |
| N | 45 | 42 | 44 | 43 | 174 |
| Mean (SD) | 28.9 (5.35) | 28.3 (2.56) | 28.2 (7.07) | 28.0 (6.94) | 28.4 (5.75) |
| Median | 28.0 | 28.0 | 28.0 | 28.0 | 28.0 |
| Minimum, maximum | 21, 60 | 21, 35 | 0, 60 | 0, 60 | 0, 60 |
| p-value | | | | | 0.960 |

Source: Table 11.c of Sponsor's Clinical Study Report (Page 62-64)
SD=standard deviation

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

No statistically significant differences in baseline CSFQ-14 total scores were seen between treatment groups.

Medical histories by preferred term were reported by <5% in any treatment group, except for asthma, which was reported in 5.5% of subjects in the vortioxetine 10 mg group. There were no clinically significant differences between groups with regards to the proportion of reported medical histories by preferred term.

The most frequently (>5%) reported concurrent conditions by SOC were: Immune System Disorders (59 subjects [16.3%]) (including seasonal allergy and drug hypersensitivity); Metabolism and Nutrition Disorders (19 subjects [5.3%]) (including overweight and obesity), and Nervous System Disorders (52 subjects [14.4%]) (including tension headache and headache). The proportion of subjects who reported the concurrent condition Immune System Disorders was higher in the vortioxetine 10 mg (19 subjects [20.9%]) group compared with the placebo (15 subjects [16.3%]), paroxetine (11 subjects [12.9%]) and vortioxetine 20 mg (14 subjects [15.1%]) groups. There were no clinically significant differences (>5%) between the groups with regards to the proportion of subjects who reported the concurrent condition Metabolism and Nutrition Disorders or Nervous System Disorders.

A total of 40 subjects (11.1%) reported any medication history. There were no clinically significant differences (<5%) between the groups with regards to medication history: placebo (eight subjects [8.7%]), paroxetine (12 subjects [14.1%]), vortioxetine 10 mg (10 subjects [11.0%]) and vortioxetine 20 mg (10 subjects [10.8%]). Ibuprofen was the only medication that was taken by >5% of subjects in any group: placebo (five subjects [5.4%]), paroxetine (seven subjects [8.2%]), vortioxetine 10 mg (4 subjects [4.4%]) and vortioxetine 20 mg (eight subjects [8.6%]).

Approximately a third of the study population (126 subjects [34.9%]) reported any concomitant medications that were started before and were ongoing at Baseline. Vitamins not otherwise specified (NOS) and paracetamol were the only concomitant medications that were started before and were ongoing at Baseline that were reported by >5% of subjects in any group.

Ibuprofen was the only concomitant medication that was started after Baseline or at the last dose by >5% of subjects in any group.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

In this trial, study drug compliance was assessed by tablet count and use of (b) (4). In addition, PK sampling was conducted at Weeks 3, 4, and 5/ET to measure plasma concentrations of study drug in the active dose arms. Overall compliance by tablet count was

close to 100%; 98.4% the placebo group, 98.9% in the paroxetine group, 98.9% in the vortioxetine 10 mg group, and 98.0% in the vortioxetine 20 mg group. Overall compliance with study drug as assessed by visual confirmation using the [redacted] (b) (4) was lower compared with tablet count at 92.6% (357 randomized subjects). For each of the groups, compliance was: placebo 93.2% (N=91), paroxetine: 91.9% (N=84), vortioxetine 10 mg 91.5% (N=91), and vortioxetine 20 mg 93.9% (N=91). Review of the PK data indicated that 41 subjects (11.5% of the total safety analysis set) had drug concentrations BLOQ at one or more time points assessed. Note that subjects in the placebo arm could not be evaluated, and the percentage increases to 15.4% if only active arms are reflected in the calculation. Of the active arms, the greatest numbers of subjects excluded were in the paroxetine arm (27.4%) versus the lowest in the vortioxetine 10 mg arm (6.6%). Of the 41 subjects with drug concentrations BLOQ, 31 completed the study, six discontinued because of protocol deviations including noncompliance, two because of a TEAE (none for TESD), one who was lost to follow-up, and one for other reasons.

**Efficacy Results - Primary Endpoint**

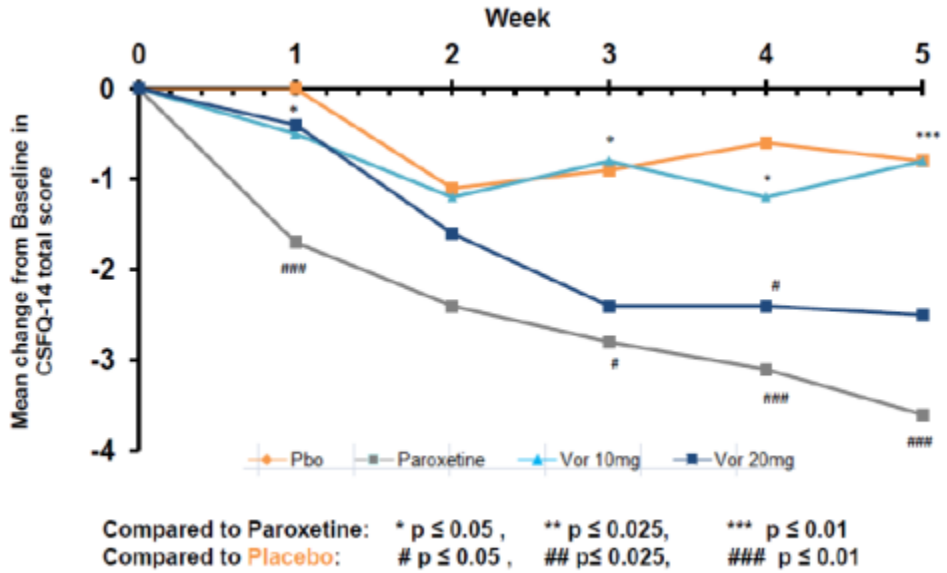
The primary efficacy analysis was the change from Baseline in the CSFQ-14 total score difference for vortioxetine versus paroxetine after five weeks of treatment. Vortioxetine 10 mg was associated with statistically significantly less TESD than paroxetine (p=0.009), with a mean CSFQ-14 difference of 2.74 points at Week 5 in healthy adults. Vortioxetine 10 mg was not significantly different from placebo. Vortioxetine 20 mg was associated with numerically less TESD compared with paroxetine at Week 5, although the difference of 1.05 points was not statistically significant. The CSFQ-14 total score for vortioxetine 20 mg was numerically greater than for placebo but not significantly different from placebo. Assay sensitivity was demonstrated by the significantly greater decrease in CSFQ-14 of -2.77 points for paroxetine compared with placebo (p=0.007).

**Table 8: Change From Baseline in CSFQ-14 Total Score at Week 5 (FAS, ANCOVA, LOCF)**

| | Placebo (N=89) | Paroxetine 20 mg/day (N=83) | Vortioxetine 10 mg/day (N=85) | Vortioxetine 20 mg/day (N=91) |
|---|---|---|---|---|
| Baseline | | | | |
| N | 89 | 83 | 85 | 91 |
| LS mean (SE) | 59.25 (0.566) | 59.27 (0.584) | 58.56 (0.578) | 59.43 (0.560) |
| Change from Baseline to Week 5 | | | | |
| N | 89 | 83 | 85 | 91 |
| LS mean (SE) | -0.79 (0.734) | -3.56 (0.758) | -0.82 (0.752) | -2.51 (0.727) |
| **Primary Efficacy Analysis** | | | | |
| Vortioxetine vs paroxetine | | | | |
| LS mean difference (SE) | | | 2.74 (1.040) | 1.05 (1.017) |
| 95% CI for diff. in LS means | | | (0.69, 4.78) | (-0.95, 3.05) |
| p-value | | | 0.009 | 0.303 |
| **Secondary Efficacy Analysis** | | | | |
| Active drug vs placebo | | | | |
| LS mean difference (SE) | | -2.77 (1.024) | -0.03 (1.018) | -1.72 (1.000) |
| 95% CI for diff. in LS means | | (-4.78, -0.75) | (-2.03, 1.97) | (-3.68, 0.25) |
| p-value | | 0.007 | 0.977 | 0.087 |

Source: Table 15.2.1.2.1.1.
Baseline value is defined as the last observation before the administration of study drug.
Baseline LS means and p-values were obtained using an ANOVA model with terms for treatment, pooled center, and gender.
Postbaseline LS means and p-values were obtained using ANCOVA model with treatment, pooled center, and gender as fixed factors and with baseline CSFQ-14 total score as a covariate.

**Figure 6: Mean Change from Baseline in CSFQ-14 Total Score at Each Visit (FAS, LOCF)**




Source: Figure 11.f of Sponsor's Clinical Study Report (Page 85). Using Holm-Bonferroni method the smallest p-value < 0.025; other p-values are compared against 0.05.

The biostatistics reviewer confirmed the Applicant's efficacy findings. Using ANCOVA (LOCF), vortioxetine 10 mg/day was shown to be associated with statistically significantly less TESD than paroxetine 20 mg/day in the mean change from baseline in CSFQ-14 at Week 5 (p = 0.009). The least square mean treatment difference was 2.74 points.

The change from baseline in CSFQ-14 total score vortioxetine 20 mg/day group did not separate statistically significantly from paroxetine 20 mg/day whether adjusting for multiplicity or not (LS Mean = 1.05; nominal p = 0.303).

**Data Quality and Integrity - Reviewers' Assessment**

The statistical reviewer found the quality and integrity of the submitted data satisfactory and acceptable for the review analysis.

**Efficacy Results - Secondary and other relevant endpoints**

No key secondary endpoints were specified.
Secondary endpoints included:

- Change from Baseline in the CSFQ-14 total score difference for vortioxetine versus paroxetine at each visit assessed.
- Change from Baseline in CSFQ-14 total score difference for paroxetine versus placebo at

each visit assessed.

- Change from Baseline in CSFQ-14 total score difference for vortioxetine versus placebo at each visit assessed.
- Percentage of subjects meeting criteria for sexual dysfunction (i.e., CSFQ-14 total score $\leq$47 for men and $\leq$41 for women) at any visit during the 5-week double-blind Treatment Period.
- Change from Baseline in CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) and 3 phases of the sexual response cycle (desire, arousal, and orgasm/completion) at each visit assessed.

Paroxetine was associated with statistically significantly greater TESD (lower CSFQ-14 score) than vortioxetine 10 mg and placebo at Weeks 1, 3, 4, and 5. Results for vortioxetine 10 mg were similar to those for placebo. Vortioxetine 20 mg followed a trend from Week 2 of TESD greater than vortioxetine 10 mg and placebo, but less than paroxetine.

Few subjects shifted from normal sexual function to abnormal (defined as CSFQ-14 total score $\leq$47 for men and $\leq$41 for women). The mean Baseline CSFQ-14 total score for all subjects was 59.3 points (range 42, 70), requiring large decreases in the total score for most to meet the criteria for sexual dysfunction. Only three subjects in placebo, eight in paroxetine, five in vortioxetine 10 mg, and nine subjects in vortioxetine 20 mg met the CSFQ-14 criterion for sexual dysfunction at Week 5 in the FAS. The numbers of subjects who shifted to sexual dysfunction during the study were too small to allow drawing distinctions between treatment groups.

There were no significant differences between vortioxetine (10 mg or 20 mg) versus paroxetine in the numbers of subjects who met criteria for sexual dysfunction at Week 5, at any visit, or at two consecutive visits (FAS).

Sexual dysfunction was also analyzed by determining negative response, defined as a decrease from Baseline CSFQ-14 total score $\geq$3 points. The number and percentage of vortioxetine 10 mg subjects with sexual dysfunction at any visit were nominally significantly lower compared with paroxetine (four subjects, 4.9% versus 12 subjects, 16.2%, vortioxetine 10 mg and paroxetine, respectively, p=0.022). Vortioxetine 20 mg had fewer subjects with sexual dysfunction at two consecutive visits compared with paroxetine (four subjects, 5.1% versus eight subjects, 13.3%; vortioxetine 20 mg and paroxetine, respectively), although the difference did not reach statistical significance.

Change from Baseline at Week 5 demonstrated nominally significant improvement favoring vortioxetine 10 mg versus paroxetine in the 3-phases of sexual functioning: desire score (p=0.010), arousal score (p=0.020), and orgasm/completion/ejaculation score (p=0.022). For all of the 5-dimensions of sexual functioning, mean differences demonstrated nominally significant

improvement favoring vortioxetine 10 mg over paroxetine for pleasure (p=0.009), desire/frequency (p=0.011), desire/interest (p=0.026), arousal/erection (p=0.020), and orgasm (p=0.022). Vortioxetine 20 mg changes from Baseline were numerically superior to paroxetine in the 3-phases and 5-dimensions of sexual functioning, but mean differences from paroxetine never reached statistical significance.

The incidence of spontaneously reported sexual dysfunction TEAEs was highest in the paroxetine group (35.7%) and lowest in the placebo group (17.6%); the incidence was 19.8% in the vortioxetine 20 mg group and 25.3% in the vortioxetine 10 mg group. There were no withdrawals because of a sexual dysfunction TEAE.

**Dose/Dose Response**

In this study of healthy subjects, dose response was examined in relation to TESD and showed that the 10 mg dose of vortioxetine had less TESD than the 20 mg dose. Although 20 mg of vortioxetine is the target dose in treating MDD, lowering the dose to address adverse effects is acceptable.

**Additional Analyses Conducted on the Individual Trial**

The statistical reviewer conducted exploratory subgroup analysis by race, gender and age according to the respective primary efficacy analyses models specified. Age subgroup is categorized using a median cutoff. Whites had larger numerical improvement in TESD than non-whites in vortioxetine groups compared to paroxetine. Subjects with median age > 28 years of age and men had numerically larger effect in vortioxetine 10 mg versus paroxetine.

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

In both studies, the primary endpoint for assessment of TESD was the CSFQ-14 total score change from baseline, vortioxetine vs the active comparator. This endpoint is discussed in detail earlier in this review. The studies were not pooled because of the different populations, one of healthy subjects with no depression or sexual dysfunction and one of patients with MDD who had TESD.

# 8. Review of Safety

## 8.1. Safety Review Approach

This submission rests on the Agency's previous safety findings. The safety data from these two sexual dysfunction trials is consistent with vortioxetine's safety profile and the current label.

## 8.2. Review of the Safety Database

Not applicable.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Categorization of Adverse Events

In Study 318, medical history and concurrent medical conditions were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. In Study 4001, medical history and concurrent medical conditions were coded using MedDRA version 20.0. I looked at a random sample of AEs in both studies and the coding appeared appropriate.

### 8.3.2. Deaths

No deaths occurred in either study.

### 8.3.3. Serious Adverse Events

No serious adverse events (SAEs) occurred in Study 4001.

In Study 318, five SAEs occurred in three patients (1.3%) on vortioxetine. None of these SAEs gave me cause for concern.

Study 318 Narratives of Serious Adverse Events
**Subject** (b) (6)**:** A 41-year-old, Caucasian female with a relevant medical history of smoking, angina pectoris, coronary artery disease, hypertension, a family history of heart disease, and a body mass index of 32.3 kg/m(2) experienced angina and was hospitalized 13 days after the initiation of blinded study medication. The subject was discharged from the hospital the next day and the event was considered resolved on that same day. Study medication was permanently discontinued after that day. The investigator's causality assessment to study medication is not related.

Ten days after the discontinuation of blinded study medication, the subject was hospitalized for exacerbation of depression. While in the hospital the subject disclosed that she had bipolar depression (an exclusionary condition for the 318 protocol). The investigator's causality

assessment to study medication is not related.
**Subject** (b) (6) A 49-year-old Caucasian male with a relevant medical history of major depressive disorder (1988), sleep apnea, suicidal attempt by overdose (1988), traumatic sexual experience during childhood, and sulfa allergy was started on blinded study drug on (b) (6) (b) (6) and completed on (b) (6). The subject was administered one-week taper-down medication from (b) (6) to (b) (6). On (b) (6), nine days after the last dose of blinded study drug, the subject experienced a non-serious intentional drug overdose of Cipralex. During the safety follow-up call, the subject indicated that he had an increase in depression and anxiety and increased his dose of Cipralex from 10 mg to 20 mg. The investigator assessed the event as not related to the study medication. On (b) (6), 18 days after the last dose of blinded study drug, the subject experienced an increase in depression and an increase in anxiety, both moderate in intensity. The subject was subsequently hospitalized on (b) (6). During the subject's stay in the hospital, numerous medication changes were made. The subject was transferred to the mood disorders unit at a different facility on (b) (6), for longer hospitalization and treatment adjustment. On (b) (6), the subject left the hospital against advice and would seek treatment as an outpatient. The investigator's causality assessment to study drug is not related for all events.

**Subject** (b) (6): a 43-year-old, Hispanic male subject with no relevant medical history was hospitalized and diagnosed with kidney stones 46 days after the initiation of blinded study drug. He was discharged the next day from the hospital and was withdrawn from the study. The investigator's causality assessment to study drug is possibly related.

### 8.3.4. Dropouts and/or Discontinuations Due to Adverse Effects

In Study 318, 22% of subjects discontinued from the study for any reason (vortioxetine 25% and escitalopram 19%). Discontinuations primarily due to a treatment-emergent adverse event (TEAE) occurred in 14/222 (6.3%) escitalopram subjects and 20/225 (8.9%) vortioxetine subjects. The TEAE that caused the greatest number of discontinuations was nausea, which resulted in discontinuation for 4.0% of subjects in the vortioxetine group. One subject in the escitalopram group withdrew due to the sexual dysfunction TEAE, ejaculation failure. The second highest reason for discontinuations was lost-to-follow-up: 13/222 (5.9%) escitalopram subjects and 12/225 (5.3%) vortioxetine. Discontinuations primarily due to lack of efficacy were low (2.7% in vortioxetine and none in escitalopram subjects).

In Study 4001, 73/361 (20.2%) subjects discontinued the study for any reason: 16/92 (17.4%) placebo; 17/85 (20.0%) paroxetine; 23/91 (25.3%) vortioxetine 10 mg; and 17/93 (18.3%) vortioxetine 20 mg. Discontinuations primarily due to a TEAE were low, 10 subjects total: two in placebo; four in paroxetine; one in vortioxetine 10 mg; and three in vortioxetine 20 mg. The TEAEs that caused discontinuation for more than one subject overall were nausea (two subjects in the paroxetine group) and dysphoria (one subject each in the paroxetine and vortioxetine 20

mg groups). The incidence of TEAEs was 67.8%. The incidence of TEAEs was highest with paroxetine (75.0%, compared with 58.2% with placebo, 71.4% with vortioxetine 10 mg, and 67.0% with vortioxetine 20 mg). The most frequently reported TEAEs (incidence ≥5%) were nausea (19.6%), decreased libido (14.8%), somnolence (7.8%), abnormal orgasm (7.3%), and headache (5.6%).

#### 8.3.5. Adverse Events of Interest

Sexual dysfunction TEAEs are the AEs of interest for this application. In Study 318, there were nine subjects that reported sexual dysfunction TEAEs, all in the escitalopram group (4.1%).

In Study 4001, A total of 87 subjects (24.4%) overall had at least one reported sexual dysfunction TEAE. The incidence was highest in the paroxetine group (35.7%) and lowest in the placebo group (17.6%); the incidence was 19.8% in the vortioxetine 20 mg group and 25.3% in the vortioxetine 10 mg group. The most frequent sexual dysfunction TEAEs were decreased libido (21.4% in the paroxetine group, 15.4% in the vortioxetine 10 mg group, 12.1% in the placebo group, and 11.0% in the vortioxetine 20 mg group) and abnormal orgasm (16.7% in the paroxetine group, 7.7% in the vortioxetine 10 mg group, 3.3% in the vortioxetine 20 mg group, and 2.2% in the placebo group). The vortioxetine 20 mg group had the lowest rates of decreased libido compared with the placebo group and the other active-treatment groups, and the lowest rate of abnormal orgasm and erectile disorder among the active-treatment groups. The vortioxetine 20 mg group had no occurrences of anorgasmia, disturbance in sexual arousal, decreased orgasmic sensation, sexual dysfunction, and inadequate lubrication.

### 8.4. Safety in the Postmarket Setting

#### 8.4.1. Safety Concerns Identified Through Postmarket Experience

Vortioxetine was first approved in the United States on 30 September 2013 and was launched as of 01 November 2013. As of 29 September 2017, vortioxetine is authorized in 74 countries and launched in 59 countries. The cumulative world-wide available postmarketing data to date is in line with the known safety profile of vortioxetine. No new safety concerns have been identified from the post marketing experience.

### 8.5. Integrated Assessment of Safety

Overall, the safety profile of vortioxetine in these 2 studies was consistent with that in the approved vortioxetine label. The postmarketing safety data is consistent with clinical data and does not highlight any new safety information. No new important potential risks of treatment with vortioxetine have been identified since the submission of the original NDA.

# 9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting is not planned.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

The Applicant has provided sufficient evidence to demonstrate potential benefit of vortioxetine for patients experiencing treatment-emergent sexual dysfunction with two prospective clinical trials.

The data from Study 318 indicate that, while maintaining antidepressant efficacy, vortioxetine is superior to escitalopram in improving sexual functioning in MDD subjects with SSRI-induced sexual dysfunction. We support the addition of the study details and results to the prescribing information.

Data from Study 4001 demonstrates that in healthy volunteers, with no sexual dysfunction, vortioxetine 10 mg caused significantly less TESD than paroxetine 20 mg. This supports the option to use a lower dose of vortioxetine to address treatment-emergent sexual dysfunction. Because the comparative effect of vortioxetine 20 mg to paroxetine 20 mg was not statistically significant in Study 4001, we (b) (4) believe that a description of the study findings is appropriate.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

REMS is not necessary because no new safety concerns have been identified and the safety issues are adequately managed through labeling.

# 12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended.

# 13. Appendices

## 13.1. Financial Disclosure

**Covered Clinical Study (Name and/or Number): 318**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 456 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

**Covered Clinical Study (Name and/or Number): 4001**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 98 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

APPEARS THIS WAY ON ORIGINAL

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

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/s/

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JAVIER A MUNIZ on behalf of ANISA D COTT
10/19/2018
Dr. Cott is no longer with the Agency. She uploaded this document into DARRTS but apparently forgot to sign it. As her TL, I am signing on her behalf.

JAVIER A MUNIZ
10/19/2018

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | 204447/S-17 |
| **Drug Name:** | Trintellix (vortioxetine) Tablets |
| **Indication:** | Treatment Emergent Sexual Dysfunction |
| **Applicant:** | Takeda Development Center America, Inc |
| **Date(s):** | Submission Date: 12/21/2017 |
| | PDUFA Date: 10/21/2018 |
| **Review Priority:** | Priority |
| | |
| **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 Products |
| **Clinical Team:** | Anisa Cott, M.D. |
| **Project Manager:** | Jasmeet Kalsi, Pharm. D. |

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# 1 EXECUTIVE SUMMARY

Takeda Global Research and Development Center, Inc. submitted two pivotal studies (Study 318 and 4001) under supplemental NDA 204447 to investigate Trintellix (vortioxetine) for the treatment of Treatment Emergent Sexual Dysfunction (TESD) which developed as a side effect of antidepressant use. Based on data from the two studies the Sponsor has sought a label change (Section 6 of labeling) (b) (4) Vortioxetine was approved by the US FDA for the treatment of Major Depressive Disorder (MDD) on September 30, 2013 under NDA 204447. The CSFQ-14 (Changes in Sexual Functioning Questionnaire) which is a 14-item structured self-report questionnaire was used as a validated primary tool to measure illness and medication related changes in sexual dysfunction.

Study 318 investigated subjects with well treated and stable mood symptoms after treatment with selective serotonin reuptake inhibitors (SSRIs) (citalopram, paroxetine, or sertraline)-flexible doses of vortioxetine (10 and 20 mg QD) versus flexible doses of escitalopram (10 and 20 mg QD). Study 4001 was a fixed dose study (vortioxetine 10 mg/day, vortioxetine 20 mg/day, paroxetine 20 mg/day, placebo) in healthy volunteers.

# 2 INTRODUCTION

## 2.1 Overview

Two studies were conducted, in US and/or North America, in support of a supplement NDA to evaluate the effect of vortioxetine (versus active drug) for treatment of treatment-emergent sexual dysfunction. Subjects in Study 318 had well-treated major depressive disorder while Study 4001 had healthy volunteers.

Previous results from a short-term, phase 3 depression studies, vortioxetine is associated with less treatment-emergent sexual dysfunction (TESD) when compared with duloxetine. Study 318 was conducted to evaluate the effect of vortioxetine versus escitalopram in improving TESD in well-treated MDD patients with abnormal sexual functioning induced due to SSRIs. In this study vortioxetine was statistically significantly superior to escitalopram in improving sexual dysfunction as measured by the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score at Week 8. The objective of Study 4001 was to further evaluate the effects of vortioxetine (10 and 20 mg/day) on sexual functioning as compared with paroxetine 20 mg/day in healthy subjects after 5 weeks of treatment. Placebo was included in this study for assay sensitivity.

The basis for sponsor's label claim of CSFQ-14 is established on two positive studies, 318 and 4001, which showed statistically significant separation between vortioxetine dose groups and the control (escitalopram and paroxetine, respectively). Emphasis in this review is put on the results of these two studies. (b) (4)

(b) (4)

### 2.2 Data Sources

The sponsor's submitted data and SAS program listings for the two pivotal studies are available in the following directory of the CDER' electronic document room (EDR):
\\Cdsesub1\evsprod\NDA204447\0160

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfactory and acceptable for the review analysis.

### 3.2 Evaluation of Efficacy

The objective of these confirmatory studies was to provide evidence of comparative efficacy of vortioxetine on TESD in adult patients with well-treated MDD.

#### 3.2.1 Study Design and Endpoints

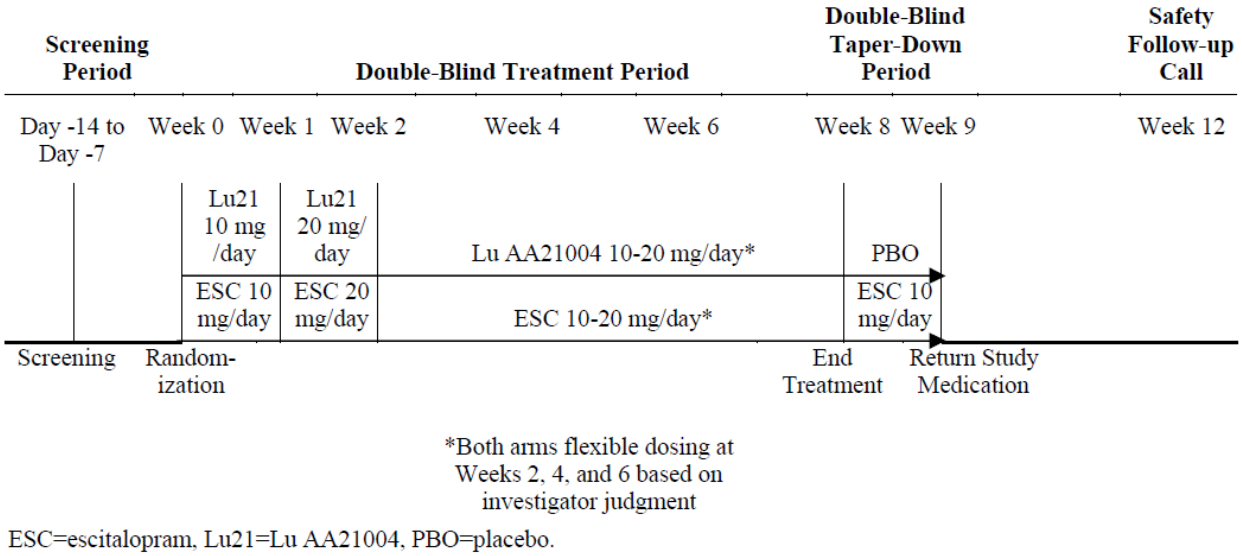
##### 3.2.1.1 Study 318

Study Design
This is a phase 3, multicenter, randomized, double-blind, active-controlled (escitalopram), parallel group, flexible dose study comparing vortioxetine (10 and 20 mg QD) and escitalopram (10 and 20 mg QD) in subjects with well-treated* MDD who were experiencing sexual dysfunction due to SSRI use. Subjects who were screened for the study were on SSRI monotherapy (citalopram, paroxetine, or sertraline; escitalopram was not allowed) to treat major depressive episode and were experiencing sexual dysfunction for at least 8 weeks.

This North American study enrolled subjects at 57 sites in the US and 9 sites in Canada. The first subject signed informed consent on 16 June 2011 and the last subject's visit was on 09 December 2013. Subjects who fulfilled the inclusion and exclusion criteria were randomized 1:1 (escitalopram or vortioxetine) and enrolled in an 8-week double-blind treatment period. Randomized patients received 10 mg of either escitalopram or vortioxetine for the first week. At the end of Week 1, dose was increased to 20 mg/day. Investigators were able to monitor and adjust doses (10 to 20 mg) during treatment period at week 2, 4, 6 based on individual response and tolerability. Subjects who completed the treatment period entered a 1-week taper down period. In the taper down period, subjects who were on vortioxetine (10/20 mg QD) received placebo; subjects treated with escitalopram (10/20 mg QD) received escitalopram (10 mg QD). There was safety follow-up 4 weeks after completion of the 8-week treatment period. The overall study period was 12 weeks.

[*]*The major depressive episode (MDE) should have been well-treated, that is, currently stable (without clinically significant fluctuation in levels of depressive symptoms) as judged by the investigator, and with a Clinical Global Impression Scale-Severity of Illness Scale (CGI-S) total score ≤3. Additionally, patients must have been experiencing SSRI-induced sexual dysfunction per investigator judgment and must have met the threshold criterion for sexual dysfunction as measured by the CSFQ-14 total score (≤41 women; ≤47 men). Subjects were to stop all disallowed medication with the exception of their current SSRI treatment. (CSR, Page 20).*

**Figure 1: Overall Study Schema-Study 318**




Source: Figure 6.a of Sponsor's Clinical Study Report (Page 26)

Study Endpoints (Primary and Key secondary efficacy)

The primary efficacy outcome was the mean change from baseline to Week 8 in CSFQ-14[†] total score between vortioxetine and escitalopram. Lower scores of CSFQ-14 total are correlated with worsened sexual functioning.

[†] CSFQ-14: *is a structured self-reported questionnaire designed to measure illness- and medication-related changes in sexual functioning consisting of 14 items that measure sexual functioning as a total score (14 items) and on the subscales of pleasure (1 item), desire/frequency (2 items), desire/interest (3 items), arousal (3 items), and orgasm (3 items). Two additional items are included in the total score, but do not map to a specific phase of the sexual response cycle (CSR, page 48).*

The original protocol was issued on March 22, 2011, and was amended once on September 12, 2011.

**Reviewer's Note:** In a meeting with the Sponsor on February 18, 2015, the FDA elaborated on the need for additional study in order to support a labeling claim.

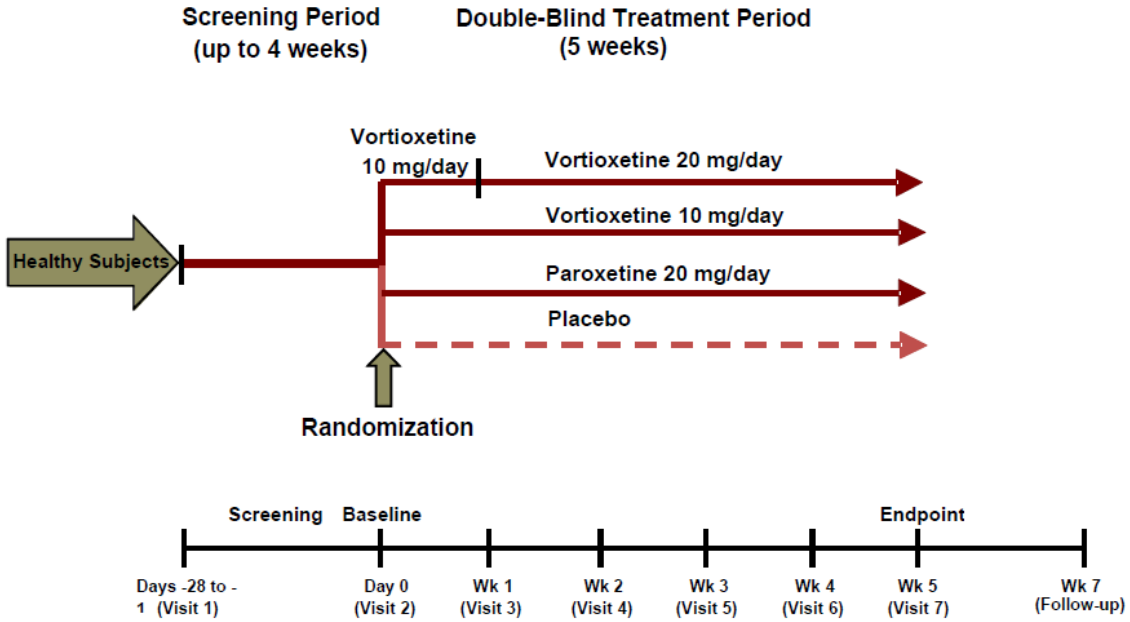
### 3.2.1.2 Study 4001

Study Design
This is a phase 4, multicenter, double-blind, placebo- and active-controlled (paroxetine), 4-arm, parallel group, fixed-dose study to assess the effect of vortioxetine (10 and 20 mg QD) versus paroxetine (20 mg QD) on sexual function for 5 weeks in healthy adult subjects. Roughly equal proportions of men and women, aged 18-40 years, participated in the trial.

The study lasted from 21 November 2016 to 31 May 2017. The study consisted of screening period up to 4 weeks. At baseline eligible patients were randomized (1:1:1:1) to double-blind vortioxetine 10mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo and will be treated for 5 weeks. Randomization was stratified by sex. Subjects who were randomized to the vortioxetine 20 mg arm had been on 10 mg dose for 1 week. Those who were put on 10 mg dose arm remained at the same dose throughout study completion. Subjects were observed every week during the double-blind treatment period and were contacted 2 weeks after the completion of treatment for a safety follow-up.

*Diagnosis and Main Criteria for Inclusion*: men and women aged 18-40, currently sexually active (≥2 times per week), had no sexual dysfunction, had been in steady sexual relationship for ≥3 months, and planned to remain in that relationship for the duration of the study.

**Figure 2: Overall Study Schema-Study 4001**




Source: Figure 6.a of Sponsor's Clinical Study Report (Page 24)

Study Endpoints (Primary and Key secondary efficacy)
The primary efficacy outcome was the change from baseline to Week 5 in CSFQ-14 total score difference between each vortioxetine dose and paroxetine.

The original protocol which was issued on 12 July 2016 was amended once on 10 January 2017.

**Reviewer's Note:** (b) (4) recommended dose of vortioxetine for the treatment of MDD in the US is 20 mg/day, (b) (4) .

### 3.2.2 Statistical Methodologies

The following statistical methodologies were pre-specified in the sponsor's statistical analysis plan.

#### 3.2.2.1 Study 318

The primary analysis for the primary and key secondary efficacy endpoints was carried out on the full analysis set (FAS). The FAS included all randomized subjects who received at least 1 dose of double-blind study medication and had at least 1 valid postbaseline value for assessment of CSFQ-14.

Efficacy Analyses Methods (Primary and Key Secondary Efficacy)
The mixed model repeated measure (MMRM) with unstructured covariance structure was used to evaluate the change from baseline to week 8 in CSFQ-14 total score. The model included terms: treatment, center, week, treatment-by-week interaction, and baseline CSFQ-14 total score-by-week.

Sample Size Calculation
Assuming a dropout rate of 15%, a total of 440 subjects (220 per treatment group) would be sufficient to provide at least 80% power to detect a treatment difference of 2.5 (SD = 8.5) in CSFQ-14 total score between vortioxetine and escitalopram groups based on a two-sample t-test at 5% (two-sided) significance level.

Sensitivity Analyses
To evaluate robustness of the main results from MMRM, the Sponsor conducted the following sensitivity analyses:

- Pattern mixture models (PMM) using standard SAS procedures. PMM uses multiple imputation methodology to impute missing values after subjects' discontinuation from the study. Missing values from control and treatment arms are imputed based on available data from control subjects via PROC MI in SAS (monotone missing data pattern). (Sensitivity) Analyses

Supportive Analyses

- An ANCOVA (LOCF, OC) model which included treatment, center, and baseline CSFQ-14 total score.

#### 3.2.2.2 Study 4001

The primary efficacy was conducted on the FAS population. The FAS includes subjects who were randomized, received at least 1 dose of study drug, and had at least 1 valid post-baseline value for assessment of primary efficacy.

Efficacy Analyses Methods (Primary and Key Secondary Efficacy)
Change in CSFQ-14 total score from baseline to Week 5. The primary endpoint was assessed using analysis of covariance (ANCOVA) which uses last observation carried forward (LOCF) technique. The model terms were treatment group, center, sex, and baseline CSFQ-14 total score.

No key secondary endpoints were specified.

Multiple Testing Procedure
The Holm-Bonferroni was used to adjust for multiplicity and control the familywise type I error. If the *smaller of the two p-values* is < 0.025, significance is obtained for the associated dose and the other dose is subsequently evaluated at 0.05 significance level. Paroxetine is compared to placebo for assay sensitivity purposes.

Sample Size Calculation
Using a fixed randomization ratio (1:1:1:1) to placebo, paroxetine 20 mg, vortioxetine 10 mg, vortioxetine 20 mg, assuming the standard deviation for change from baseline in CSFQ-14 total score is equal to 8.5, a total of 352 subjects (88 per group) would be sufficient to provide a power of ≥80% to detect a treatment difference of 4.0 points vortioxetine 20 mg versus paroxetine 20 mg or for vortioxetine 10 mg versus paroxetine 20 mg at Week 5 by a 2-sample t-test with 0.025 2-sided significance level. Given the Holm-Bonferroni method for multiplicity control, the power to achieve the significance for each vortioxetine dose was approximately 85%.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

#### 3.2.3.1 Study 318

There were 66 sites: United States (57), Canada (9).

Of 711 subjects who were screened, 447 subjects (62.9%) were randomized in North America (222 subjects in escitalopram group and 225 subjects in Lu AA21004 group).

**Table 1**: **Subject Eligibility**

| | N (%) |
|---|---|
| Number of subjects screened | 711 |
| Number of subjects randomized | 447 (62.9) |
| Number of subjects not randomized | 264 (37.1) |
| Primary reason subject discontinued prior to treatment phase (a) | |
| Pretreatment event or AE | 0 |
| Did not meet inclusion criteria | 69 (9.7) |
| Met exclusion criteria | 174 (24.5) |
| Had a major protocol deviation | 0 |
| Withdrawal of consent | 19 (2.7) |
| Lost to follow-up | 15 (2.1) |
| Study termination | 0 |
| Other | 12 (1.7) |

Source: Table 10.a of Sponsor's Clinical Study Report (Page 62)
(a) More than 1 reason for discontinuation may have been reported for a subject.

The FAS population contains a total of 424 subjects: escitalopram (207), vortioxetine (217).

**Table 2: Summary of Patient Populations**

| | Number of Subjects (%) | | |
|---|---|---|---|
| | **Escitalopram (N=222)** | **Lu AA21004 (N=225)** | **Total (N=447)** |
| Data set | | | |
| Randomized | 222 (100) | 225 (100) | 447 (100) |
| Safety set (a) | 221 (99.5) | 224 (99.6) | 445 (99.6) |
| Full analysis set (b) | 207 (93.2) | 217 (96.4) | 424 (94.9) |
| Per-protocol set (c) | 195 (87.8) | 192 (85.3) | 387 (86.6) |
| Study completion/withdrawal | | | |
| Completed | 179 (80.6) | 169 (75.1) | 348 (77.9) |
| Prematurely discontinued | 43 (19.4) | 56 (24.9) | 99 (22.1) |
| Primary reason for discontinuation of study (d) | | | |
| Pretreatment event or AE | 14 (6.3) | 20 (8.9) | 34 (7.6) |
| Elevated liver enzymes | 0 | 0 | 0 |
| Lack of efficacy | 0 | 6 (2.7) | 6 (1.3) |
| Non-compliance with IMP | 0 | 1 (0.4) | 1 (0.2) |
| Protocol deviations | 8 (3.6) | 4 (1.8) | 12 (2.7) |
| Withdrawal of consent | 7 (3.2) | 9 (4.0) | 16 (3.6) |
| Lost to follow-up | 13 (5.9) | 12 (5.3) | 25 (5.6) |
| Other | 1 (0.5) | 4 (1.8) | 5 (1.1) |

Source: Table 10.b of Sponsor's Clinical Study Report (Page 63)

(a) Safety set=all randomized subjects who received at least 1 dose of double-blind study medication. Subjects were analyzed according to the study medication they received.
(b) Full analysis set=all randomized subjects who received at least 1 dose of double-blind study medication and had at least 1 valid postbaseline value for assessment of primary efficacy. Subjects were analyzed according to the treatment group to which they were randomized.
(c) Per-protocol set=all full analysis set subjects who had no major protocol violations.
(d) Primary reasons for discontinuation are mutually exclusive and exhaustive categories.

Table 2 above shows that 348 (77.9%) subjects completed the study (179 (80.6%) subjects in the escitalopram arm; 169 (75.1%) subjects in vortioxetine arm). Ninety-nine (99) subjects (22.1%) prematurely discontinued the study (43 (19.4%) subjects in the escitalopram arm; 56 (24.9%) subjects in vortioxetine arm). The most common reason for study discontinuation was due to AE (7.6%), followed by lost to follow-up (5.6%), consent withdrawal (3.6%), protocol deviation (2.7%), and lack of efficacy (1.3%). All the subjects that withdrew due to lack of efficacy were in the Lu AA21004 group (2.7%).

Summary of baseline characteristics in the randomized set are presented in Table 3. The average age of patients was 39.8 years, ranging from 19 to 55 years. Overall, treatment groups were fairly balanced with respect to age, sex, weight, BMI and race. Many of the participants were Caucasians (Whites including Hispanic) (80.3%) followed by Black or African American (17.0%). Majority of the patients were of Non-Hispanic and non-Latino origin (88.8%).

*Baseline Depression and POMS (profile of mood states) Assessment*: the scores at baseline were similar across the treatment groups. The mean (SD) MADRS total score, CGI-S score, POMS-Brief at baseline were [escitalopram: 8.3 (6.53); vortioxetine: 7.9 (6.28)], [escitalopram: 2.0 (0.84); vortioxetine: 2.0 (0.81)], [escitalopram: 19.7 (19.45); vortioxetine: 18.8 (19.36)], respectively.

**Table 3: Summary of Demographics and Baseline Characteristics (All Randomized Set; N=447)**

| | Escitalopram (N=222) | Lu AA21004 (N=225) | Total (N=447) |
|---|---|---|---|
| Age (years) (a) | | | |
| Mean | 40.2 | 39.3 | 39.8 |
| SD | 10.01 | 9.96 | 9.98 |
| Median | 41.0 | 40.0 | 40.0 |
| Minimum/Maximum | 19/55 | 19/55 | 19/55 |
| Age category [n(%)] | | | |
| ≤41 years | 112 (50.5) | 122 (54.2) | 234 (52.3) |
| >41 years | 110 (49.5) | 103 (45.8) | 213 (47.7) |
| Sex n (%) | | | |
| Male | 87 (39.2) | 97 (43.1) | 184 (41.2) |
| Female | 135 (60.8) | 128 (56.9) | 263 (58.8) |
| Ethnicity [n(%)] | | | |
| Hispanic or Latino | 36 (16.2) | 14 (6.2) | 50 (11.2) |
| Non-Hispanic and non- Latino | 186 (83.8) | 211 (93.8) | 397 (88.8) |
| Race n [n(%)] | | | |
| Caucasian (or White, including Hispanic) | 181 (81.5) | 178 (79.1) | 359 (80.3) |
| Black of African American | 35 (15.8) | 41 (18.2) | 76 (17.0) |
| Asian | 3 (1.4) | 4 (1.8) | 7 (1.6) |
| American Indian or Alaska Native | 3 (1.4) | 1 (0.4) | 4 (0.9) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.4) | 1 (0.2) |
| Height (cm) | | | |
| Mean | 170.3 | 169.6 | 169.9 |
| SD | 8.81 | 9.73 | 9.28 |
| Median | 170.0 | 169.0 | 170.0 |
| Minimum/Maximum | 150/204 | 146/198 | 146/204 |
| Weight (kg) | | | |
| Mean | 81.22 | 79.62 | 80.41 |
| SD | 16.012 | 16.202 | 16.110 |
| Median | 80.95 | 79.40 | 80.00 |
| Minimum/Maximum | 47.5/135.0 | 42.2/121.8 | 42.2/135.0 |
| BMI ($kg/m^2$) (b) | | | |
| Mean | 27.90 | 27.54 | 27.72 |
| SD | 4.440 | 4.352 | 4.395 |
| Median | 27.75 | 27.50 | 27.70 |
| Minimum/Maximum | 16.6/35.0 | 18.2/34.9 | 16.6/35.0 |
| Waist Circumference (cm) | | | |
| Mean | 93.31 | 90.85 | 92.07 |
| SD | 13.074 | 13.274 | 13.218 |
| Median | 93.65 | 92.00 | 92.40 |
| Minimum/Maximum | 58.0/129.2 | 38.0/121.0 | 38.0/129.2 |
| Smoking classification [n(%)] | | | |
| Never smoked | 126 (56.8) | 112 (49.8) | 238 (53.2) |
| Current smoker | 55 (24.8) | 69 (30.7) | 124 (27.7) |
| Ex-smoker | 41 (18.5) | 44 (19.6) | 85 (19.0) |
| Alcohol consumption [n(%)] | | | |
| Never | 65 (29.3) | 65 (28.9) | 130 (29.1) |
| Once monthly or less often | 82 (36.9) | 86 (38.2) | 168 (37.6) |
| Once a week | 37 (16.7) | 40 (17.8) | 77 (17.2) |
| 2 to 6 times per week | 36 (16.2) | 33 (14.7) | 69 (15.4) |
| Daily | 2 (0.9) | 1 (0.4) | 3 (0.7) |

Source: Summary of Demographics of Sponsor's CSR (Table 11.b, Page 67-68)
SD=standard deviation
(a) Age is calculated relative to the date of informed consent.
(b) BMI was calculated using the weight collected at the first screening visit (Visit 1): BMI=weight (kg)/[height (m)]$^2$.

### 3.2.3.2 Study 4001

The study involved 16 sites in United States. The FAS population included 348 subjects met the eligibility criteria and were randomized placebo (89), Paroxetine 20 mg/day (83), Vortioxetine 10 mg/day (85), or Vortioxetine 20 mg/day (91).

**Table 4: Analysis Sets (All Randomized Subjects)**

| | Number of Subjects (%) | | | | |
|---|---|---|---|---|---|
| | **Placebo (N=92)** | **Paroxetine 20 mg/day (N=85)** | **Vortioxetine 10 mg/day (N=91)** | **Vortioxetine 20 mg/day (N=93)** | **Total (N=361)** |
| Safety analysis set (a) | 91 (98.9) | 84 (98.8) | 91 (100.0) | 91 (97.8) | 357 (98.9) |
| FAS (b) | 89 (96.7) | 83 (97.6) | 85 (93.4) | 91 (97.8) | 348 (96.4) |
| mFAS1 (c) | 89 (96.7) | 74 (87.1) | 82 (90.1) | 84 (90.3) | 329 (91.1) |
| mFAS2 (d) | 89 (96.7) | 60 (70.6) | 79 (86.8) | 79 (84.9) | 307 (85.0) |
| PPS (e) | 84 (91.3) | 76 (89.4) | 79 (85.7) | 82 (88.2) | 320 (88.6) |

Source: Table 11.a of Sponsor's Clinical Study Report (Page 60)
(a) Safety analysis set included all randomized subjects who received at least 1 dose of study drug.
(b) FAS included all subjects who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline value for assessment of primary efficacy.
(c) mFAS1 included all subjects in the FAS except those who had active drug concentrations BLOQ at all study visits where PK samples were collected.
(d) mFAS2 included all subjects in the FAS except those who had drug concentrations BLOQ at any study visit where PK samples were collected.
(e) PPS included all subjects in the FAS who had no major protocol violations.

Table 5 displays overall subject dispositions, including the percentage of discontinuation for all randomized subjects in the 4 treatment groups: placebo (17.4%), paroxetine 20 mg/day (20.0%), vortioxetine 10 mg/day (25.3%), and vortioxetine 20 mg/day (18.3%), which was similar across treatment groups. Overall discontinuation rate was 20.2%. The frequent discontinuation reasons included loss to follow-up (5.8%), voluntary withdrawal (3.9%), significant protocol deviation (3.3%), adverse events (2.8%), and non-compliance with study drug (3.3%).

**Table 5: Overall Subject Disposition (All Randomized Subjects)**

| | Number of Subjects (%) | | | | |
|---|---|---|---|---|---|
| | Placebo (N=92) | Paroxetine 20 mg/day (N=85) | Vortioxetine 10 mg/day (N=91) | Vortioxetine 20 mg/day (N=93) | Total (N=361) |
| Randomized but not treated | 1 | 1 | 0 | 2 | 4 |
| **Study visits** | | | | | |
| Completed all planned study visits | 76 (82.6) | 68 (80.0) | 68 (74.7) | 76 (81.7) | 288 (79.8) |
| Did not complete all planned study visits | 16 (17.4) | 17 (20.0) | 23 (25.3) | 17 (18.3) | 73 (20.2) |
| Reason for premature discontinuation of study visits | | | | | |
| PTE/TEAE | 2 (2.2) | 4 (4.7) | 1 (1.1) | 3 (3.2) | 10 (2.8) |
| Significant protocol deviation | 2 (2.2) | 3 (3.5) | 6 (6.6) | 1 (1.1) | 12 (3.3) |
| Lost to follow-up | 6 (6.5) | 4 (4.7) | 8 (8.8) | 3 (3.2) | 21 (5.8) |
| Voluntary withdrawal | 3 (3.3) | 2 (2.4) | 5 (5.5) | 4 (4.3) | 14 (3.9) |
| Study termination | 0 | 0 | 0 | 0 | 0 |
| Pregnancy | 0 | 1 (1.2) | 0 | 0 | 1 (0.3) |
| Noncompliance with study drug (a) | 2 (2.2) | 3 (3.5) | 2 (2.2) | 5 (5.4) | 12 (3.3) |
| Other | 1 (1.1) | 0 | 1 (1.1) | 1 (1.1) | 3 (0.8) |
| **Study drug** | | | | | |
| Completed study drug | 76 (82.6) | 67 (78.8) | 68 (74.7) | 79 (84.9) | 290 (80.3) |
| Prematurely discontinued study drug | 15 (16.3) | 17 (20.0) | 23 (25.3) | 12 (12.9) | 67 (18.6) |
| Reason for discontinuation of study drug (a) | | | | | |
| PTE/TEAE | 3 (3.3) | 5 (5.9) | 1 (1.1) | 3 (3.2) | 12 (3.3) |
| Significant protocol deviation | 2 (2.2) | 3 (3.5) | 6 (6.6) | 1 (1.1) | 12 (3.3) |
| Lost to follow-up | 5 (5.4) | 3 (3.5) | 6 (6.6) | 0 | 14 (3.9) |
| Voluntary withdrawal | 2 (2.2) | 1 (1.2) | 4 (4.4) | 2 (2.2) | 9 (2.5) |
| Study termination | 0 | 1 (1.2) | 0 | 0 | 1 (0.3) |
| Pregnancy | 0 | 1 (1.2) | 1 (1.1) | 0 | 2 (0.6) |
| Noncompliance with study drug | 2 (2.2) | 3 (3.5) | 3 (3.3) | 4 (4.3) | 12 (3.3) |
| Other | 1 (1.1) | 0 | 2 (2.2) | 2 (2.2) | 5 (1.4) |

Source: Table 10.a of Sponsor's Clinical Study Report (Page 57)

Percentages are based on the total number of subjects in each treatment group.

(a) Subjects may have stopped study drug permanently or transiently; not all subjects who stopped study drug discontinued from the study.

Baseline demographic characteristics in all randomized population are summarized in Table 6. The average age of patients was 28.4 years, ranging from 18 to 40 years. Broadly, treatment groups were comparable in baseline characteristics. But, majority of participants were whites (57.3%), and overwhelming majority were of Non-Hispanic or Latino origin (76.7%).

**Table 6: Demographic and Baseline Characteristics (All Randomized Subjects)**

| | Placebo (N=92) | Paroxetine (N=85) | Vortioxetine 10 mg (N=91) | Vortioxetine 20 mg (N=93) | Total (N=361) |
|---|---|---|---|---|---|
| Age (years) (a) | | | | | |
| Mean (SD) | 27.8 (5.45) | 28.9 (5.96) | 28.1 (5.56) | 28.8 (5.91) | 28.4 (5.72) |
| Median | 27.0 | 28.0 | 28.0 | 28.0 | 28.0 |
| Minimum, maximum | 18, 40 | 18, 40 | 18, 40 | 18, 40 | 18, 40 |
| p-value | | | | | 0.469 |
| Median age categories (N [%]) | | | | | |
| ≤28 years | 51 (55.4) | 43 (50.6) | 52 (57.1) | 47 (50.5) | 193 (53.5) |
| >28 years | 41 (44.6) | 42 (49.4) | 39 (42.9) | 46 (49.5) | 168 (46.5) |
| p-value | | | | | 0.774 |
| Gender (n [%]) | | | | | |
| Male | 46 (50.0) | 43 (50.6) | 47 (51.6) | 49 (52.7) | 185 (51.2) |
| Female | 46 (50.0) | 42 (49.4) | 44 (48.4) | 44 (47.3) | 176 (48.8) |
| p-value | | | | | 0.947 |
| Ethnicity (n [%]) | | | | | |
| Hispanic or Latino | 21 (22.8) | 20 (23.5) | 25 (27.5) | 18 (19.4) | 84 (23.3) |
| Non-Hispanic and Latino | 71 (77.2) | 65 (76.5) | 66 (72.5) | 75 (80.6) | 277 (76.7) |
| p-value | | | | | 0.539 |
| Race (n [%]) | | | | | |
| American Indian or Alaska Native | 0 | 0 | 3 (3.3) | 0 | 3 (0.8) |
| Asian | 7 (7.6) | 3 (3.5) | 2 (2.2) | 3 (3.2) | 15 (4.2) |
| Black or African American | 30 (32.6) | 29 (34.1) | 31 (34.1) | 34 (36.6) | 124 (34.3) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (1.2) | 0 | 0 | 1 (0.3) |
| White | 51 (55.4) | 49 (57.6) | 52 (57.1) | 55 (59.1) | 207 (57.3) |
| Multiracial (b) | 4 (4.3) | 3 (3.5) | 3 (3.3) | 1 (1.1) | 11 (3.0) |
| p-value | | | | | 0.237 |
| Race categories (n [%]) | | | | | |
| White | 51 (55.4) | 49 (57.6) | 52 (57.1) | 55 (59.1) | 207 (57.3) |
| Non-White | 41 (44.6) | 36 (42.4) | 39 (42.9) | 38 (40.9) | 154 (42.7) |
| p-value | | | | | 0.920 |

| | | | | | |
|---|---|---|---|---|---|
| Height (cm) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 172.0 (10.75) | 172.1 (10.59) | 171.3 (9.14) | 170.8 (10.04) | 171.5 (10.12) |
| Median | 173.0 | 173.0 | 173.0 | 170.0 | 172.0 |
| Minimum, maximum | 151, 201 | 152, 195 | 152, 193 | 149, 199 | 149, 201 |
| p-value | | | | | 0.827 |
| Weight (kg) (c) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 76.49 (15.523) | 80.19 (16.808) | 78.67 (14.850) | 75.12 (13.282) | 77.56 (15.19 |
| Median | 76.55 | 79.30 | 78.00 | 76.00 | 77.30 |
| Minimum, maximum | 51.9, 112.5 | 42.2, 125.0 | 49.9, 118.8 | 47.3, 108.4 | 42.2, 125.0 |
| p-value | | | | | 0.131 |
| BMI ($kg/m^2$) (d) | | | | | |
| N | 92 | 85 | 91 | 93 | 361 |
| Mean (SD) | 25.72 (3.925) | 26.91 (4.245) | 26.77 (4.306) | 25.70 (3.668) | 26.26 (4.062 |
| Median | 24.59 | 26.62 | 26.53 | 25.34 | 25.86 |
| Minimum, maximum | 18.4, 34.0 | 18.3, 35.0 | 18.3, 34.9 | 18.2, 34.8 | 18.2, 35.0 |
| p-value | | | | | 0.075 |
| Smoking classification (n [%]) | | | | | |
| Subject has never smoked | 73 (79.3) | 70 (82.4) | 70 (76.9) | 77 (82.8) | 290 (80.3) |
| Subject is a current smoker | 7 (7.6) | 2 (2.4) | 4 (4.4) | 7 (7.5) | 20 (5.5) |
| Subject is an ex-smoker | 12 (13.0) | 13 (15.3) | 17 (18.7) | 9 (9.7) | 51 (14.1) |
| p-value | | | | | 0.383 |
| Female reproductive status (n [%]) | | | | | |
| Postmenopausal | 0 | 0 | 0 | 0 | 0 |
| Surgically sterile | 3 (3.3) | 4 (4.7) | 2 (2.2) | 3 (3.2) | 12 (3.3) |
| Female of childbearing potential | 43 (46.7) | 38 (44.7) | 42 (46.2) | 41 (44.1) | 164 (45.4) |
| NA/subject is male | 46 (50.0) | 43 (50.6) | 47 (51.6) | 49 (52.7) | 185 (51.2) |
| p-value | | | | | 0.986 |
| Duration of menstruation (days) | | | | | |
| N | 45 | 42 | 44 | 43 | 174 |
| Mean (SD) | 4.9 (1.36) | 4.4 (1.27) | 4.2 (1.27) | 4.6 (1.37) | 4.5 (1.33) |
| Median | 5.0 | 4.0 | 4.0 | 5.0 | 4.0 |
| Minimum, maximum | 3, 7 | 2, 7 | 0, 7 | 0, 7 | 0, 7 |
| p-value | | | | | 0.087 |
| Duration of menstrual cycle (days) | | | | | |
| N | 45 | 42 | 44 | 43 | 174 |
| Mean (SD) | 28.9 (5.35) | 28.3 (2.56) | 28.2 (7.07) | 28.0 (6.94) | 28.4 (5.75) |
| Median | 28.0 | 28.0 | 28.0 | 28.0 | 28.0 |
| Minimum, maximum | 21, 60 | 21, 35 | 0, 60 | 0, 60 | 0, 60 |
| p-value | | | | | 0.960 |

Source: Table 11.c of Sponsor's Clinical Study Report (Page 62-64)

SD=standard deviation

P-values are from ANOVA with treatment and pooled center as fixed effects for continuous variables and Cochran- Mantel-Haenszel general association test, stratified by pooled center, for discrete variables.

a. Age at the date of informed consent.
b. Subject checked more than 1 race option on the case report form.
c. Baseline weight used is the last observation before the first dose of study drug.
d. BMI is calculated from baseline weight and height taken at Screening.

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Study 318

**Primary Endpoint**

A total of 424 patients were included in the Full Analysis set (FAS). The reviewer confirmed sponsor's efficacy findings (see Table 7). Vortioxetine was statistically significantly superior to escitalopram in the mean change from baseline in CSFQ-14 total score at week 8 (FAS, MMRM), with a least square mean treatment difference from placebo of 2.2 (p-value = 0.013).

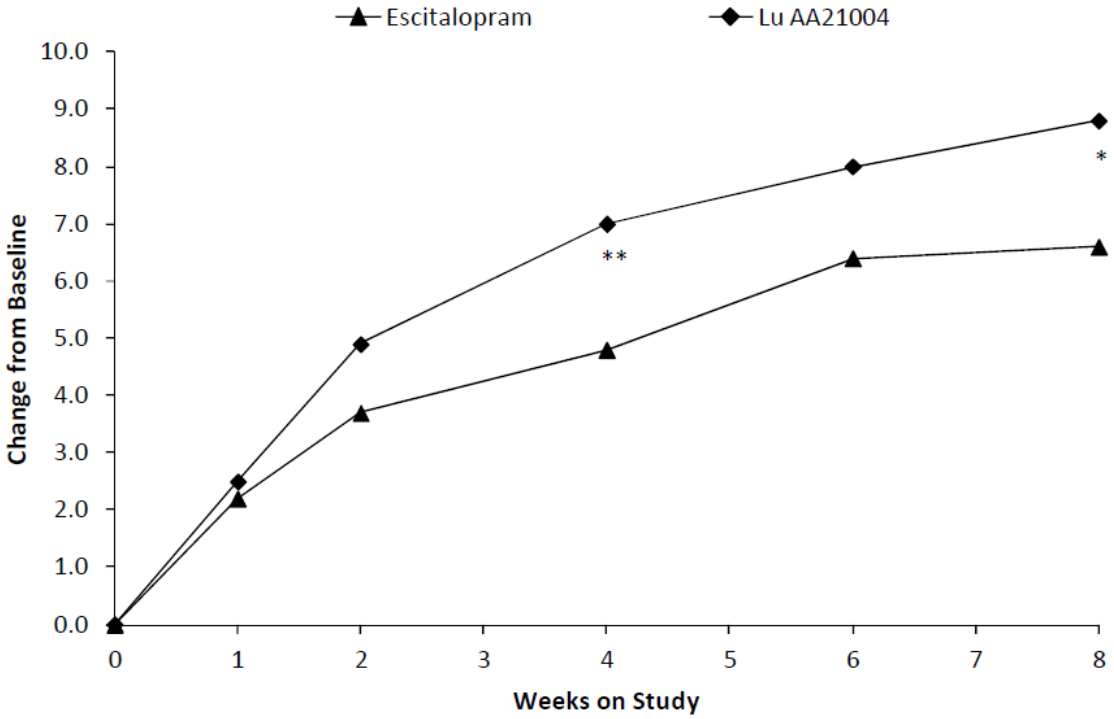
**Table 7: Change from Baseline in CSFQ-14 Total Score At Week 8 (FAS; MMRM)**

| Visit | Escitalopram N=207 | Vortioxetine N=217 |
|---|---|---|
| Baseline | | |
| N | 207 | 217 |
| LS Mean ± SE (a) | 36.0 ±0.40 | 36.1 ±0.39 |
| Change from Baseline at Week 8 | | |
| N | 173 | 165 |
| Change from Baseline LS Mean ± SE | 6.6±0.40 | 8.8 ±0.64 |
| p-value, Lu AA21004 vs Escitalopram (b) | | 0.013 |
| LS mean differences ± SE from Escitalopram (b) | | 2.2 ±0.90 |
| 95% CI for differences | | (0.48-4.02) |

Source: Table 11.f of Sponsor's Clinical Study Report (Page 73)
CI = confidence interval; LS = least-squares; MMRM = mixed model repeated measures; SE = standard error; FAS = Full Analysis Set; SD= Standard Deviation
Note: Increase in CSFQ-14 total score indicates improvement.
Note: Baseline value was defined as the last observation prior to the first dose of double-blind medication.
(a) Baseline LS means and p-values were from an ANOVA model with terms for treatment and pooled center.
(b) Postbaseline LS means and p-values were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

**Reviewer's Notes:** 10 subjects (all male, 6 randomized to escitalopram and 4 randomized to vortioxetine) who had major protocol violation were excluded from the FAS. Per the sponsor's clarification (dated May 17, 2018 in Sequence No. 0173), it was because they were identified as having utilized the incorrect CSFQ-14 at Baseline (at a minimum), were given an unauthorized version of the male CSFQ-14, which did not contain the same questions. As a result, the individual scores to the questions could not be entered into the database as the response options did not match. Consequently, these subjects did not have valid baseline CSFQ-14 total scores and according to Section 8.3 of the SAP could not be included in efficacy analyses.

**Figure 3: Changes from Baseline in CSFQ-14 Total Score by Visit (FAS, MMRM)**

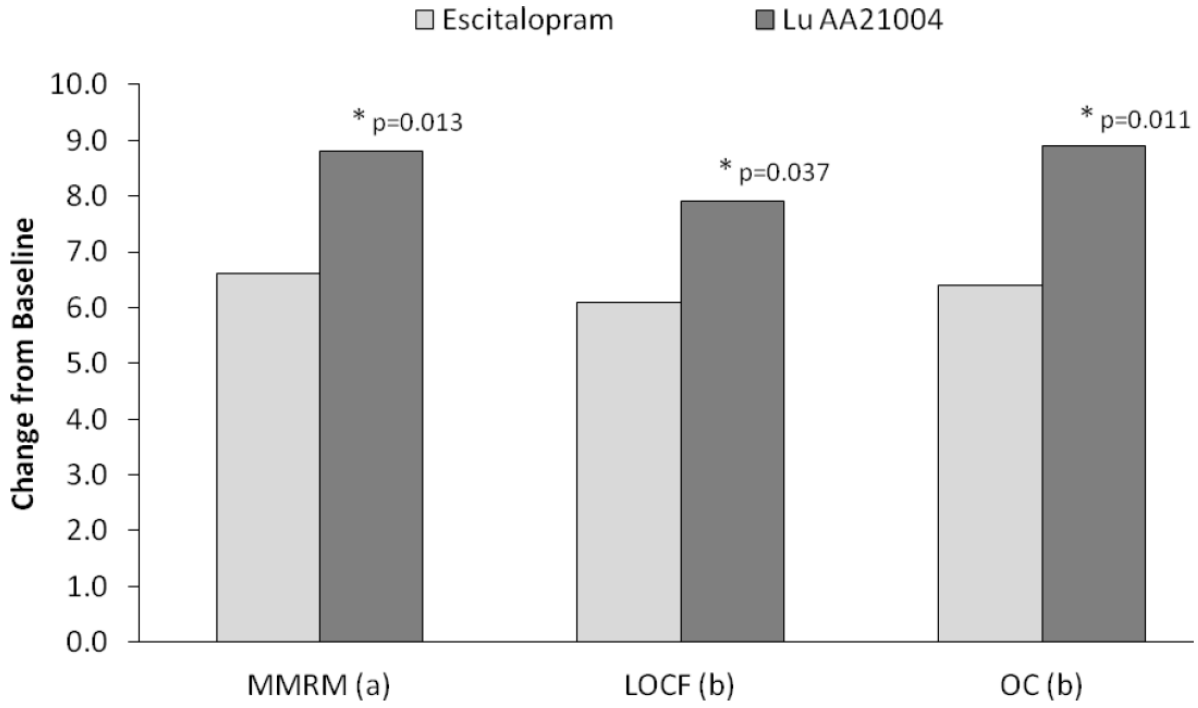



Source: Figure 11.b of Sponsor's Clinical Study Report (Page 75)
*p<0.05 vs escitalopram, **p<0.01 vs escitalopram.
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.

Supportive analyses using ANCOVA with LOCF (LS Mean (SE) = 1.8 (0.84); p = 0.037) and OC (LS Mean (SE) = 2.5 (0.96), p = 0.011) yielded the same conclusions as the primary efficacy analysis results. Also, pattern mixture model* sensitivity results (LS Mean (SE) = 2.0 (0.95); 95% CI: (0.15, 3.88)) were consistent with the main efficacy conclusions. Figure 4 below gives the primary and secondary summary results pictorially.

**Pattern mixture model: the LS means and 95% CI were obtained from a control-based pattern imputation using PROC MI methodology in SAS. The model is adjusted for treatment group, pooled center, and baseline value.*

**Figure 4: Change from Baseline in CSFQ-14 Total Score at Week 8 Across Analysis Methods (FAS, MMRM, LOCF, OC)**




Source: Figure 11.b of Sponsor's Clinical Study Report (Page 74)
*p<0.05 vs escitalopram. (a) LS means and p-values were from an MMRM model and with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.
(b) LS means were from an ANCOVA model with treatment and pooled center as fixed factors and the baseline value as a covariate.

Analyses based on only observed cases (OC) and LOCF where follow-up missing data can be replaced by a subject's previously observed value. Both supportive analyses might have shown consistency with the MMRM based approach; however, these analyses make restrictive assumptions about missing data and results might not adequately generalize the population under investigation. Compared to MMRM, inference based on LOCF and OC are more likely biased as they would more likely overestimate or underestimate treatment effects.

**Exploratory Secondary Endpoints**

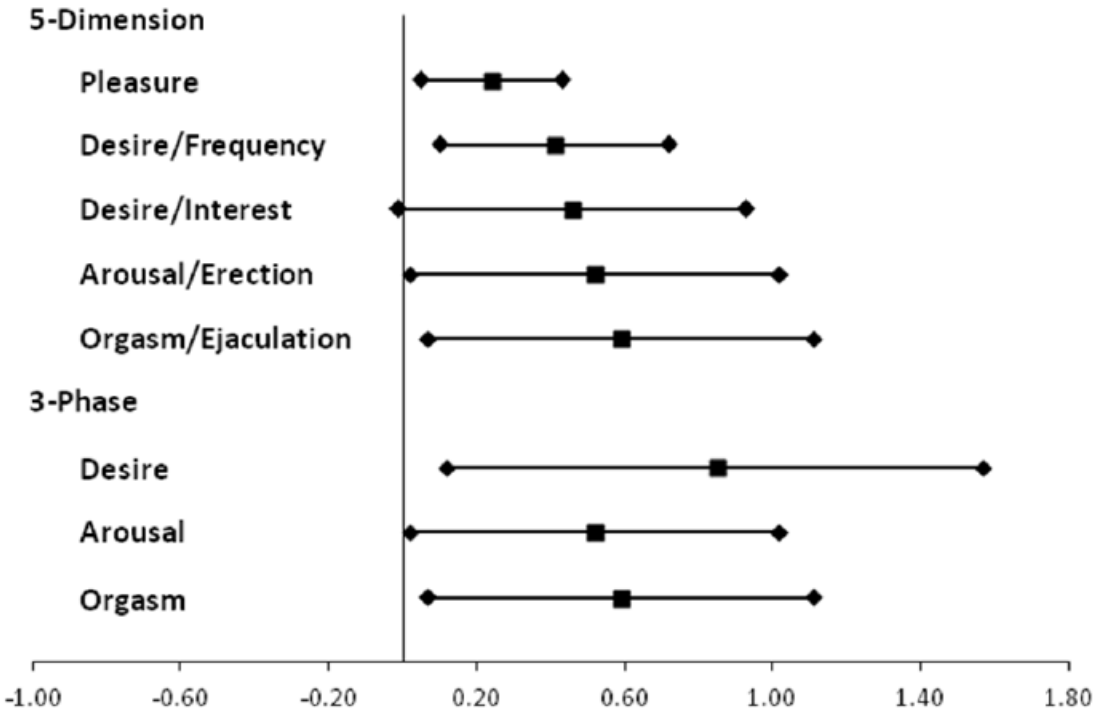
This reviewer confirmed analysis of the CSFQ-14 subscales. In addition to the CSFQ-14 total score, sexual function was assessed using the subscales: 5-dimension and 3-phase of the sexual function questionnaire.

1. 5-dimensions of CSFQ-14 subscales: pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation.
2. 3-phases of CSFQ-14 subscales: desire, arousal, and orgasm/completion.

Vortioxetine showed a statistically significant separation from escitalopram at week 8 in the 5-dimension subscale measures of pleasure (p=0.015), desire/frequency

(p=0.010), arousal/erection (p=0.042), and orgasm (p=0.026) at a nominal significance level of 0.05 (that is, without multiplicity adjustment). There was numerical improvement at week 8 for desire/interest. Similarly, statistically significant difference was achieved over escitalopram at week 8 for the 3-phases of sexual functioning with respect to measures of desire (p=0.022), arousal (p=0.042), and orgasm (p=0.026) at a nominal significance level of 0.05.

**Figure 5: Change from Baseline in CSFQ-14 Subscales: 5-Dimension and 3 Phases of Sexual Functioning at Week 8 (FAS, MMRM)**




Source: Figure 11.d from Clinical Study Report (Page 78)
Note: LS means were from an MMRM model with Baseline×week, pooled center, week, treatment and week×treatment as factors in the analysis.
Note: Measures of arousal/erection and orgasm on the 5-dimension subscale are the same as measures of arousal and orgasm on the 3-phases of sexual functioning.

**Major Protocol Deviations**

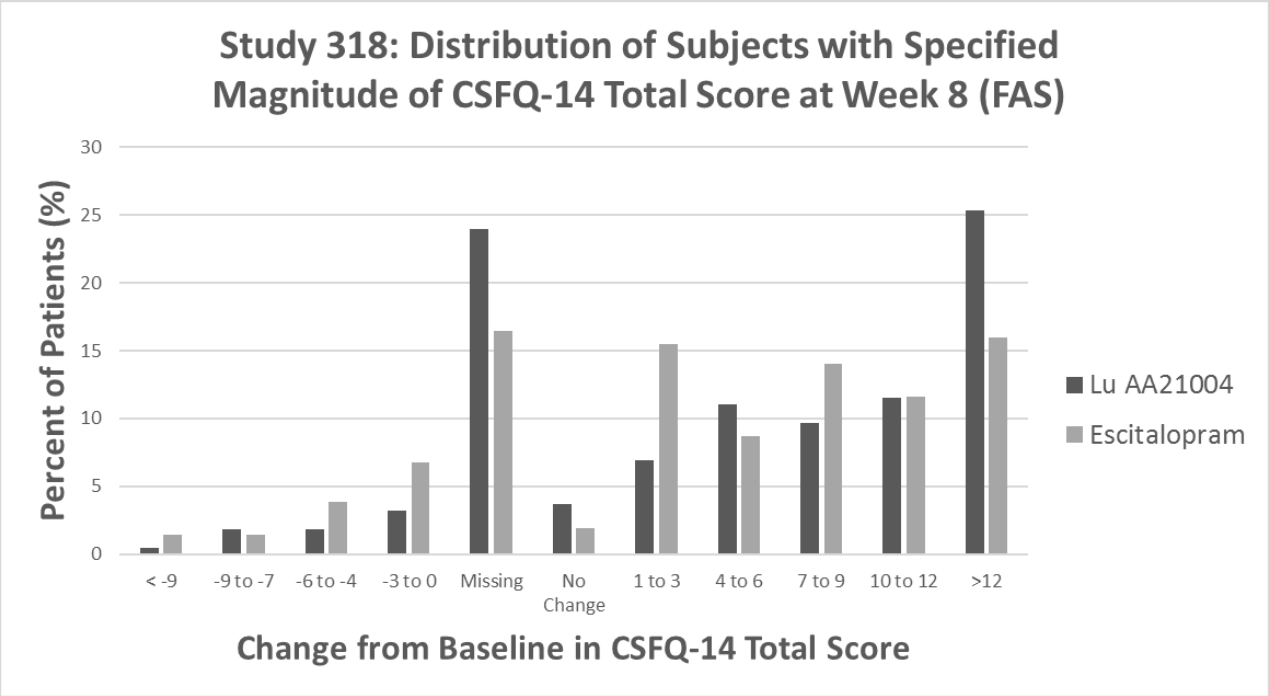
Based on the PPS (Per-Protocol Set), efficacy conclusions were consistent with the primary efficacy results. Vortioxetine is statistically significantly different from escitalopram at week 8 (LS mean (SE) = 2.2 (0.92); p = 0.016).

*PPS*: all FAS subjects with no major protocol violations.

**Reviewer's Note:** This reviewer has included two figures to visualize the distribution of change in CSFQ-14 total score and percent of improved subjects (Figure 6, Figure 7).

Figure 6 captures the distribution of change from baseline in CSFQ-14 total score, where a positive change corresponds to improvement and a negative change corresponds to worsening. As seen in this figure, the vortioxetine group had a larger proportion of patients with more than 12 points improvement. It is also noted that a larger proportion of patients in the vortioxetine group dropped out.

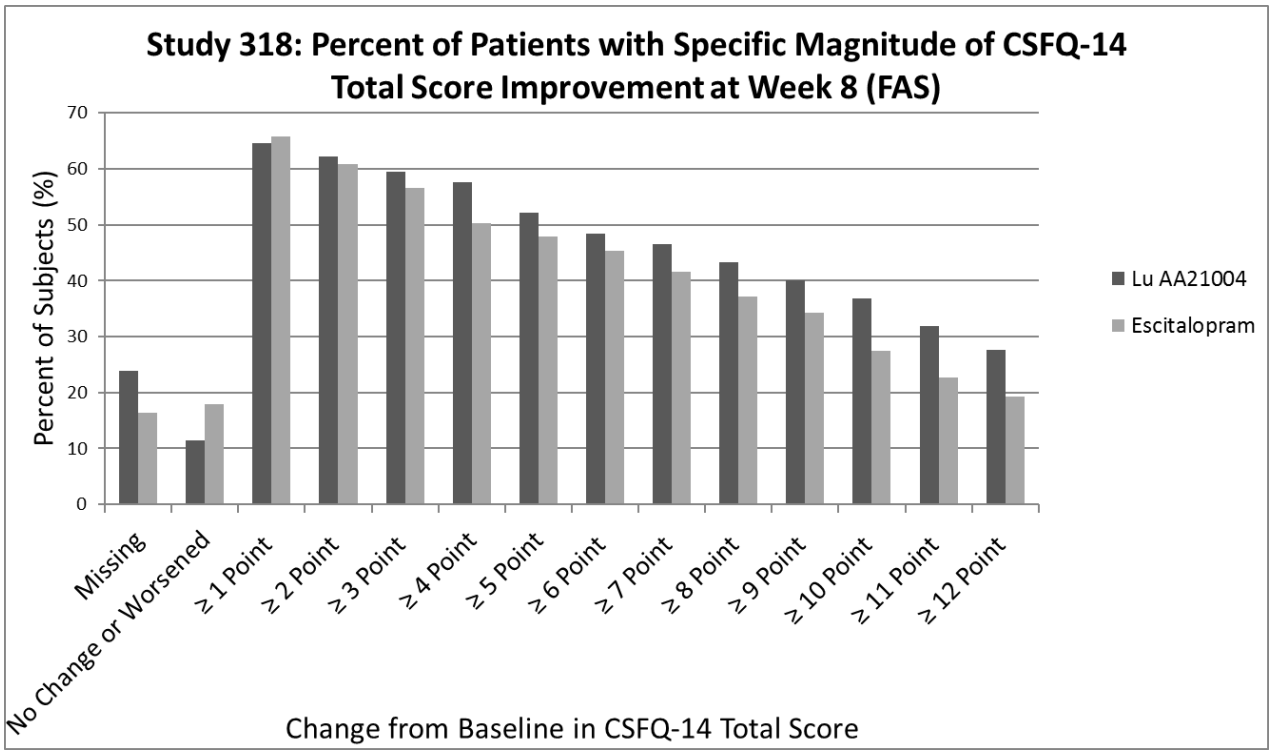
**Figure 6: Percent of Patients with Specified Magnitude of CSFQ-14 Total Score Improvement at Week 8 (FAS)**




Source: Reviewer's Result. Note that a positive change indicates improvement, and a negative change indicates worsening.

The graph in Figure 7 shows a trend of improvement in change from baseline in CSFQ-14 total score at Week 8 at various subjective response cutoffs. As observed in this figure, slightly more than 60% of the patients in each treatment group improved at least by 2 points.

**Figure 7: Percent Response (CSFQ-14 Total Score) for Each Treatment Group at Week 8 by Response Threshold**




Source: Reviewer's Result

### 3.2.4.2 Study 4001

**Primary Endpoint**

The reviewer confirmed sponsor's efficacy findings as shown in Table 8. Using ANCOVA (LOCF), vortioxetine 10 mg/day was shown to be associated with statistically significantly less TESD than paroxetine 20 mg/day in the mean change from baseline in CSFQ-14 at Week 5 (p = 0.009). The least square mean treatment difference was 2.74 points.

The change from baseline in CSFQ-14 total score vortioxetine 20 mg/day group did not separate statistically significantly from paroxetine 20 mg/day whether adjusting for multiplicity or not (LS Mean = 1.05; nominal p = 0.303).

**Table 8: Change from Baseline in CSFQ-14 Total Score at Week 5 (FAS, ANCOVA, LOCF)**

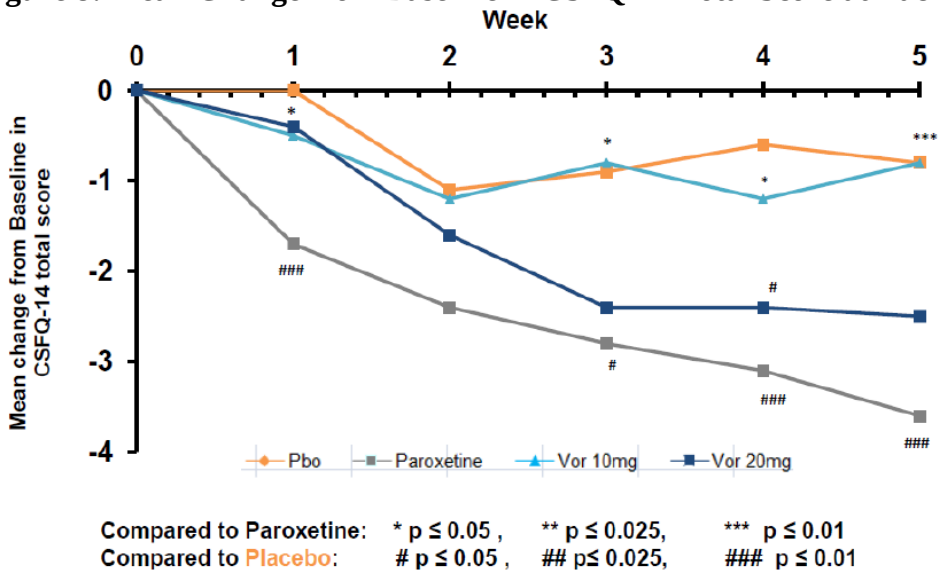
| | Placebo (N=89) | Paroxetine 20 mg/day (N=83) | Vortioxetine 10 mg/day (N=85) | Vortioxetine 20 mg/day (N=91) |
|---|---|---|---|---|
| Baseline | | | | |
| N | 89 | 83 | 85 | 91 |
| LS mean (SE) | 59.25 (0.566) | 59.27 (0.584) | 58.56 (0.578) | 59.43 (0.560) |

| | | | | |
|---|---|---|---|---|
| Change from Baseline to Week 5 | | | | |
| N | 89 | 83 | 85 | 91 |
| LS mean (SE) | -0.79 (0.734) | -3.56 (0.758) | -0.82 (0.752) | -2.51 (0.727) |
| **Primary Efficacy Analysis** | | | | |
| Vortioxetine vs paroxetine | | | | |
| LS mean difference (SE) | | | 2.74 (1.040) | 1.05 (1.017) |
| 95% CI for diff. in LS means | | | (0.69, 4.78) | (-0.95, 3.05) |
| p-value† | | | 0.009† | 0.303 |
| **Secondary Efficacy Analysis** | | | | |
| Active drug vs placebo | | | | |
| LS mean difference (SE) | | -2.77 (1.024) | -0.03 (1.018) | -1.72 (1.000) |
| 95% CI for diff. in LS means | | (-4.78, -0.75) | (-2.03, 1.97) | (-3.68, 0.25) |
| p-value† | | 0.007 | 0.977 | 0.087 |

Source: Table 11.h of Sponsor's Clinical Study Report (Page 75)
†: p-values were not adjusted for multiplicity. For the primary comparison (each vortioxetine dose compared with paroxetine), the Holm-Bonferroni method was used to control the overall Type I error rate. Based on this approach, only vortioxetine 10 mg is shown superior to paroxetine.
CI = confidence interval; LS mean = least-squares means; MMRM = mixed model repeated measures; SE = standard error
Baseline value is defined as the last observation before the administration of study drug.
Postbaseline LS means and p-values were obtained using ANCOVA model with treatment, pooled center, and gender as fixed factors and with baseline CSFQ-14 total score as a covariate.

Figure 8 presents the mean profile plot for each treatment group by visit along with the least square mean change from baseline.

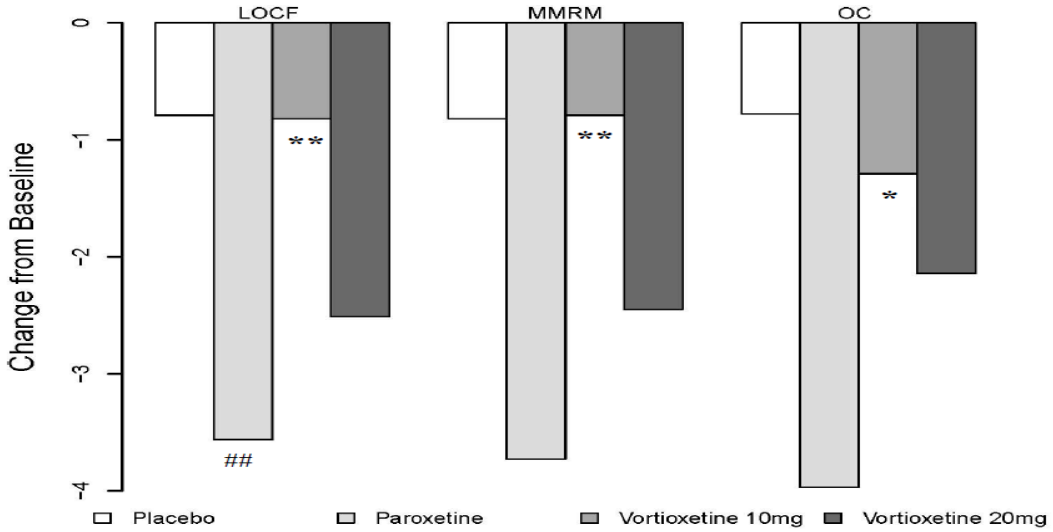
**Figure 8: Mean Change from Baseline in CSFQ-14 Total Score at Each Visit (FAS, LOCF)**




Source: Figure 11.f of Sponsor's Clinical Study Report (Page 85). Using Holm-Bonferroni method the smallest p-value < 0.025; other p-values are compared against 0.05.

Supportive analyses using observed data and MMRM confirmed the primary efficacy analysis (Vortioxetine 10 mg/day compared to paroxetine 20 mg/day was statistically significant across the methods).

**Figure 9: Change from Baseline in CSFQ-14 Total Score at Week 5 Across Analysis Methods (FAS, LOCF, MMRM, OC)**




Source: Figure 11.a of Sponsor's Clinical Study Report (Page 76)

**Reviewer's Note 1**: Figure 9 suggests that paroxetine treatment group has the worst change from baseline in CSFQ-14 total score compared to vortioxetine 10 mg and vortioxetine 20 mg groups. Improvement in sexual dysfunction is correlated with increasing CSFQ-14 total score. However, since the population enrolled in Study 4001 was healthy volunteers, it is expected that some of the volunteers will have experienced some degree of sexual dysfunction, hence the negative change from baseline in the primary endpoint. Thus, the group that performs the worst will have large negative change from baseline in CSFQ-14 total score at week 5.

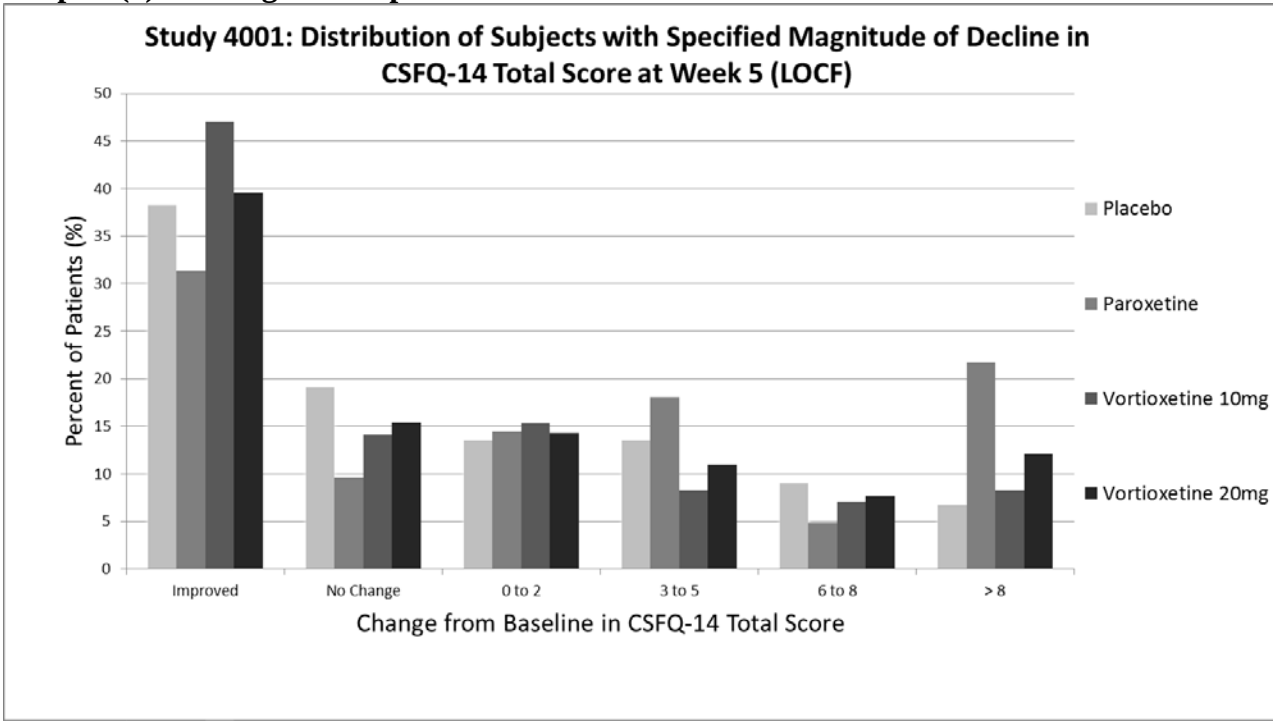
On the other hand, Study 318 enrolled subjects with MDD and improvement in TESD is associated with positive shift from baseline in CSFQ-14 total score.

**Reviewer's Note 2**: Figure 10 and Figure 11 below display distribution of change in CSFQ-14 total score and percent of worsened subjects for further data exploration. Figure 10 shows the distribution of worsening data categorized in a 2-unit bin; subjects who improved are lumped together in the far left bin. Because the enrolled subjects are expected to be normal in sexual function at baseline, the review focus is on whether they got worsened. In the subplot (a) of this figure, missing data were imputed using the LOCF approach, whereas in the subplot (b) of this figure, missing data were not imputed and a bin associated with missing data is thus added to this subplot. Both subplots suggest that a larger proportion of subjects in the vortioxetine 20 mg generally had worse outcomes than those in the vortioxetine 10 mg. Also, paroxetine had the largest proportion of subjects who got worsened followed by vortioxetine 20mg and vortioxetine 10mg, in patients with > 8 points magnitude of decline. However, for the improved subgroup, the two subplots display different patterns: slightly more proportion of subjects improved in the vortioxetine 20 mg compared with the vortioxetine 10 mg if missing data are not imputed.

The empirical percentage decline in response for each treatment group by arbitrary response cutoffs at week 5 is shown in Figure 11. Again, in subplot (a) missing data were imputed by the LOCF approach, whereas in subplot (b) missing data were not imputed. For the subgroup of subjects who got worsened, the two subplots reveal similar patterns: a consistently smaller proportion of subjects who got worsened at Week 5 for both vortioxetine groups versus paroxetine, as well as for vortioxetine 20 mg versus vortioxetine 10 mg, at several arbitrary decline magnitudes.

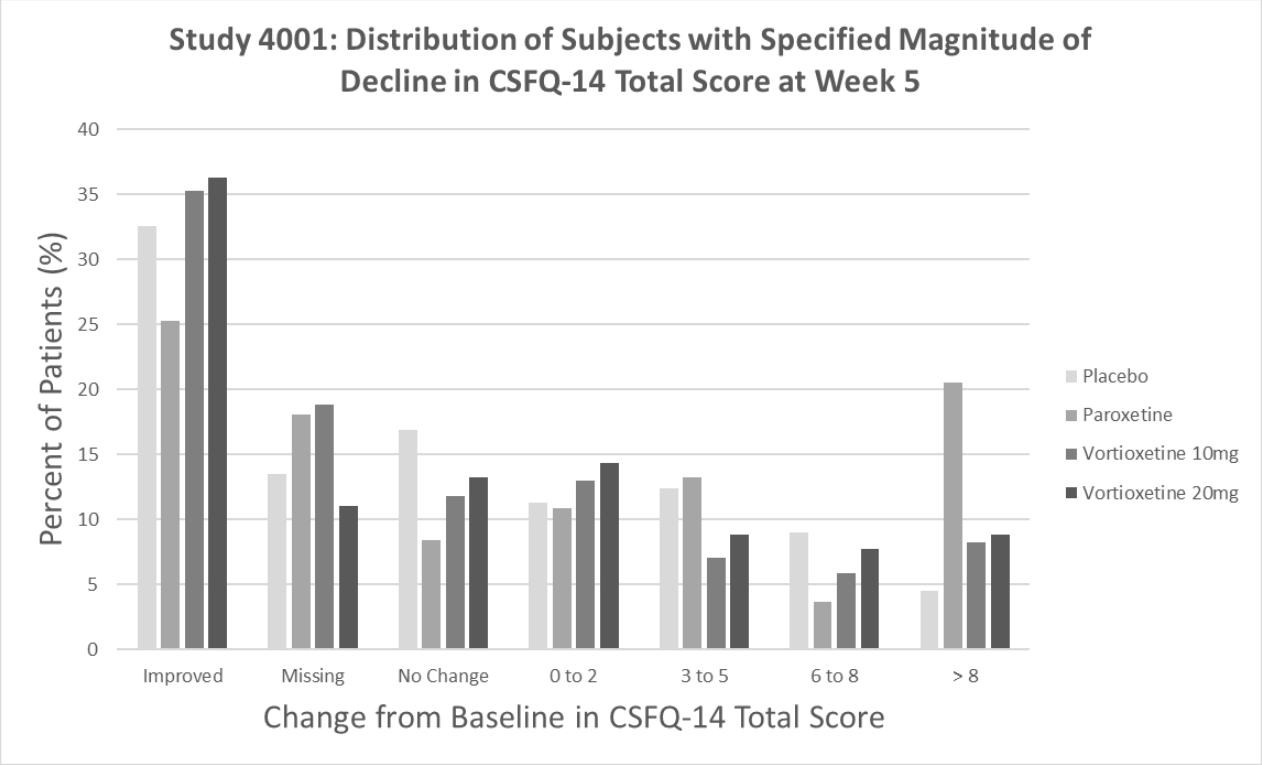
**Figure 10: Percent of Patients with Specified Magnitude of Decline in CSFQ-14 Total Score at Week 5 (FAS)**

**Subplot (a): missing data imputation based on LOCF**




Source: Reviewer's Result

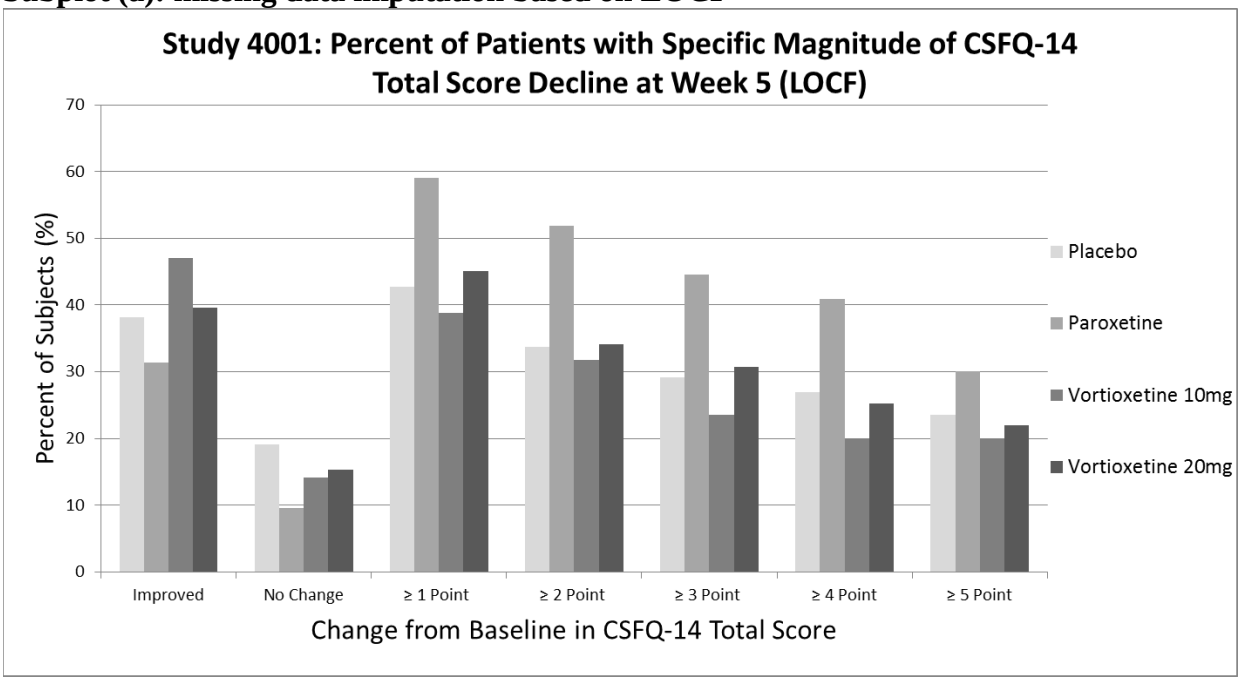
**Subplot (b): missing data not imputed**




Source: Reviewer's Result

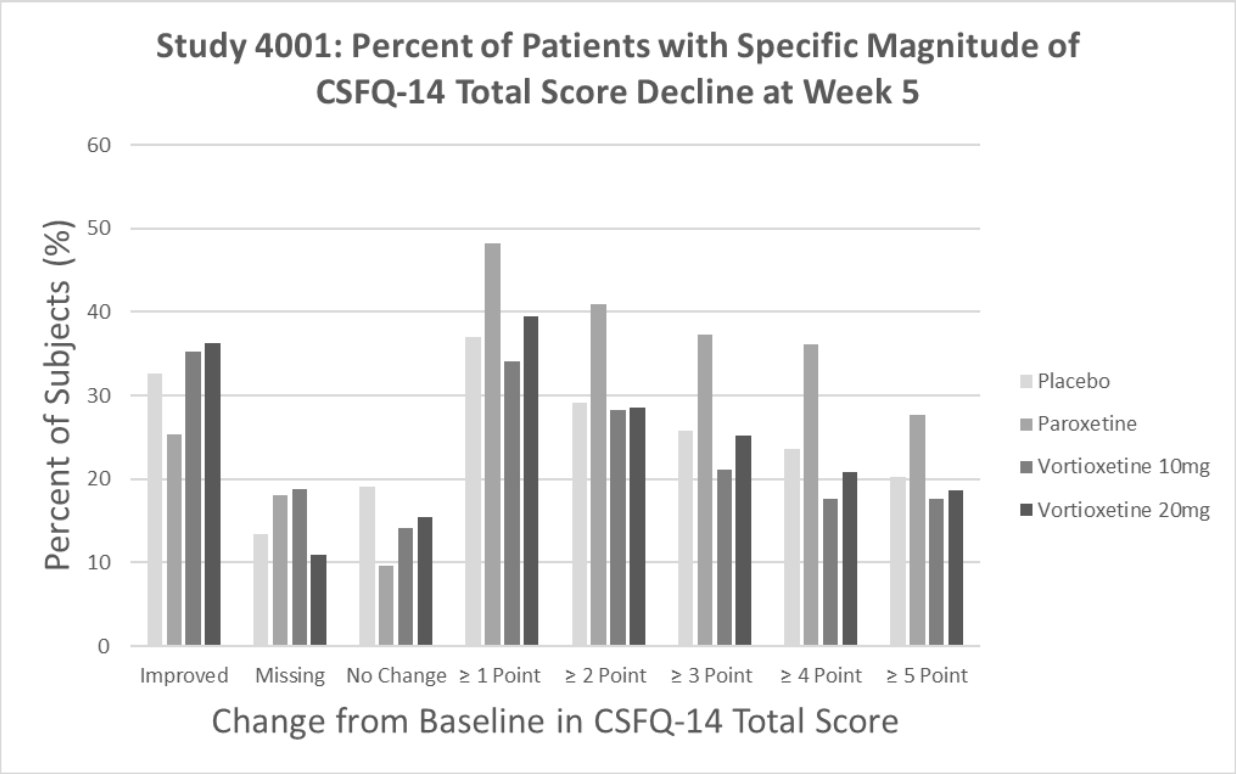
**Figure 11: Percent of Subjects with Certain Magnitude of Decline (CSFQ-14 Total Score) for Each Treatment Group at Week 5 by Decline Threshold**

**Subplot (a): missing data imputation based on LOCF**




Source: Reviewer's Result

**Subplot (b): missing data not imputed**




Source: Reviewer's Result

### 3.3 Evaluation of Safety

Safety evaluation was not conducted in this review.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the reviewer's results of subgroup analyses. For exploratory purposes, the primary efficacy models were used to investigate treatment effect in the subgroups.

### 4.1 Gender, Race, Age, and Geographic Region

This reviewer conducted exploratory subgroup analysis by race, gender and age according to the respective primary efficacy analyses models specified. Age subgroup is categorized using a median cutoff.

In both studies, whites had larger numerical improvement in TESD than non-whites in vortioxetine groups compared to either escitalopram (Study 318) or paroxetine (Study 4001). In study 318, subjects who had median age $\leq 41$ years of age and men subgroups had greater numerical improvement in TESD. In Study 4001, subjects with median age > 28 years of age and men had numerically larger effect in vortioxetine 10 mg versus paroxetine.

**Study 318**

**Table 9: Study 318 Subgroup Analysis by Race: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS[◊] Mean Change from Baseline | | | LS[◊] Mean Difference from Escitalopram | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD[*]) | N | Mean | SE[#] | Mean | SE[#] |
| **White** | | | | | | | |
| **Escitalopram** | 171 | 36.33 (5.49) | 141 | 6.12 | 0.70 | -- | -- |
| **Vortioxetine** | 174 | 36.44 (5.61) | 131 | 8.67 | 0.72 | 2.55 | 0.99 |
| **Non-White** | | | | | | | |
| **Escitalopram** | 36 | 35.64 (6.52) | 32 | 7.31 | 1.69 | -- | -- |
| **Vortioxetine** | 43 | 36.07 (6.50) | 34 | 9.20 | 1.50 | 1.89 | 2.24 |

[*]Standard Deviation, [#]Standard Error, [◊]Least Squares
Source: Reviewer's Results

**Table 10: Study 318 Subgroup Analysis by Gender: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS[◊] Mean Change from Baseline | | | LS[◊] Mean Difference from Escitalopram | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD[*]) | N | Mean | SE[#] | Mean | SE[#] |
| **Male** | | | | | | | |
| **Escitalopram** | 78 | 40.5 (4.03) | 65 | 5.4 | 1.08 | -- | -- |
| **Vortioxetine** | 91 | 39.8 (5.38) | 69 | 8.4 | 1.02 | 3.0 | 1.42 |
| **Female** | | | | | | | |
| **Escitalopram** | 129 | 33.6 (4.94) | 108 | 7.0 | 0.84 | -- | -- |
| **Vortioxetine** | 126 | 33.9 (4.73) | 27 | 9.2 | 0.88 | 2.3 | 1.20 |

[*]Standard Deviation, [#]Standard Error, [◊]Least Squares
Source: Reviewer's Results

**Table 11: Study 318 Subgroup Analysis by Age: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS[◊] Mean Change from Baseline | | | LS[◊] Mean Difference from Escitalopram | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD[*]) | N | Mean | SE[#] | Mean | SE[#] |
| **Age <= 41** | | | | | | | |
| **Escitalopram** | 107 | 35.6 (5.90) | 91 | 7.3 | 0.89 | -- | -- |
| **Vortioxetine** | 117 | 36.3 (5.67) | 91 | 10.3 | 0.87 | 3.1 | 1.23 |
| **Age > 41** | | | | | | | |
| **Escitalopram** | 100 | 36.9 (5.37) | 82 | 5.3 | 0.97 | -- | -- |
| **Vortioxetine** | 100 | 36.4 (5.95) | 74 | 6.8 | 0.98 | 1.5 | 1.37 |

[*]Standard Deviation, [#]Standard Error, [◊]Least Squares
Source: Reviewer's Results

## Study 4001

**Table 12: Study 4001 Subgroup Analysis by Race: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS◊ Mean Change from Baseline | | | LS◊ Mean Difference from Paroxetine | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD*) | N | Mean | SE# | Mean | SE# |
| **White** | | | | | | | |
| **Placebo** | 50 | 58.5 (6.73) | 50 | -0.12 | 0.78 | -- | -- |
| **Paroxetine** | 49 | 60.1 (5.79) | 49 | -4.12 | 0.82 | -- | -- |
| **Vortioxetine 10 mg** | 48 | 59.9 (4.47) | 48 | 0.31 | 0.80 | 4.42 | 1.07 |
| **Vortioxetine 20 mg** | 53 | 59.8 (4.18) | 53 | -1.29 | 0.80 | 2.82 | 1.04 |
| **Non-White** | | | | | | | |
| **Placebo** | 39 | 60.7 (6.18) | 39 | -1.02 | 1.51 | -- | -- |
| **Paroxetine** | 34 | 58.5 (5.07) | 34 | -1.45 | 1.70 | -- | -- |
| **Vortioxetine 10 mg** | 37 | 57.6 (5.71) | 37 | -1.70 | 1.62 | -0.25 | 2.01 |
| **Vortioxetine 20 mg** | 38 | 59.5 (5.04) | 38 | -3.17 | 1.62 | -1.72 | 2.00 |

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Reviewer's Results

**Table 13: Study 4001 Subgroup Analysis by Gender: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS◊ Mean Change from Baseline | | | LS◊ Mean Difference from Paroxetine | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD*) | N | Mean | SE# | Mean | SE# |
| **Male** | | | | | | | |
| **Placebo** | 43 | 61.5 (5.33) | 43 | -0.46 | 0.91 | -- | -- |
| **Paroxetine** | 41 | 60.9 (4.77) | 41 | -3.70 | 0.93 | -- | -- |
| **Vortioxetine 10 mg** | 44 | 60.8 (4.44) | 44 | -0.06 | 0.88 | 3.65 | 1.23 |
| **Vortioxetine 20 mg** | 48 | 60.3 (4.54) | 48 | -0.48 | 0.86 | 3.22 | 1.20 |
| **Female** | | | | | | | |
| **Placebo** | 46 | 57.5 (7.02) | 46 | -0.74 | 1.16 | -- | -- |
| **Paroxetine** | 42 | 58.0 (5.91) | 42 | -3.15 | 1.21 | -- | -- |
| **Vortioxetine 10 mg** | 41 | 56.8 (5.10) | 41 | -1.31 | 1.24 | 1.84 | 1.71 |
| **Vortioxetine 20 mg** | 43 | 59.1 (4.48) | 43 | -4.43 | 1.21 | -1.28 | 1.67 |

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Reviewer's Results

**Table 14: Study 4001 Subgroup Analysis by Age: CSFQ-14 Total Score (FAS, MMRM)**

| | Baseline | | LS◊ Mean Change from Baseline | | | LS◊ Mean Difference from Paroxetine | |
|---|---|---|---|---|---|---|---|
| Treatment Group | N | Mean (SD*) | N | Mean | SE# | Mean | SE# |
| **Age <= 28** | | | | | | | |
| **Placebo** | 50 | 59.22 (6.55) | 50 | -0.78 | 1.07 | -- | -- |
| **Paroxetine** | 43 | 59.88 (5.34) | 43 | -2.60 | 1.15 | -- | -- |
| **Vortioxetine 10 mg** | 48 | 58.79 (4.98) | 48 | -0.72 | 1.11 | 1.89 | 1.54 |
| **Vortioxetine 20 mg** | 47 | 59.70 (4.69) | 47 | -2.27 | 1.10 | 0.33 | 1.53 |
| **Age > 28** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Placebo** | 39 | 59.74 (6.61) | 39 | -1.12 | 1.17 | -- | -- |
| **Paroxetine** | 40 | 58.97 (5.77) | 40 | -4.55 | 1.09 | -- | -- |
| **Vortioxetine 10 mg** | 37 | 59.03 (5.43) | 37 | -1.23 | 1.20 | 3.32 | 1.50 |
| **Vortioxetine 20 mg** | 44 | 59.73 (4.41) | 44 | -3.15 | 1.12 | 1.41 | 1.42 |

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Reviewer's Results

### 4.2 Other Special/Subgroup Populations: U.S. versus Non-US

Both studies were conducted either in the US and/or Canada.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

In study 4001, (b) (4) Whether adjusting for multiplicity or not, however, vortioxetine 20 mg/day did not meet statistical significance compared to paroxetine in the change from baseline in CSFQ-14 total score (LS Mean = 1.05; nominal p = 0.303).

### 5.2 Collective Evidence

Study 318 showed that the flexible vortioxetine dose was beneficial for the treatment of TESD caused because of antidepressant use. Study 4001 was conducted in healthy volunteers to assess comparative effectiveness of vortioxetine versus other antidepressants with respect of TESD.

Sexual dysfunction has become a common adverse event because of continuous use of antidepressant medications such as SSRIs and SNRIs. As a public health concern, Takeda has conducted two studies which investigated comparative advantage of vortioxetine over existing antidepressant treatments if it improves treatment emergent sexual dysfunction (TESD). TESD was assessed using the 14-item instrument, Changes in Sexual Functioning Questionnaire, CSFQ-14.

### 5.3 Conclusions and Recommendations

In Study 318, the flexible vortioxetine dose, was efficacious for the treatment of TESD in patients well-treated with MDD. In Study 4001, which enrolled healthy volunteers, vortioxetine (10 mg/day) was associated with statistically significantly less TESD than paroxetine (20 mg/day). Vortioxetine (20 mg/day) failed to reach statistical significance whether adjusting for multiplicity or not.

(b) (4) recommended dose of vortioxetine for the treatment of MDD in the US is 20 mg/day, (b) (4)

(b) (4) decision is deferred to the clinical review team.

---

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

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/s/
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SEMHAR B OGBAGABER
08/31/2018

PEILING YANG
08/31/2018

HSIEN MING J HUNG
09/04/2018

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204447Orig1s017

# ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 204447 SUPPL # S-017 HFD # 130

Trade Name Trintellix

Generic Name vortioxetine

Applicant Name Takeda Pharmaceuticals USA, Inc.

Approval Date, If Known October 19, 2018

**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

SE4

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 Trintellix (vortioxetine) approved on 9/30/2013

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:

- Study 318 (n=447, 57 sites in the U.S. and 9 sites in Canada, flexible doses of vortioxetine (VOR) 10 mg and 20 mg Q day versus flexible doses of Escitalopram (ESC) 10 mg and 20 mg Q day). The primary endpoint in this study was the change from baseline in Changes in Sexual Functioning Questionnaire-Brief (CSFQ-14) total score VOR vs ESC after 8 weeks of treatment. The secondary endpoint was the change from baseline in CSFQ-14 total score VOR vs ESC in each visit assessed and a shift in baseline CSFQ-14 from abnormal (defined as a CSFQ-14 total score ≤ 41 for women and ≤47 for men) to normal (no sexual dysfunction) at each visit.
- Study 4001 (n=361, 16 sites in the U.S., fixed-dose of VOR 10 mg or 20 mg Q day versus fixed-dose of Paroxetine (PAR) 20 mg Q day, and placebo (PBO). The primary endpoint in this study was the change from baseline in CSFQ-14 total score VOR vs PAR after 5 weeks of treatment. The secondary endpoints are change from baseline in:
  - CSFQ-14 total score VOR vs PAR at each visit assessed.
  - CSFQ-14 total score PAR vs PBO at each visit assessed (to validate study)
  - CSFQ-14 total score VOR vs PBO at each visit assessed.
  - Percentage of subjects meeting criteria for sexual dysfunction at any visit during the 5-week double-blind treatment period
  - CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation); and 3 phases of the sexual response cycle (desire, arousal, and orgasm/completion) at each visit assessed

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 318 (n=447, 57 sites in the U.S. and 9 sites in Canada, flexible doses of vortioxetine (VOR) 10 mg and 20 mg Q day versus flexible doses of Escitalopram (ESC) 10 mg and 20 mg Q day). The primary endpoint in this study was the change from baseline in Changes in Sexual Functioning Questionnaire-Brief (CSFQ-14) total score VOR vs ESC after 8 weeks of treatment. The secondary endpoint was the change from baseline in CSFQ-14 total score VOR vs ESC in each visit assessed and a shift in baseline CSFQ-14 from abnormal (defined as a CSFQ-14 total score ≤ 41 for women and ≤47 for men) to normal (no sexual dysfunction) at each visit.
- Study 4001 (n=361, 16 sites in the U.S., fixed-dose of VOR 10 mg or 20 mg Q day versus fixed-dose of Paroxetine (PAR) 20 mg Q day, and placebo (PBO). The primary endpoint in this study was the change from baseline in CSFQ-14 total score VOR vs PAR after 5 weeks of treatment. The secondary endpoints are change from baseline in:
  - CSFQ-14 total score VOR vs PAR at each visit assessed.
  - CSFQ-14 total score PAR vs PBO at each visit assessed (to validate study)
  - CSFQ-14 total score VOR vs PBO at each visit assessed.
  - Percentage of subjects meeting criteria for sexual dysfunction at any visit during the 5-week double-blind treatment period
  - CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency,

desire/interest, arousal/erection, and orgasm/ejaculation); and 3 phases of the sexual response cycle (desire, arousal, and orgasm/completion) at each visit assessed

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 # 76307 | 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: Jasmeet (Mona) Kalsi
Title: Regulatory Project Manager
Date: 10/15/18

Name of Division Director signing form: Mitchell V. Mathis, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/
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JASMEET K KALSI
10/19/2018

MITCHELL V Mathis
10/19/2018

## Kalsi, Jasmeet (Mona)

**From:** Kalsi, Jasmeet (Mona)
**Sent:** Monday, October 15, 2018 10:26 AM
**To:** 'Sambor, Joanna'
**Subject:** NDA 204447/S-017 Labeling | Round 2
**Attachments:** Round 2_FDA Response_Trintellix_NDA204447-s017_15Oct2018.docx

**Importance:** High

Good Morning Joanna,

I apologize for the delay - Please find attached the label for NDA 204447/s-017 with the requested changes which are tracked and/or enclosed in highlighted comments. Please accept all tracked changes, and use this as the base document. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text/not accepting our request.

If you accept all of our edits, please submit your label formally to the application as the final label. Please let me know if you have any questions or concerns.

Thank you,
Mona

**Jasmeet (Mona) Kalsi, PharmD**
*LT, United States Public Health Service*
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

**U.S. Food and Drug Administration**
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov



31 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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JASMEET K KALSI
10/15/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration**
**Silver Spring, MD 20993**

NDA 204447/S-017

**LABELING PMR/PMC DISCUSSION COMMENTS**

Takeda Pharmaceuticals, USA, Inc.
Attention: Joanna Sambor, MS
Senior Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your supplemental New Drug Application (sNDA) dated December 21, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trintellix (vortioxetine) 5mg, 10mg, and 20mg tablets.

We also refer to our February 15, 2018, letter in which we notified you of our target date of September 21, 2018, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2018 Through 2022."

On September 5, 2018, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by September 27, 2018. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, call me at (240) 402-8977 or e-mail Jasmeet.Kalsi@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Jasmeet (Mona) Kalsi, PharmD
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

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JASMEET K KALSI
09/21/2018

## Kalsi, Jasmeet (Mona)

**From:** Kalsi, Jasmeet (Mona)
**Sent:** Friday, August 24, 2018 12:27 PM
**To:** Sambor, Joanna
**Cc:** Kalsi, Jasmeet (Mona)
**Subject:** NDA 204447/s-017 Labeling IR

**Importance:** High

Hi Joanna,

This is in reference to your label for NDA 204447/s-017. We would like to request the label be resubmitted with the following changes:

- Details of studies are typically discussed in the CLINICAL STUDIES section of labeling. Please describe the study designs and the primary analysis results of the two studies (Study 318 and Study 4001) in section 14; that is, treat the two studies as typical clinical studies in labeling. Section 14 should include a figure of visit-wide mean change from baseline in CSFQ-14 total score for the fixed-dose study (Study 4001).
- Safety in terms of frequency, severity, or characterization of adverse reactions are reserved for the ADVERSE REACTIONS section. Please update your proposal for section 6 accordingly.
- For additional information on the proper placement and description of comparative data (for sections 6 and 14), refer to the following guidances:
    - Guidance for Industry Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format
    - Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format

So that we can stay on track with the timeline, please submit the updated label by **August 29, 2018**, or sooner.

Thank you,
Mona

**Jasmeet (Mona) Kalsi, PharmD**
*LT, United States Public Health Service*
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

**U.S. Food and Drug Administration**
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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/s/

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JASMEET K KALSI
08/24/2018

U.S. FOOD & DRUG ADMINISTRATION

Sarah D. Atkinson, M.D.
885 Winton Road South
Rochester, NY 14618-1609

Dear Dr. Atkinson:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between April 24 and April 27, 2018. Investigator Benton Ketron, representing FDA, reviewed your conduct of a clinical investigation (Protocol Lu AA21004-318, "A Randomized, Double-Blind, Parallel-Group, Active-Controlled, Flexible-Dose Study Evaluating the Effect of Lu AA21004 vs Escitalopram on Sexual Functioning in Adults with Well-Treated Major Depressive Disorder Experiencing Selective Serotonin Reuptake Inhibitor–Induced Sexual Dysfunction") of the investigational drug vortioxetine, performed for Takeda Pharmaceuticals, USA, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Mr. Ketron presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the FDA Establishment Inspection Report, and the documents submitted with the report. We acknowledge your May 16, 2018 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspection findings.

We appreciate the cooperation shown to Investigator Ketron during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please write to me at the address below.

Sincerely,

*{See appended electronic signature page}*

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 5222
Silver Spring, MD 20993-0002

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/s/

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PHILLIP D KRONSTEIN
07/31/2018

U.S. FOOD & DRUG ADMINISTRATION

Michael J. Downing, M.D.
5445 La Sierra Drive, Suite 101
Dallas, TX, 75231-3442

Dear Dr. Downing:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between May 23 and May 30, 2018. Investigator Camille Brown, representing FDA, reviewed your conduct of a clinical investigation (Protocol Vortioxetine-4001, "A Randomized, Double-Blind, Parallel Group, Placebo- and Active-Controlled, Phase 4 Study Evaluating the Effect of Vortioxetine 10 and 20 mg/day vs Paroxetine 20 mg/day on Sexual Functioning in Healthy Subjects") of the investigational drug vortioxetine, performed for Takeda Pharmaceuticals, USA, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Ms. Brown presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the FDA Establishment Inspection Report, and the documents submitted with the report. We acknowledge your June 15, 2018 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspection findings.

We appreciate the cooperation shown to Investigator Brown during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please write to me at the address below.

Sincerely,

*{See appended electronic signature page}*

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 5222
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PHILLIP D KRONSTEIN
07/30/2018

## Kalsi, Jasmeet (Mona)

**From:** Kalsi, Jasmeet (Mona)
**Sent:** Monday, May 14, 2018 3:38 PM
**To:** Sambor, Joanna
**Cc:** Kalsi, Jasmeet (Mona)
**Subject:** NDA 204447/S-017 Information Request

Hi Joanna,

This is in reference to your NDA 204447/S-017 submitted on December 21, 2017. The review team has requested the following information:

Reference is made to the Major Protocol Violations on Table 10.d (cross-reference: Table 15.1.5) in Clinical Study Report for Study 318. On page 64 of the CSR, it is specifically mentioned that "*Major protocol violations resulting in removal of subjects from the PPS are summarized in Table 10.d and Appendix 16.2.3. Of note, 10 subjects (2.2%) used the wrong scale or incorrect version of the CSFQ-14 at the Baseline visit and/or during the study they are excluded from all efficacy analyses*." However, exclusion of such patients from the primary analysis set was not pre-specified in your SAP. If it was, please clarify the submission serial numbers. Be aware that in principle, the primary analysis set should include all randomized patients whether there was a major protocol violation.

Please submit a SAS code and relevant datasets to produce efficacy results by adding in the 10 excluded subjects.

To ensure timely review of this application, please respond by **Wednesday, May 16, 2018,** if possible.

Thank you,
Mona

**Jasmeet (Mona) Kalsi, PharmD**
*LT, United States Public Health Service*
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

**U.S. Food and Drug Administration**
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov


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/s/

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JASMEET K KALSI
05/14/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447/S-017

**FILING COMMUNICATION –**
**NO FILING REVIEW ISSUES IDENTIFIED**

Takeda Pharmaceuticals, USA, Inc.
Attention: Joanna Sambor, MS
Senior Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your supplemental New Drug Application (sNDA) dated December 21, 2017, received December 21, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Trintellix (vortioxetine) 5mg, 10mg, and 20mg tablets.

We also refer to your amendments dated January 18, February 5 and 8, 2018.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 21, 2018.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 21, 2018. This date conforms to the 21st Century Review timeline for your application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

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

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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MITCHELL V Mathis
02/15/2018

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

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Mail: OSE**

FROM: **Jasmeet (Mona) Kalsi, PharmD, RPM, Division of Psychiatry Products (DPP)/240-402-8977**
**Anisa Cott, MD, Clinical Reviewer, MO, DPP**
**Javier Muniz, MD, Clinical Reviewer TL, MO, DPP**

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| **2/12/18** | | **204447/S-017** | **sNDA Submission** | **December 21, 2017** |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| **Trintellix (Vortioxetine) Tablets** | **Standard** | | **August 20, 2018** |

NAME OF FIRM: **Takeda Pharmaceuticals**

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
- ☒ **OTHER *(SPECIFY BELOW)*: sNDA Submission**

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ 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:**
**Trintellix (vortioxetine) tablets was approved on Sept 2013. This supplemental NDA is to update the text in the United States Prescribing Information for Trintellix (vortioxetine) and include clinically relevant information for the prescriber and patient describing vortioxetine's superior (comparative) effect on treatment-emergent sexual dysfunction (TESD) based on the outcome of 2 prospective clinical studies.**
**DPP is kindly requesting DMEPA as well as any necessary divisions within OSE to review and attend relevant meetings for this NDA. The PDUFA date is: October 21, 2018 (sign-off date: 10/19/18).**

| | |
|---|---|
| Filing meeting | 2/13/18 |
| Mid-Cycle | 5/14/18 |
| Label Planning | TBD |
| Labeling Meetings | TBD |
| Wrap-up | 9/4/18 |

EDR: \\Cdsesub1\evsprod\NDA204447\0160
SharePoint: NDA 204447 s-017

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check all that apply) |
|---|---|
| Jasmeet Kalsi, PharmD, RPM | ☒ MAIL ☒ DARRTS ☐ HAND |

| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |
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/s/

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JASMEET K KALSI
02/12/2018

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

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Mail: OSE**

FROM: **Jasmeet (Mona) Kalsi, PharmD, RPM, Division of Psychiatry Products (DPP)/240-402-8977**
**Anisa Cott, MD, Clinical Reviewer, MO, DPP**
**Javier Muniz, MD, Clinical Reviewer TL, MO, DPP**

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| **2/12/18** | | **204447/S-017** | **sNDA Submission** | **December 21, 2017** |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| **Trintellix (Vortioxetine) Tablets** | **Standard** | | **August 20, 2018** |

NAME OF FIRM: **Takeda Pharmaceuticals**

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
- ☒ **OTHER *(SPECIFY BELOW)*: sNDA Submission**

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
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- ☐ PHASE IV STUDIES
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**
**Trintellix (vortioxetine) tablets was approved on Sept 2013. This supplemental NDA is to update the text in the United States Prescribing Information for Trintellix (vortioxetine) and include clinically relevant information for the prescriber and patient describing vortioxetine's superior (comparative) effect on treatment-emergent sexual dysfunction (TESD) based on the outcome of 2 prospective clinical studies.**
**DPP is kindly requesting DMEPA as well as any necessary divisions within OSE to review and attend relevant meetings for this NDA. The PDUFA date is: October 21, 2018 (sign-off date: 10/19/18).**

| | |
|---|---|
| Filing meeting | 2/13/18 |
| Mid-Cycle | 5/14/18 |
| Label Planning | TBD |
| Labeling Meetings | TBD |
| Wrap-up | 9/4/18 |

EDR: \\Cdsesub1\evsprod\NDA204447\0160
SharePoint: NDA 204447 s-017

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check all that apply) |
|---|---|
| Jasmeet Kalsi, PharmD, RPM | ☒ MAIL ☒ DARRTS ☐ HAND |

| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |
| --- | --- |
| | |

06/18/2013

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JASMEET K KALSI
02/12/2018

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

# 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)

**Jasmeet (Mona) Kalsi, PharmD, RPM, Division of Psychiatry Products (DPP)/240-402-8977**

**Anisa Cott, MD, Clinical Reviewer, MO, DPP**

**Javier Muniz, MD, Clinical Reviewer TL, MO, DPP**

| REQUEST DATE: | IND NO. | NDA/BLA NO. | TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) |
|---|---|---|---|
| **2/12/18** | | **204447/S-017** | |

| NAME OF DRUG: | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) |
|---|---|---|---|
| **Trintellix (Vortioxetine) Tablets** | **Standard** | | **August 20, 2018** |

NAME OF FIRM:

**Takeda Pharmaceuticals**

PDUFA Date: **October 21, 2018 (sign-off date: 10/19/18)**

## TYPE OF LABEL TO REVIEW

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

**TYPE OF APPLICATION/SUBMISSION**
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

**REASON FOR LABELING CONSULT**
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

**For OSE USE ONLY**
☐ REMS

**EDR link to submission:**

EDR: \\Cdsesub1\evsprod\NDA204447\0160

**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:**
**DPP is requesting OPDP to review the proposed labeling and comment as necessary. We also request your attendance to the meetings listed below and any other relevant meetings which are subject to change. Thanks!**

| | |
|---|---|
| Filing meeting | 2/13/17 |
| Mid-Cycle | 5/14/18 |
| Label Planning | TBD |
| Labeling Meetings | TBD |
| Wrap-up | 9/4/18 |

SIGNATURE OF REQUESTER
**Jasmeet Kalsi, PharmD**

SIGNATURE OF RECEIVER | METHOD OF DELIVERY (Check one)

| | | |
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JASMEET K KALSI
02/12/2018

## Kalsi, Jasmeet (Mona)

**From:** Kalsi, Jasmeet (Mona)
**Sent:** Friday, February 02, 2018 1:09 PM
**To:** Sambor, Joanna
**Cc:** Kalsi, Jasmeet (Mona)
**Subject:** NDA 204447/s-017 Information Request

Hi Joanna,

This is in reference to your NDA 204447/s-017 submitted on December 21, 2017. The review team would like to request the following information regarding studies 318 and 4001:

Reference is made to 'Overview of Treatment-Emergent Adverse Events Safety Set' results listed on Table 15.3.1.1 in Clinical Study Report for Study 318. Also, reference is made to 'Study Medication Exposure and Compliance Safety Analysis Set' results listed on Table 15.1.4 in Clinical Study Report for Study 4001. However, the SAS program that produced the results (t15_3_1_1.sas and t15_1_14.sas) are not submitted to us. Please attach the SAS code and relevant datasets used to produce them.

To ensure timely review of this application, please respond **before 4 PM on Monday, February 5, 2018**.

Thank you,
Mona

**Jasmeet (Mona) Kalsi, PharmD**
*LT, United States Public Health Service*
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

**U.S. Food and Drug Administration**
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov


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/s/

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JASMEET K KALSI
02/02/2018

## Kalsi, Jasmeet (Mona)

**From:** Kalsi, Jasmeet (Mona)
**Sent:** Wednesday, January 17, 2018 2:24 PM
**To:** Sambor, Joanna
**Cc:** Kalsi, Jasmeet (Mona)
**Subject:** NDA 204447/S-017 Information Request

Hi Joanna,

This is in reference to your sNDA submitted on December 21, 2017 for NDA 204447/S-017. The review team would like to request the following:

Reference is made to the primary efficacy results listed on Table 15.2.1.1.5 in Clinical Study Report for Study 318. The SAS program that produced the results (t15_2_1_1_5.sas) is however not submitted to us. Please attach the SAS code and relevant datasets used to produce the efficacy results.

In order to ensure timely review of this application, please respond before **3 PM on Friday, January 19, 2018.**

Thanks,
Mona

**Jasmeet (Mona) Kalsi, PharmD**
*LT, United States Public Health Service*
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Drug Evaluation I**
**Division of Psychiatry Products**

**U.S. Food and Drug Administration**
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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/s/

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JASMEET K KALSI
01/17/2018