NDA Multi-Disciplinary Review and Evaluation

Application Type	PREA PMR Efficacy Supplements
Application Number	204447/S-021; S-022
Priority or Standard	Priority
Submit Date(s)	7/24/20
Received Date(s)	7/24/20
PDUFA Goal Date	1/24/21
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	1/22/21
Established/Proper Name	Vortioxetine
(Proposed) Trade Name	Trintellix
Pharmacologic Class	Antidepressant
Code name	2020100
Applicant	Takeda Pharmaceuticals USA Inc
Doseage form	Oral tablets
Applicant proposed Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	Revisions to the Prescribing Information based upon a fixed-dose study of vortioxetine in pediatric patients aged 12 to 17 years with major depressive disorder
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000 | Major depressive disorder
Recommendation on Regulatory Action	The approved age range (adults) will not be expanded; relevant pediatric information added to labeling
Recommended Indication(s)/Population(s) (if applicable)	N/A (Negative pediatric study in patients aged 12 to 17 years with major depressive disorder)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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

Signatures

See separately archived review memos.

Glossary

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRS	all-patients-randomized set
APTS	all-patients-treated set
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
Avg	average
Beta	β globulin
BMI	body mass index
BPI	brief psychosocial intervention
BW	body weight
CDRS-R	Children's Depression Rating Scale-Revised version
CFR	Code of Federal Regulations
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
Cl	chloride
C_{max}	maximum concentration
CNS	central nervous system
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	double-blind
DMC	data monitoring committee
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	electrocardiogram
eCTD	electronic common technical document
FAS	full-analysis set
Fe	Fisher's Exact Test
FLU	fluoxetine
GBI	General Behavior Inventory
HD	high-dose
HDF	high-dose female
HDM	high-dose male
IND	Investigational New Drug
JAS	Juvenile animal study

K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version
kg	kilogram
LD	low-dose
LDF	low-dose female
LDM	low-dose male
LLT	lowest level term
MD	mid-dose
MDF	mid-dose female
MDM	mid-dose male
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MMRM	mixed model for repeated measurements
N/A	not applicable
NC	not calculated
NDA	new drug application
OLE	open-label extension
OLEXA	baseline in Study 12712A
OLEXB	baseline in Study 12712B
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PBO	placebo
PCS	potentially clinically significant
PedsQL-VAS	Pediatric Quality of Life
PGA	Parent Global Assessment-Global Improvement
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	post-natal day
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
PWR	Pediatric Written Request
REML	restricted maximum likelihood
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SB	single-blind
SD	standard deviation
SDMT	Symbol Digit Modalities Test

Sh	Shirley's test
SIADH	syndrome of inappropriate antidiuretic hormone
SMQ	Standardized MedDRA Query
TK	toxicokinetics
VAS	visual analogue scale
VOR	vortioxetine
Wi	William's test

1 Executive Summary

1.1. Product Introduction

Vortioxetine is a bis-aryl-sulfanyl amine. Its mechanism of action in treating major depressive disorder (MDD) is unknown, but it is a selective inhibitor of the serotonin transporter without significant activity at the norepinephrine and dopamine transporters. In addition, vortioxetine is a potent antagonist at 5-HT3 receptor, a moderate antagonist at 5-HT1D receptor, a moderate agonist at 5-HT1A receptor, a moderate-to-weak partial agonist at 5-HT1B, and a weak antagonist at 5-HT7 receptor. It is available as immediate-release tablets, taken daily, in strengths of 5, 10, and 20 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted an 8-week, randomized, double-blind, placebo-controlled, active-reference study in 615 pediatric patients with MDD ages 12 to 17. This adequate and well-controlled study was negative. The Applicant is not seeking an expansion of the indicated population (adults); relevant pediatric information will be added to labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment
MDD is a serious and debilitating illness affecting approximately 3.2% of U.S. children and adolescents. Effective treatments are needed; however, the clinical trials presented in this supplement did not demonstrate efficacy. Relevant pediatric information will be included in labeling, but the indicated population (adults) will not be expanded.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MDD is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. In severe cases, MDD can result in suicide. • The most recent National Survey of Children's Health study revealed a prevalence of pediatric MDD of 3.2% (approximately 1.9 million U.S. children and adolescents).	MDD is a debilitating and chronic illness, the leading cause of disability worldwide, and a major contributor to the global burden of disease. Although less common than in adults, it is none the less a public health concern among pediatric patients.
Current Treatment Options	• To date, only two antidepressants have been approved for treatment of MDD in pediatric patients. Several other antidepressants have failed to demonstrate efficacy in pediatrics.	There is a need for more treatment options for pediatric MDD.
Benefit	• The vortioxetine adolescent (ages 12 to 17) clinical trail failed to demonstrate efficacy for MDD.	Vortioxetine's indicated population (adults) will not be expanded to include pediatric patients.
Risk and Risk Management	• There were two completed suicides during the study. One after screening (prior to randomization) and the other in a placebo-treated patient. Both had prior histories of suicidal ideation. • Most common adverse events in the adolescent study were nausea, headache, abdominal discomfort/pain, nasopharyngitis, and dizziness.	Safety findings will be reflected in Section 8.4. Based on the data presented with this supplement, the pediatric and adult safety profiles for vilazodone are largely similar.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		8.1.1
		X	Patient reported outcome (PRO)	8.1.1
		X	Observer reported outcome (ObsRO)	8.1.1
		X	Clinician reported outcome (ClinRO)	8.1.1, 8.1.2
		□	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

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), MDD is characterized by depressed mood and loss of interest or pleasure coupled with significant weight or appetite changes, changes in sleep pattern, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide (American Psychiatric Association 2013). An estimated 17.3 million adults in the United States had at least one major depressive episode in 2017, with an estimated incidence of approximately 242 million people worldwide (SAMHSA 2018; GBD 2018). Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and is associated with increased mortality rates (at a median rate of 10 years of life lost; Walker et al. 2015). The most recent National Survey of Children's Health study revealed a prevalence of pediatric MDD of 3.2% (approximately 1.9 million U.S. children and adolescents).

2.2. Analysis of Current Treatment Options

Although pediatric and adult MDD are symptomatically similar, the response to treatment between these populations is markedly different. To date, only two antidepressants (fluoxetine and escitalopram) have demonstrated safety and effectiveness in adequate and well-controlled studies with resultant pediatric indications in product labeling. Clinical studies of other antidepressants have failed to demonstrate efficacy in pediatric patients despite efficacy in adults (e.g., desvenlafaxine, duloxetine, paroxetine, sertraline, venlafaxine). Fluoxetine is approved for the treatment of MDD in pediatric patients ages 8 to 17 years. However, escitalopram is approved for MDD only in patients age 12 years and older. Because of the differential response to treatment between adult and pediatric patients, extrapolation of efficacy from adults to pediatrics is not feasible and pediatric clinical studies are required in order to gain a marketing indication. See Table 1 for a summary of information regarding the antidepressants with labeled indications for pediatric MDD.

Table 1. Antidepressants with Labeled Indications for Pediatric Major Depressive Disorder

Product Name	Year of Approval Adult/Pediatric	Ages of Pediatric Approval	Formulation/ Recommended Dosage	Efficacy Supporting Label	Safety Concerns in Pediatrics
Fluoxetine	1987/2003	8 to 17 years	Capsule: 10, 20, 40 mg Liquid: 20 mg/5ml Dosage: 10 to 20 mg/day (initial dose)	Two 8- to 9- week placebo-controlled clinical trials with 315 pediatric out-patients 8 to ≤18 years	• Mania/hypomania • Decreased weight gain • Decrease in alkaline phosphatase
Escitalopram	2002/2009	12 to 17 years	Tablets: 5, 10, 20 mg Oral solution: 1 mg/mL 10 mg once daily with maximum recommended dose of 20 mg (titration after 3 weeks)	One 8-week flexible-dose (10-20 mg Lexapro), placebo-controlled outpatient study in patients 12 to 17 years with MDD Extrapolation from one 8-week, flexible-dose (citalopram 20 to 40 mg), placebo-controlled study in patients 7 to 17 years; statistically significant, but positive results were mostly in adolescent group. Negative efficacy studies in the label: Two flexible-dose, placebo-controlled MDD studies (one escitalopram in ages 7 to 17 years and one citalopram study in adolescents)	Most common adverse reaction: insomnia Similar safety profile to adults but higher incidence of back pain, urinary infection, vomiting, nasal congestion

Source: Clinical reviewer-created from fluoxetine and escitalopram U.S. labels

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Trintellix was approved for the treatment of MDD in adults on September 30, 2013 with the following Pediatric Research Equity Act (PREA)-related postmarketing requirements:

2084-2 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 and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

2084-3 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 and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

In June 2018, following discussions with PeRC and the Division regarding removal of the fluoxetine arm, these PMRs were released and replaced by:

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.

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.

On September 24, 2015, a Pediatric Written Request (PWR) was issued for Takeda and a PWR Amendment was issued on February 7, 2019.

- Study 1: A pediatric pharmacokinetic study
- Study 2: An efficacy and safety study for pediatric subjects ages 7 to 11 years old with MDD (corresponding to PMR 2048-7)
- Study 3: An efficacy and safety study for pediatric subjects ages 12 to 17 years old with MDD (corresponding to PMR 2048-8)
- Study 4: An open-label, long-term pediatric safety study

The Applicant has completed studies 1 (12708A) and 3 (12710A); studies 2 (1209A) and 4 (12712A) are ongoing.

3.2. Summary of Presubmission/Submission Regulatory Activity

Takeda has been co-developing vortioxetine since 2007 with H. Lundbeck A/S (Lundbeck). Takeda is the Applicant and the Sponsor for NDA 204447 and IND 076307, respectively. Lundbeck is the Sponsor for IND 112581, where Takeda provided a Letter of Authorization for Lundbeck to cross-reference IND 076307. Data generated by both INDs have been submitted to NDA 204447 by Takeda.

Takeda is submitting the data from Study 12710A, titled, "Interventional, randomized, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in pediatric patients aged 12 to 17 years, with major depressive disorder (MDD)" to fulfill PMR 2084-8 as well as the relevant efficacy study requested in the Amended PWR. This submission is Efficacy Supplement #21 and received a priority review.

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

4.1. Office of Scientific Investigations (OSI)

N/A

4.2. Product Quality

N/A

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Study 12710A included subjects as young as 12 years of age. As such, the results of the juvenile animal study (JAS) are relevant to the enrolled population. The results of the 10-week JAS in Sprague Dawley rats indicate that there may be neurobehavioral effects during treatment and lasting treatment effects that affect the viability of offspring from treated animals.

The peak amplitude of the auditory startle responses were significantly increased in high-dose (HD) male animals and increased in HD female animals when tested after 6-weeks of treatment. Though not statistically significant, a trend in dose-related increases in the peak amplitude across doses was observed. These changes to the peak amplitude were reversible after the recovery period. Auditory startle response behavioral tests have not been conducted in adult animals so no comparison of the effects can be made. The startle response is a neurobehavior that is seen across species and can be relevant to psychiatric diseases. Therefore, the test-article related changes could be relevant to administration in pediatric populations.

More importantly, there was a significantly reduced viability index in the offspring of the females that had received the HD between post-natal day (PND) 21 to PND 91. Further, clinical signs of being cold to the touch or apparently unfed/no milk in stomach were observed in the offspring of the treated females. The clinical signs observations increased in incidence as the dose increased. These findings are particularly notable because the mating pairs that littered the offspring had been allowed a 4-week period without treatment prior to being mated. The offspring themselves were not exposed to the test article at all. This indicated that the 10-week treatment period of Lu AA21004 was able to affect the health of offspring of treated animals even after the cessation of treatment, and washout. The nature of these changes, whether through behavioral modifications of the mothers or changes to physiology, is unknown but the lasting nature of these changes is concerning.

Notable kidney and liver toxicities consisting of both histopathological findings and complimentary hematological, clinical chemistry, or urinalysis changes were observed in the pivotal JAS study. However, these changes do not appear to be increased in incidence or severity compared to the findings in adult animals.

Based on these findings, we added the following to the label in Section 8.4, Pediatric Use:

> Administration of vortioxetine to juvenile rats (oral doses of 10, 20, and 40 mg/kg/day twice daily from Postnatal Day 21 to 91) resulted in a neurobehavioral effect at the highest dose of 40 mg/kg twice daily (increased peak auditory startle amplitude) during the treatment period. The effect was not seen at the end of the recovery period. When animals were mated after the 4-week recovery period, viability index was decreased in

the offspring of mated pairs treated with 40 mg/kg twice daily. The no-observed adverse effect dose was 20 mg/kg twice daily based on both the neurobehavioral and reproductive effects. This dose was associated with plasma vortioxetine exposure (AUC) approximately 2 times that in pediatric patients.

5.5. Toxicology

Juvenile Animal Study

Study title/ number: Lu AA21004: Toxicity study in the juvenile CD rat by twice daily oral gavage administration/ NKT0006

Key Study Findings

- The peak startle amplitude was increased in HD male (significantly) and HD female animals compared to the control group at 6-weeks.
- The significant decrease in viability index at the HD (90.8%) compared to control (98.4%) reflects the decreased in litter size over the first 7 days.
- The offspring of the HD animals had an increased incidence of being cold to touch, and being apparently unfed with no milk in stomach when compared to the offspring of the control animals .

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 10, 20, 40 mg/kg Twice daily, 10 hours apart from PND 21 to 91 of age
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous solution/ 10% hydroxypropyl-β-cyclodextrin and 4.4% glucose
Species/Strain:	Rat/Crl:CD Sprague Dawley
Number/Sex/Group:	12

Satellite groups:	Recovery – 12 animals/sex/dose Reproductive – 20 animals/sex/dose
Study design:	Two dose range-findings studies were conducted to determine the appropriate doses for this JAS. The first administered single doses of 10, 20, or 40 mg/kg to PND 21 rats. The first study was determined to be insufficient based on low plasma exposure compared to previous toxicology studies. The second dose range-finding study administered doses of 0, 10, 20, and 40 mg/kg twice daily to rats from PND 21 to 48/49. Based on the second dose range-finding study, the Sponsor determined that doses of 0, 10, 20, and 40 mg/kg given twice daily were appropriate for the pivotal JAS. Treatment, recovery, and reproductive groups were administered Lu AA21004 from PND 21 to 91 of age. The recovery and reproductive groups then went 4 weeks without treatment. The reproductive group animals were paired for mating after the 4-week recovery period. Females were sacrificed 7 days after littering. Mortality, Clinical Signs, Body Weight (BW), Food Consumption, Ophthalmology, Hematology, Clinical Chemistry, Urinalysis, Sexual Maturation, Reproductive Capacity, CNS/Neurobehavioral Assessment, Bone Growth, Gross Pathology, Organ Weights, Histopathology, Toxicokinetics (TK) were evaluated.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Mortality

Methods: Animals were inspected at least twice daily for signs of wellbeing.

Results: Five animals died or were sacrificed prematurely during the entire study, three during the treatment phase, and two during the reproductive phase. None of the deaths or premature sacrifices were attributed to Lu AA21004.

Clinical Signs

Method: Animals were inspected at least twice daily. Detailed observations were conducted daily during Week 1, and twice weekly starting from Week 2 onwards.

Results: Several clinical signs were observed after dosing of Lu AA21004 including chin rubbing, paddling of forelimbs, and salivation. These three observations were seen across dosing days, and increased in incidence as dose increased. No other clinical signs were notable. The Sponsor attributed the occurrence of these dosing related clinical signs with the taste of the test formulation. These clinical signs were considered not to be adverse.

Body Weight

Methods: BW of each juvenile animal was measured 18 times during the dosing period, and 4 times during the recovery period.

Results: At the end of the treatment period, the average BW gain of the treatment groups ranged from 96 to 100%, and 104 to 106% compared to the control group for male and female animals, respectively. However, all of the treatment groups had lower BW gains during the recovery period compared to the control group.

The reproductive groups treated with Lu AA21004 had increases in BW gain during several time points during the recovery period. However, the increases in BW gain did not result in a meaningful increase in BW for either sex at the end of the treatment period or recovery period. There were no treatment effects of Lu AA21004 on BW or BW gain during the gestation or lactation period.

Food Consumption

Methods: The weight of food supplied to each cage was recorded during each phase of the study.

Results: There were no notable findings for the main study food consumption data. The food consumption for treated male and female animals is within 5% of the control group at the end of the main study and at the end of the recovery period. There were no notable alterations in food consumption for the reproductive phase females that had been treated with Lu AA21004 compared to the control group.

Ophthalmoscopy

Methods: Both eyes of the main study groups and recovery groups were examined prior to treatment on Day19/20 of age, and during Week 10 of treatment (control and HD animals only).

Results: Examination of the recovery group at the end of the recovery period was planned but was not conducted. There were no notable findings from the main study animals after 10 weeks of treatment. The animals in the recovery group did not undergo ophthalmic examination at the end of the recovery period because no toxicities were observed at the end of the treatment period.

Hematology

Methods: Blood samples were obtained from all main phase animals during Week 10 and during Week 4 of the recovery phase. Repeat samples were taken from six animals in each group at necropsy on Day 92.

Results: Slight prolongation in prothrombin time in MD female animals and both HD male and female animals was observed after 10 weeks of treatment. There were no other notable alterations in hematology parameters.

Clinical Chemistry

Methods: At the same time and using the same animals as for hematology, further blood samples were collected into tubes containing lithium heparin as anticoagulant.

Results: Alkaline phosphatase (ALP), glucose, chloride (Cl), and β globulin (Beta) levels for HD animals were increased compared to control animals at the end of treatment. Alanine amino-transferase (ALT) and urea levels for HD animals were decreased compared to control animals at the end of treatment (Table 2).

Only Urea, Glucose, and Cl levels were tested in recovery animals. ALP levels were only tested in the recovery males. The levels did not completely recover compared to control animals. The changes in clinical chemistry parameters were not great enough to be classified as adverse. However, the increases in ALT levels correlated with the histopathological findings of minimal centrilobular hepatocyte vacuolation and centrilobular hepatocyte hypertrophy.

Table 2. Summary of Blood Chemistry Parameters with Notable Changes

Treatment								
	Males				Female			
mg/kg	0	10	20	40	0	10	20	40
ALP	122	123	133	144*	77	77	79	83
ALT	43	48	50	48	80	60	53	67
Urea	4.75	4.31	4.53	4.27	6.08	5.62	6.16	5.45*
Glucose	6.19	6.33	7.24*	7.31**	5.86	6.14	6.38	7.38**
Cl	100	100	101*	103**	101	101	101	103**
Beta	15	15	15	16	14	14	15*	15*
Recovery								
	Male				Females			
	0	10	20	40	0	10	20	40
ALP	83	79	77	78	-	-	-	-
ALT	-	-	-	-	-	-	-	-
Urea	5.24	5.66	6.15	5.48	6.57	6.13	6.75	7.11
Glucose	7.67	8.48	8.38	9.17**	7.77	8.55	8.67	8.49
Cl	101	101	101	102**	101	101	101	102*
Beta	-	-	-	-	-	-	-	-

Source: Reviewer- created table from Sponsor data in Study No. NTK0006, page 128-135. William's and Shirely's statistical test were used, * = $p < 0.05$, ** = $p < 0.01$. For ALT, the data were log transformed for the statistical analysis.

Urinalysis

Methods: Overnight urine samples were collected from all main phase animal during Week 10, and recovery phase animals during recovery Week 4 using individual metabolism cages.

Results: Urine volume was significantly increased in HDF animals at the end of the treatment period. In HDM animals, urine volume was increased as well, but not significantly so. There was a trend for increased urine sodium in both the male and female dosing groups at the end of the treatment period. HDM, and HDF animals had an average urine chloride concentration that was higher than controls groups at the end of the treatment period.

Urine volumes of both male and female treatment groups returned to control group levels by the end of the recovery period. Urine-Na, and Urine-Cl was still slightly increased in male and female treatment groups compared to control groups at the end of the recovery period. The increase in sodium and chloride could be related in the mineralization found in the kidneys. There was an increase in crystals in the urine sediment of HD male and female animals compared to controls.

Table 3. Summary of Urinalysis Parameters with Notable Changes

	Treatment							
	Males				Female			
mg/kg	0	10	20	40	0	10	20	40
Urine Volume	6.7	6.9	7.4	8.8	4.7	3.9	4.4	6.4*
Urine-Na	76.8	73.6	78.4	81.5	78.3	93.3	97.3	91.3
Urine-Cl	73.8	59.8	76.3	89.7	53.3	63.8	67.4	87.4**
	Recovery							
	Male				Females			
	0	10	20	40	0	10	20	40
Urine Volume	9.9	8.8	9.3	9.7	5.7	6.3	5.5	5.7
Urine-Na	56.2	71.3	69.5	69.7	58.9	75.0	80.3	72.4
Urine-Cl	48.4	46.6	49.3	50.1	37.9	57.6*	61.8*	50.8*

Source: Reviewer created table from Sponsor date in Study No. NTK0006, page 136-139. William's statistical test was used with * = $p < 0.05$, ** = $p < 0.01$.

Sexual Maturation

Methods: For reproductive phase males, sexual maturation was assessed by daily examination from Day 38 of age until balano-preputial separation occurred. Male animal BW was recorded on the day of completion of separation. For reproductive phase females, sexual maturation was assessed by daily visual examination from Day 28 of age until vaginal opening occurred. Female animal BW was recorded on the day of vaginal opening.

Results: There were no notable differences in the age at which preputial separation or vaginal opening was completed across dosing groups. The LD, MD, and HD female animals did have increased bodyweights compared to the control group at the time of completion of vaginal opening; 10.4%, 6.4%, and 12.8 %, respectively.

Reproductive Capacity

Methods: To evaluate estrous cycles, daily vaginal smears were taken using cotton swabs moistened with saline for ten days before pairing. After pairing with the male, smearing was continued using pipette lavage until evidence of mating was observed. To evaluate mating procedure, mating pairs were placed in cages with trays underneath to catch ejected copulation plugs. Vaginal smears were prepared and examined for the presence of spermatozoa.

Results: There were no treatment related effects on the oestrous cycles of the reproductive females. There were no differences in the pre-coital interval between treatment and control groups. There were no notable differences in the percentage of mating, conception rate (%), or fertility index (%) between treatment and control groups. A shortened gestation period length tended to be seen in HDF animals with 33% of HDF animals having a gestation length of 22 days compared to 21% in control animals, and 28% of HDF animals having a gestation length of 23

day compared to 42% in control animals (Table 4). There was no notable difference in the number of live litters born between the treatment and control animals (Table 4). There were two instances of total litter loss post-partum, one litter of a LDF on Day 2 of age and one litter of a MDF on Day 3 of age—neither of which were considered to be due to parental treatment.

No treatment effect was observed on the mean number of implantation sites, total and live litter size on Day 1 of age, or the sex ratio. No treatment effect was observed on the post-implantation survival index or live birth index. No treatment effect was observed on the BW of the offspring on Day 1, 4, or 7 of age. There were no macropathology findings of note in the reproductive animal groups or their offspring.

Table 4. Gestation Length and Gestation Index in Female Reproductive Groups

Group	:	1	2	3	4				
Compound	:	Control	Lu AA21004	Lu AA21004	Lu AA21004				
Dose (mg/kg b.i.d.)	:	0	10	20	40				
				Gestation length (days)				Number of	
Group	Number of pregnant animals		22	22.5	23	23.5	24	live litters born	Gestation index (%)
1	19	n	4	7	8	0	0	19	100
		(%)	(21)	(37)	(42)				
2	20A	n	3	9	6	0	1	19	95
		(%)	(16)	(47)	(32)		(5)		
3	18B	n	4	7	6	0	0	17	94
		(%)	(24)	(41)	(35)				
4	18	n	6	7	5	0	0	17	94
		(%)	(33)	(39)	(28)				

A Percentage distribution of gestation lengths calculated from 19 animals - one pregnant female failed to litter
B Percentage distribution of gestation lengths calculated from 17 animals - one pregnant female failed to litter

Source: Sponsor Table 24, Study No. NTK0006, page 197.

A negative treatment effect was observed on the live litter size on Day 4 and Day 7. The average litter size of the control group decreased by -0.3 whereas the LD, MD, and HD decreased by -0.5, -0.6, and -1.2, respectively. The significant decrease in viability index at the HD (90.8%) compared to control (98.4%) reflects the decreased in litter size over the first 7 days (.

Table 6). The offspring of the HD animals had an increased incidence of being cold to touch and being apparently unfed/no milk in stomach when compared to the offspring of the control animals (Table 7).

Table 5. Average Litter Size in Female Reproductive Groups

Group		:	1	2	3	4
Compound		:	Control	Lu AA21004	Lu AA21004	Lu AA21004
Dose (mg/kg b.i.d.)		:	0	10	20	40

Group		Implantations	Total litter size Day 1	Live litter size on Day 1	Live litter size on Day 4	Live litter size on Day 7
Statistical test:		Sh	Wi	Wi	Wi	Wi
1	Mean	15.2	13.7	13.3	13.2	13.0
	SD	2.7	3.0	3.0	2.9	2.8
	N	19	19	19	19	19
2	Mean	15.9	14.5	14.1	13.7	13.6
	SD	4.3	4.1	4.0	4.3	4.2
	N	18	18	18	18	18
3	Mean	16.5	15.1	14.6	14.1	14.0
	SD	2.2	2.4	2.6	2.2	2.0
	N	16	16	16	16	16
4	Mean	16.1	14.2	13.9	12.9	12.7
	SD	2.1	2.9	2.8	3.6	3.6
	N	17	17	17	17	17

Source: Sponsor Table 25, Study No. NTK0006, page 198. Statistical Test: Sh = Shirley's, Wi = William's.

Table 6. Average Offspring Survival Indices for Reproductive Groups

Group	:	1	2	3	4
Compound	:	Control	Lu AA21004	Lu AA21004	Lu AA21004
Dose (mg/kg b.i.d.)	:	0	10	20	40

Group		Post implantation survival index (%)	Live birth index (%)	Viability index (%)
Statistical test:		Wi	Fe	Sh
1	Mean	90.3	96.8	98.4
	N	19	19	19
2	Mean	91.3	97.2	96.2
	N	18	18	18
3	Mean	90.8	97.1	96.4
	N	16	16	16
4	Mean	88.5	98.0	90.8*
	N	17	17	17

Source: Sponsor Table 26, Study No. NTK0006, page 199. Viability index (%) = (Number live offspring on Day 7/ Number live offspring on Day1 after littering) x 100. Statistical Test: Sh = Shirley's, Wi = William's, Fe = Fisher's Exact, * = $p < 0.05$, ** = $p < 0.01$.

Table 7. Clinical Signs of the Offspring of the Reproductive Groups

Sign	No. of offspring (litters) showing sign			
	Group 1	Group 2	Group 3	Group 4
Cold to touch	14(2)	25(3)	23(2)	55(7)
Apparently unfed/ No milk in stomach	-	9(1)	8(2)	5(5)

Source: Sponsor Study No. NTK0006, page 60.

CNS/ Neurobehavioral Assessment

Methods: Neurobehavioral examinations were performed at least 2 hours after the first administration of the day. All main phase animals were used, but only the males were used in the recovery phase examinations. Locomotor activity was tested on Day 58 and Day 113. Auditory startle response habituation was assessed on Day 59 and Day 114. Learning and

memory examinations using Morris water maze were tested on Day 61 and consisted of a series of three trials on each of 4 consecutive days.

Results:
Auditory startle response habituation: Peak startle amplitudes were increased in HDM (+17%, $p<0.05$) and in HDF (11%) animals when tested during week 6 of treatment. There was no observed effect of treatment on the latency to peak, or habituation in animals when tested during Week 6 of treatment. The data from the male recovery groups showed that the peak amplitude returned to control levels, but there was a dramatic increase in habituation in for the control animals that did not occur in the HDM group at the end of the recovery period (Table 8, Table 9, Table 10). The data for the female recovery group was not presented.

Table 8. Auditory Startle Response Habituation Test Resuls in Male Animals after 6 Weeks of Treatment

Group			1		2		3		4							
Compound			Control		Lu AA21004		Lu AA21004		Lu AA21004							
Dose (mg/kg b.i.d.)			0		10		20		40							
	Number		Latency to peak (ms) Trial number						Peak amplitude (g) Trial number							
Group /Sex	of animals		1-10	11-20	21-30	31-40	41-50	1-50	1-10	11-20	21-30	31-40	41-50	1-50	Habituation
Statistical test:			Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	lWi	lWi	Sh	Wi	Wi
1M	12	Mean	22.6	21.5	20.2	20.6	20.0	21.0	549.3	519.0	513.8	496.4	481.8	512.0	-15.8
		SD	9.2	9.8	8.6	10.0	7.0	5.6	79.4	87.4	91.6	79.8	53.5	70.4	12.2
2M	12	Mean	29.3	22.2	28.2	20.4	23.4	24.7	524.8	474.4	458.7	468.5	452.8	475.9	-15.0
		SD	8.6	5.5	13.7	10.1	7.7	5.6	73.9	74.2	61.2	56.2	51.4	56.3	13.6
3M	11	Mean	24.8	17.4	16.0	19.9	17.5	19.1	555.3	579.3	554.5	523.5	518.1	546.1	-13.0
		SD	9.3	8.2	5.9	11.2	6.9	7.4	90.7	166.6	117.7	101.0	118.4	110.9	14.3
4M	12	Mean	25.3	18.9	18.0	20.3	19.5	20.4	609.4	622.9	632.8	574.9	565.2	601.1*	-13.7
		SD	11.5	7.5	10.8	11.0	7.6	7.4	146.0	176.6	183.6	162.2	137.3	146.1	20.0

Source: Sponsor Table 6, Study No. NTK0006, page 106. Statistical Test: Sh = Shirley's, Wi = William's, 1 = data were log transformed for the statistical analysis,* = $p < 0.05$, ** = $p < 0.01$.

Table 9. Auditory Startle Response Habituation Test Resuls in Female Animals after 6 Weeks of Treatment

Group	:	1	2	3	4										
Compound	:	Control	Lu AA21004	Lu AA21004	Lu AA21004										
Dose (mg/kg b.i.d.)	:	0	10	20	40										
			Latency to peak (ms) Trial number						Peak amplitude (g) Trial number						
Group /Sex	Number of animals		1-10	11-20	21-30	31-40	41-50	1-50	1-10	11-20	21-30	31-40	41-50	1-50	Habituation
Statistical test:			Wi	Wi	Wi	Wi	Wi	Wi	Wi	Sh	Wi	Wi	lWi	Wi	Wi
1F	12	Mean	31.1	26.0	23.4	26.0	21.4	25.6	350.5	323.2	325.4	304.3	307.3	322.1	-10.5
		SD	6.6	8.1	9.1	13.5	6.5	6.2	70.3	51.1	64.5	45.5	47.6	52.3	10.4
2F	12	Mean	28.5	24.8	21.3	25.1	22.2	24.4	352.0	315.3	300.8	304.6	294.3	313.4	-12.6
		SD	10.6	6.7	6.9	9.7	6.1	4.5	71.1	29.6	38.1	47.3	36.8	42.4	9.7
3F	12	Mean	26.8	20.5	21.3	20.7	22.1	22.3	368.8	351.1	339.8	327.8	333.3	344.2	-9.4
		SD	6.6	6.0	10.3	11.7	9.5	5.5	48.4	43.3	37.8	53.3	42.4	34.6	12.6
4F	12	Mean	31.2	28.0	22.4	22.4	24.6	25.7	385.3	359.6	356.4	342.5	341.5	357.1	-10.5
		SD	11.2	8.6	7.6	6.7	10.5	5.5	98.1	98.4	76.8	71.0	92.7	82.4	16.4

Source: Sponsor Table 6 continued, Study No. NTK0006, page 107. Source: Sponsor Table 6, Study No. NTK0006, page 106. Statistical Test: Sh = Shirley's, Wi = William's, 1 = data were log transformed for the statistical analysis,* = $p < 0.05$, ** = $p < 0.01$.

Table 10. Auditory Startle Response Habituation Test Resuls in Male Animals after the Recovery Period

Group	:	1	2	3	4										
Compound	:	Control	Lu AA21004	Lu AA21004	Lu AA21004										
Dose (mg/kg b.i.d.)	:	0	10	20	40										
			Latency to peak (ms) Trial number						Peak amplitude (g) Trial number						
Group /Sex	Number of animals		1-10	11-20	21-30	31-40	41-50	1-50	1-10	11-20	21-30	31-40	41-50	1-50	Habituation
Statistical test:			Wi	Wi	Wi	lWi	Wi	Wi	Wi	Wi	lWi	lWi	Sh	Wi	Sh
1M	12	Mean	23.8	23.8	22.5	25.3	21.8	23.4	873.9	885.2	801.4	768.9	730.8	812.0	-40.3
		SD	6.1	8.6	9.0	12.0	8.3	7.7	255.9	310.4	227.0	187.4	111.3	197.0	53.5
2M	12	Mean	26.3	21.8	20.0	19.8	27.9	23.2	815.3	747.8	700.6	706.8	698.4	733.8	-27.5
		SD	5.5	8.4	6.0	4.7	11.2	5.4	157.5	129.9	98.3	105.8	96.1	107.6	28.2
3M	12	Mean	28.8	19.8	21.7	28.9	27.0	25.2	848.3	846.7	760.0	728.9	724.1	781.6	-36.6
		SD	13.1	7.8	8.8	14.0	8.2	7.9	145.7	156.2	117.4	111.9	119.3	115.0	29.0
4M	12	Mean	23.3	20.1	21.5	20.1	20.6	21.1	788.9	793.4	793.6	796.5	803.2	795.1	3.2
		SD	7.3	7.0	9.1	9.1	9.2	7.5	108.2	195.2	259.0	293.7	353.3	221.3	81.9

Source: Sponsor Table 6 continued, Study No. NTK0006, page 108. Statistical Test: Sh = Shirley's, Wi = William's, 1 = data were log transformed for the statistical analysis,* = $p < 0.05$, ** = $p < 0.01$.

Morris water maze:
There were no notable treatment effects of Lu AA21004 on performance in the Morris water maze. Morris water maze was not conducted with recovery animals.

Motor activity:
There were no treatment effects of Lu AA21004 on the motor activity in female animals when tested during Week 6 of treatment. The motor activity of all of the male treatment groups was increased when tested during the treatment period compared to the control group. The Sponsor attributes the observed increases in activity to the abnormally low activity in the

control groups. Motor activity of the male groups was tested after the 4-week recovery period and no increases in activity were observed.

Bone Evaluation
Methods: The length of the ulna was recorded on Days 21, 49, and 91 of age for all Main Study animals.

Results:There was no notable difference in the ulna lengths of the treated HDM animals compared to the controls at the end of the treatment period. HDF animals had an average ulna length that was 4.9% greater than control animals at the end of the treatment period. These observations are not significant enough to indicate that the treatment had an effect on ulna length.

Gross Pathology
Methods: All animals were subjected to a detailed necropsy. All external features and orifices were examined visually. Any abnormal position, morphology or interaction was recorded.

Results: There were no notable macropathological findings in the treatment groups after 10 weeks of treatment—or the recovery groups after 4 weeks of recovery.

Organ Weights
Methods: The organs in the following list were taken from each main and recovery phase animal at the time of sacrifice. Bilateral organs were weighed together. Adjusted organ weights were adjusted with the BW recorded immediately before necropsy.

Results: Both the unadjusted and adjusted liver weights were increased in both LD, MD, and HD male and female animals. Salivary glands weight of MDM and HDM were decreased compared to control at the end of the treatment period (MDM: -10%, HDM: -10.9%), and continued to be decreased at the end of the recovery period (MDM: -10%, HDM: -8.8%). At the end of the treatment period, seminal vesicles weight was decreased in only the HDM male animals (-13.5%), but there was a trend for decreased weights in the LDM and MDM animals as well. No differences in the seminal vesicle weights were noted at the end of the recovery period. There was an increase in the adjusted uterus + cervix weights of LDF (+29%) and MDF (+17%) at the end of the recovery period.

Histopathology
Methods: Tissue samples were dehydrated, embedded in paraffin wax, sectioned at approximately 4- to 5-micron thickness, and stained with haematoxylin and eosin.

Results: At the end of the treatment period, histopathological findings were noted in both the liver and the kidney. The incidence of the findings were decreased, but not entirely resolved at the end of the recovery period for both the liver and kidney findings.

Liver: Centrilobular hepatocyte vacuolation was observed and increased in incidence and severity in MD and HD male animals. Centrilobular hepatocyte hypertrophy was observed , and increased in incidence and severity for LD (female only), MD, and HD animals. The vacuolation and hypertrophy that was observed at the end of the treatment period appeared to be partially reversible because the incidence and severity decreased in the recovery animals. The two hepatic histopathological findings, the increased ALT, glucose, and prothrombin levels may be related and could indicate a larger effect on the liver.

Table 11. Summary of Treatment Related Findings in the Liver at the End of the Treatment Period

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg b.i.d.)	0	10	20	40	0	10	20	40
Hepatocyte Vacuolation, Centrilobular								
Minimal	0	0	3	4	0	0	0	0
Slight	0	0	1	6	0	0	0	0
Total	0	0	4	10	0	0	0	0
Hepatocyte Hypertrophy, Centrilobular								
Minimal	0	0	4	6	0	1	3	5
Total	0	0	4	6	0	1	3	5
Number of animals examined	12	12	11	11	12	12	12	12

Source: Sponsor Study No. NTK0006, page 56.

Table 12. Summary of Treatment Related Findings in the Liver at the End of the Recovery Period

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg b.i.d.)	0	10	20	40	0	10	20	40
Hepatocyte Vacuolation, Centrilobular								
Minimal	0	0	1	2	0	0	0	0
Total	0	0	1	2	0	0	0	0
Hepatocyte Hypertrophy, Centrilobular								
Minimal	0	0	0	0	0	0	2	1
Total	0	0	0	0	0	0	2	1
Number of animals examined	12	12	12	12	12	12	12	12

Source: Sponsor Study No. NTK0006, page 58.

Kidney: Minimal mineralization of the corticomedullary areas of the kidneys was observed in LDF, MDF, HDF and HDM animals. The incidence of the mineralization was highest for HDF animals. The increase in incidence of mineralization with dose, the significantly elevated urea, urine volume, urine sodium, and chloride concentrations in HDF animals could indicate Lu AA21004 related changes. At the end of the recovery period, the incidence of mineralization was reduced in the HDF animals but increased in the LDF and MDF groups. The Sponsor notes that mineralization can be a spontaneous. However, and specifically for the HDF animals, the findings are likely test article related because similar kidney toxicities were observed in the 26-week rat general toxicity study (Study No. LBK). Though, the kidney toxicities in the 26-week rat study appear to be far more severe than in this JAS. Based on the reduced incidence of mineralization at the HD, the effect on the kidney appears to be partially reversible as the Sponsor claimed.

Table 13. Summary of Treatment Related Findings in the Kidney at the End of the Treatment Period

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg b.i.d.)	0	10	20	40	0	10	20	40
Mineralisation, Corticomedullary								
Minimal	0	0	0	1	0	1	1	6
Total	0	0	0	1	0	1	1	6
Number of animals examined	12	12	11	11	12	12	12	12

Source: Sponsor Study No. NTK0006, page 57.

Table 14. Summary of Treatment Related Findings in the Kidney at the End of the Recovery Period

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg b.i.d.)	0	10	20	40	0	10	20	40
Mineralisation, Corticomedullary								
Minimal	0	0	0	1	1	2	3	3
Total	0	0	0	1	1	2	3	3
Number of animals examined	12	12	12	12	12	12	12	12

Source: Sponsor Study No. NTK0006, page 58.

Toxicokinetics

Methods: Blood samples were obtained from reproductive phase animals after dosing on Days 21 and 91.

Results: Lu AA21004, and two metabolites; LuAA34443 and Lu AA39835, were quantified. Continuous exposure of Lu AA21004 and Lu AA34443 was detected on both Day 21 and 91. Whereas plasma concentrations of Lu AA39835 were generally below the lower limit of quantitation on Day 21, levels were generally quantifiable up to at least 10 hours post-dose at all dose levels on day 91. The C_{max} and AUC of Lu AA21004, LuAA34443, and Lu AA39835 increased between Day 21 and 91, ranging from 4- to 13-fold higher for the C_{max}, and 3- to 7-fold higher for the AUC. There was generally a greater-than-dose-proportional increase in the concentration of Lu AA21004 and its metabolites on both Day 21 and Day 91. The terminal half-lives were reported to range between 2.1 to 6.8 hours for Lu AA21004, 1.9 to 4.5 hours for Lu AA34443, and 2.8 to 21.0 hours for Lu AA39835.

Table 15. Dose Proportionality of C_{max} and AUC in Male(A) and Female (B) Animals on Day 21, and Male(C) and Female (D) Animals on Day 91

A

Lu AA21004

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	51.1	-	284	-
20	2.0	249	4.9	1017	3.6
40	2.0	197	0.8	1299	1.3
Overall~	4.0		3.9		4.6

Lu AA34443

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	191	-	1382	-
20	2.0	1066	5.6	4417	3.2
40	2.0	877	0.8	5814	1.3
Overall~	4.0		4.6		4.2

Lu AA39835

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	NCi	-	NCi	-
20	2.0	NCi	NC	NCi	NC
40	2.0	1.38	NC	7.68	NC
Overall~	4.0		NC		NC

B

Lu AA21004

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	47.9	-	246	-
20	2.0	163	3.4	935	3.8
40	2.0	392	2.4	1548	1.7
Overall~	4.0		8.2		6.3

Lu AA34443

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	264	-	1312	-
20	2.0	827	3.1	4851	3.7
40	2.0	1531	1.9	7009	1.4
Overall~	4.0		5.8		5.3

Lu AA39835

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	NCi	-	NCi	-
20	2.0	NCi	NC	NCi	NC
40	2.0	NCi	NC	NCi	NC
Overall~	4.0		NC		NC

C

Lu AA21004

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	281	-	915	-
20	2.0	1316	4.7	4188	4.6
40	2.0	1807	1.4	8748	2.1
Overall~	4.0		6.4		9.6

Lu AA34443

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	2501	-	9153	-
20	2.0	6150	2.5	22029	2.4
40	2.0	7199	1.2	38397	1.7
Overall~	4.0		2.9		4.2

Lu AA39835

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	4.07	-	14.0	-
20	2.0	11.1	2.7	46.5	3.3
40	2.0	23.7	2.1	98.4	2.1
Overall~	4.0		5.8		7.0

D

Lu AA21004

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	370	-	1089	-
20	2.0	1084	2.9	3593	3.3
40	2.0	2405	2.2	10496	2.9
Overall~	4.0		6.5		9.6

Lu AA34443

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	1645	-	4913	-
20	2.0	3856	2.3	13874	2.8
40	2.0	6252	1.6	30345	2.2
Overall~	4.0		3.8		6.2

Lu AA39835

Dose (mg/kg/b.i.d.)	Fold increase in Dose #	C_{max} (nmol/L)	Fold increase in C_{max} #	AUC_{0-10h} (h*nmol/L)	Fold increase in AUC_{0-10h} #
10	-	4.04	-	18.7	-
20	2.0	6.61	1.6	39.7	2.1
40	2.0	10.9	1.7	96.6	2.4
Overall~	4.0		2.7		5.2

Source: Sponsor Study No. NTK0006, pages 1028-1031 # = Fold increase between adjacent dose levels
~ = Overall fold increase in dose or TK parameter from 10 to 40 mg/kg/b.i.d. NC = Not calculated
NCi = Not calculated; insufficient number of plasma samples above the lower limit of quantitation

There were no dramatic differences in the exposure of Lu AA21004 between male and female animals across the doses on Day 21 or Day 91. However, male animals tended to have higher exposures to Lu AA34443 than female animals on Day 91.

Table 16. Exposure Comparison for Lu AA21004 between Male and Female Animals

Day	Toxicokinetic Parameter	Dose (mg/kg/b.i.d.)	Estimate		Female / Male Ratio
			Male	Female	
21	C_{max}	10	51.1	47.9	0.94
		20	249	163	0.65
		40	197	392	1.99
	AUC_{0-10h}	10	284	246	0.87
		20	1017	935	0.92
		40	1299	1548	1.19
91	C_{max}	10	281	370	1.32
		20	1316	1084	0.82
		40	1807	2405	1.33
	AUC_{0-10h}	10	915	1089	1.19
		20	4188	3593	0.86
		40	8748	10496	1.20

Source: Sponsor Study No. NTK0006, pages 1033.

6 Clinical Pharmacology

6.1. Executive Summary

Vortioxetine was approved for the treatment of MDD in adults. In this efficacy supplement, the Applicant did not propose any change in sections relevant to clinical pharmacology for the TRINTELLIX label. The Applicant submitted a pediatric pharmacokinetics (PK) study (12708A) of vortioxetine in children (≥7 years to <12 years) and adolescents (≥12 years to <18 years) with a DSM-IV-TR diagnosis of depressive or anxiety disorder. This study was previously reviewed to fulfill the postmarketing requirement issued under NDA 204447. Please refer to the clinical pharmacology review by Di Zhou submitted into DARRTS on 04/04/2017. This review was conducted without the bioanalytical report for vortioxetine and its metabolites, LuAA34443 and LuAA39835. In addition to Study 12708A, sparse PK samples were collected in adolescents with MDD in Study 12710A and the PK of vortioxetine was analyzed using a population PK approach. The Applicant also proposed, under S-022 submitted on December 22, 2020, to include a laboratory test interaction relevant to the false positive urine drug screen for methadone in patients who have taken vortioxetine, in Section 7. This review is focused on 1) the population PK of vortioxetine in adolescents with MDD in study 12710A; 2) whether the bioanalytical report for study 12708A satisfies the Agency's bioequivalence criteria; 3) assessment of the false positive urine drug screen for methadone in patients who have taken vortioxetine.

6.2. Summary of Clinical Pharmacology Assessment

Population PK analyses suggest that the simulated dose-normalized peak plasma exposures (Cmax,ss) and area under the plasma concentration-time curve (AUCss) at steady state in children (≥7 years to <12 years) and adolescents (≥12 years to <18 years) are relatively similar to those observed in adults. Please refer to Section 19.3 of this review for additional information.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the guidance for industry, *Bioanalytical Method Development* (May 2018), and is acceptable. See Section 19.3 for additional information.

The false positive results in urine enzyme immunoassays for methadone have been reported in patients who have taken vortioxetine. Therefore, an alternative analytical technique (e.g., chromatographic methods) should be considered to confirm positive methadone urine drug screen results. See Section 19.34 for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Controlled efficacy data for the adolescent 12-to-17 year-old population consists of results from Study 12710A. Additional safety information comes from the pharmacokinetic (PK) Study 12708A (including its open-label extension), the ongoing efficacy Study 12709A in pediatric 7-to-11 year-old subjects, the ongoing open-label 6-month extension Study 12712A, and the completed open-label 18-month extension Study 12712B. See Table 17 for a listing of clinical trials relevant to this NDA efficacy supplement.

Table 17. Listing of Clinical Trials Relevant to NDA 204447-S021

Trial/ Status	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Endpoint	Duration/ Follow Up	Patients enrolled	Study Population	Countries (Number of Sites)
Controlled Studies to Support Efficacy and Safety								
12710A Completed	02709746	Randomized, double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine), multicenter, fixed-dose study	SB Period: oral placebo DB Period: oral vortioxetine 10 mg or 20 mg once daily or fluoxetine 20 mg once daily (including titrations), or placebo	Change from randomization to Week 8 in CDRS-R total score	SB Period: 4 weeks DB Period: 8 weeks	784 SB enrolled 616 DB randomized	Ages 12 to 17 with MDD	United States (41), Russia (16), Mexico, Poland (7 each), Germany, Italy, Serbia, Spain (5 each), Colombia, Latvia, Ukraine (4 each), France, Republic of Korea (3 each), Bulgaria, Hungary, United Kingdom (2 each), Canada, Estonia, South Africa (1 each)
Studies to Support Safety								
12709A Ongoing	02709655	Randomized, double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine)[1], multicenter, fixed-dose study	SB Period: oral placebo DB Period: oral vortioxetine 10 mg or 20 mg once daily or fluoxetine 20 mg[1] once daily (including titrations), or placebo	Change from randomization to Week 8 in CDRS-R total score	SB Period: 4 weeks DB Period: 8 weeks	As of September 29, 2019: 415 SB treated 316 DB blinded	Ages 7 to 11 with MDD	100 sites planned; active in United States, Bulgaria, Canada, Colombia, Germany, Estonia, France, Hungary, Israel, Italy, Republic of Korea, Latvia, Mexico, Poland, Russia, Serbia, South Africa, Spain, Ukraine

Trial/ Status	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Endpoint	Duration/ Follow Up	Patients enrolled	Study Population	Countries (Number of Sites)
12712A Ongoing	0287 1297	Open-label, flexible-dose, multicenter, long-term extension	Oral vortioxetine 5, 10, 15, or 20 mg once daily	Safety	6 months	As of September 29, 2019: 523 treated, 327 completed, 94 ongoing	Ages 7 to 18 with MDD, completed 12709A or 12710A	120 sites planned; active in United States, Bulgaria, Canada, Colombia, Germany, Estonia, France, Hungary, Israel, Italy, Republic of Korea, Latvia, Mexico, Poland, Russia, Serbia, South Africa, Spain, Ukraine, United Kingdom
12712B Completed	0310 8625	Open-label, flexible-dose, multicenter, long-term extension	Oral vortioxetine 5, 10, 15, or 20 mg once daily	Safety	18 months	94 treated, 58 completed	Ages 7 to 17 with MDD, completed 12712A	40 sites planned; active in Bulgaria, Germany, Estonia, France, Hungary, Italy, Latvia, Poland, Russia, Serbia, Spain, United Kingdom, South Africa
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
12708A Completed	0149 1035	Open-label, multiple-dose (main treatment); flexible-dose (extension)	Oral vortioxetine 5, 10, 15, or 20 mg once daily	PK	14 to 20 days; 6 months (extension)	48 (main treatment), 41 (extension)	Ages 7 to 17 with DSM-IV-TR depressive or anxiety disorder	United States (6) and Germany (1)

Source: Reviewer-created from Tabular Listing of All Clinical Studies, Study 12710A, 12708A, and 12712B Clinical Study Reports, and clinicaltrials.gov, accessed September 2020

Abbreviations: CDRS-R: Children's Depression Rating Scale – Revised version, DB = double-blind, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision, MDD = major depressive disorder, NCT = National Clinical Trial, No = number, SB = single-blind

[1] Study 12709A has been amended to remove the active reference (fluoxetine) arm because of recruitment difficulty

7.2. Review Strategy

The efficacy review focuses on the phase 3 study, 12710A, a randomized, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose, multicenter trial. The study is described in more detail in Section 8.1.1. Agency statistician, Semhar Ogbagaber, PhD, reviewed the Applicant's statistical analysis.

The safety review includes Study 12710A as well as data from the ongoing, similarly-designed Study 12709A in pediatric subjects ages 7 to 11 years (except for subsequent removal of the fluoxetine arm given recruitment difficulty), the open-label extensions Study 12712A (6 months, ongoing) and Study 12712B (18 months, completed), and the clinical pharmacology Study 12708A, which included a 14-to-20 day main treatment period, followed by a 6-month open-label extension.

8 Statistical and Clinical Review of Individual Efficacy Trials, Integrated Review of Effectiveness, and Review of Safety

8.1. Study 12710A

8.1.1. Study Design

Trial Design

Study 12710A was a randomized, double-blind, placebo-controlled, active-reference (fluoxetine), multicenter, fixed-dose study evaluating the safety and efficacy of vortioxetine for the treatment of MDD in male and female pediatric subjects aged 12 to 17 years. The study was conducted at 118 sites internationally, including 41 sites in the United States.

To be eligible for inclusion in the study, subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD, with diagnosis confirmed via the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version (K-SADS-PL) criteria. Subjects were also required to have a Children's Depression Rating Scale-Revised version (CDRS-R) total score ≥45 and a Clinical Global Impression-Severity (CGI-S) score ≥4 at screening and enrollment (Baseline A), and to use adequate contraception if sexually active. Female subjects were required to have a confirmed negative serum pregnancy test at screening. Subjects were excluded from the study based on a number of psychiatric, treatment-related, and other medical criteria. Notable exclusion criteria included:

- Any current DSM-5 psychiatric diagnosis established as the primary diagnosis (other than MDD). Comorbid anxiety disorders were permitted (if not considered clinically relevant in the context of the study). Post-traumatic stress disorder and obsessive compulsive disorder were excluded.

- Suicide attempt within the last 12 months or significant risk of suicide (either in the opinion of the investigator or defined by Columbia Suicide Severity Rating Scale (C-SSRS) answer of 4 or 5 on suicidal ideation or suicidal behavior in last 12 months).

Concomitant treatment with other antidepressants, anxiolytics, antipsychotics, and anticonvulsants/mood stabilizers was prohibited (monoamine oxidase inhibitors were specifically contraindicated). Prohibited medications were washed-out per a schedule consistent with drug half-lives. If the subject was on stimulant medication for attention deficit/hyperactivity disorder, the dose had to have been stable for 4 weeks prior to enrollment. Zolpidem, zaleplon, and zopiclone were allowed for severe insomnia at a maximum of 2 nights/week; melatonin was allowed at a maximum of 3 nights/week. No sedative/hypnotics were permitted the night before a study visit.

The study consisted of four periods (see Figure 1 for the Applicant's study design schematic):

- Screening Period: 5 to 15 days.

- Phase A Single-blind (SB) Period: 4 weeks of SB treatment with standardized brief psychosocial intervention (BPI) and placebo. Subjects who fulfilled the randomization criteria for incomplete improvement in depressive symptoms (see below) at the end of the SB Period entered the DB Period. Subjects who did not were withdrawn from the study at Week 3 and were offered up to four outpatient visits for consultations.

- Phase B Double-blind (DB) Period: To be included, subjects had to demonstrate the following at the SB Week 3 and Week 4 visits:

  - A CDRS-R total score ≥40

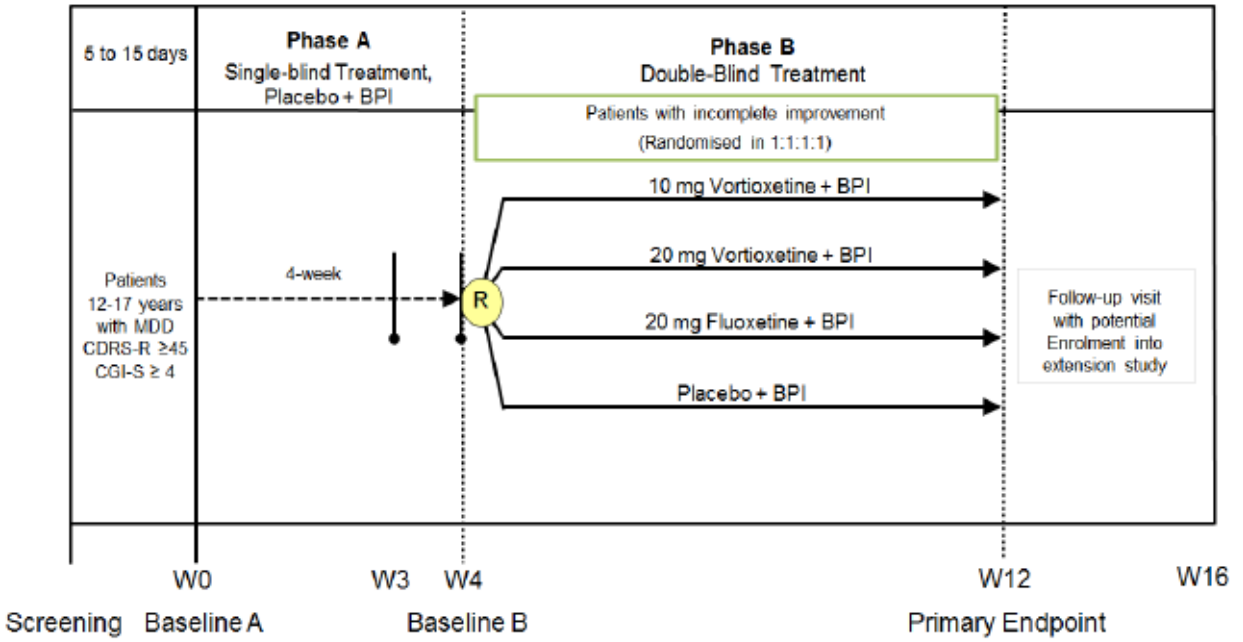
  - A <40% decrease in CDRS-R total score (subtracted by 17 to avoid a flooring effect) compared to enrollment (Baseline A)

  - A Parent Global Assessment – Global Improvement (PGA) score >2

  Eligible subjects were randomized 1:1:1:1 to 8 weeks of DB treatment with BPI and placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day (stratified by site). Doses of vortioxetine were selected based upon adult studies and information from the pediatric PK Study 12708A. Doses of vortioxetine and fluoxetine were titrated during the first 3 to 7 days of the DB Period. Based on tolerability, the investigator could reduce the dose once at Week 4 in the DB Period (by 5 mg/day for vortioxetine and 10 mg/day for fluoxetine). No further dose adjustments were allowed, and subjects stayed on that dose for the remainder of the study.

- Safety Follow-Up Period: 4 weeks following completion or withdrawal; this procedure did not apply to subjects who entered the 6-month open-label extension Study 12712A.

Figure 1. Study 12710A Study Design Schematic



= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

Source: Study 12710A Protocol, Panel 1, p. 9
Abbreviations: BPI = Brief Psychosocial Intervention, CDRS-R = Children's Depression Rating Scale-Revised version, CGI-S = Clinical Global Impression-Severity, MDD = major depressive disorder, R = randomization, W = week

<u>Clinical Reviewer's Comment</u>: The study design described above appears reasonable for an adequate and well-controlled trial. The Applicant designed the study with the SB period including BPI and placebo treatment in an attempt to enrich the DB population to minimize placebo response; the design also meant to ensure that only subjects with an insufficient response to psychotherapy would receive pharmacological treatment. The fluoxetine arm was included to provide evidence of assay sensitivity.

Study Endpoints

The primary efficacy endpoint was the change from randomization (Baseline B) in the CDRS-R total score after 8 weeks of treatment. The CDRS-R is a clinician-rated scale consisting of 17 items. Depression symptoms are rated on a 5-point scale from 1 to 5 for the 14 items that rate verbal observations, and a 7-point scale from 1 to 7 for the three items that rate nonverbal observations. The total score ranges from 17 ("normal") to 113 ("severe depression").

Secondary efficacy endpoints evaluated:

- Depressive symptoms:
    - Change from randomization (Baseline B) in the CDRS-R total score during the 8 weeks of treatment
    - Change from Baseline B in the CDRS-R mood (4 items), somatic (6 items), subjective (4 items), and behavior (3 items) subscores during the 8-week treatment period
    - CDRS-R response (defined as ≥50% reduction in the CDRS-R total score, calculated as: [change from Baseline B] / [Baseline B value - 17 points]) during the 8-week treatment period
    - Remission over the 8-week treatment period (defined as CDRS-R ≤28), at each visit assessed
    - Change from Baseline B in the General Behavior Inventory (GBI), using the 10-item depression subscale, during the 8 weeks of treatment
    - Change from Baseline B in the PGA score during the 8-week treatment period
- Cognitive performance: change from Baseline B in the Symbol Digit Modalities Test (SDMT) (number of correct numbers) during the 8-week treatment period
- CGI:
    - Change from Baseline B in the CGI-S score during the 8-week treatment period
    - Score on the CGI-Improvement (CGI-I) from 1 week after Baseline B during the 8-week treatment period
    - Remission on the CGI-S score (defined as a CGI-S score of 1 or 2) during the 8-week treatment period, at each visit assessed
- Functionality:
    - Change from Baseline B in the Children's Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire Assessment Scale (CGAS) score during the 8-week treatment period
    - Change from Baseline B in the Pediatric Quality of Life (PedsQL) visual analogue scale (VAS) score in each of 6 domains during the 8-week treatment period

  - Change from Baseline B in the PedsQL average score in each of 6 domains during the 8-week treatment period

  - Change from Baseline B in the PedsQL emotional distress summary score during the 8-week treatment period

- Health-related quality of life:

  - Change from Baseline B in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total score (items 1 to 14) during the 8-week treatment period

  - Change from Baseline B in the PQ-LES-Q overall evaluation score (item 15) during the 8-week treatment period

Safety endpoints included adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiogram (ECG) parameters, C-SSRS categorization, and GBI using the 10-item mania subscale (patient and parental versions).

Statistical Analysis Plan (SAP)

The Applicant originally planned Study 12710A such that it was powered to find at least one of the fixed vortioxetine doses statistically significantly different from placebo using a Hochberg testing strategy. The Applicant assumed a standard deviation (SD) of 11 on the treatment comparisons for the primary endpoint and a withdrawal rate of 15 to 20%. The Applicant originally planned a total sample size of 600 which was randomized equally into vortioxetine (10 mg, 20 mg), fluoxetine (20 mg), and placebo. Applying Hochberg's test at an overall significance level of 5% would provide a power of approximately 87% for finding at least one dose statistically significantly different from placebo if both doses have an effect of 4 points using a t-test comparison for the primary analysis at Week 8 in Phase B (Week 12).

In the first amendment to the SAP (October 12, 2015), the Applicant added a plan for a blinded sample size re-estimation to ensure that the study was sufficiently powered. The variability of the primary endpoint and withdrawal rate were estimated after at least 75% of the initially planned randomized patients had either completed or withdrawn from the study. The Applicant conducted a blinded sample size reassessment when 450 patients were randomized. The assessment revealed SD estimates at 12.5-12.7 and withdrawal estimates at 10 to 15%. Based on the interim assessments, the Applicant found that randomizing 150 per group (total sample size 600) would provide a power of approximately 85% for the primary analysis.

In subsequent amendment (July 5, 2018), the Applicant changed the primary analysis to first test the averaged effect of the two, fixed vortioxetine doses versus placebo followed by the comparison of the individual vortioxetine doses versus placebo. A total sample size of 480 were

randomized equally (120 patients per group). The Applicant applied a closed testing procedure to keep the overall significance level at 5% and which would provide a power of at least 85% for claiming statistical significance of the averaged effect of the two vortioxetine doses if both doses had an effect of 4 points at Week 8 in Phase B (Week 12). The Applicant assumed a standard deviation (SD) of 11 on the treatment comparisons for the primary endpoint and a withdrawal rate of 15 to 20%.

The Applicant analyzed the change from randomization in CDRS-R total score at Week 8 using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment, country, and week and the continuous covariates of CDRS-R total score at randomization, treatment-by-week interaction, and CDRS-R at randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Protocol Amendments

There were two statistically-relevant protocol amendments. The first amendment (October 12, 2015), before the study started, revised the interim analysis for the blinded sample size re-assessment. The second amendment (July 5, 2018), after study commenced, modified the testing strategy such that the primary analysis would compare the averaged effect of the two, fixed vortioxetine doses (10 mg and 20 mg) versus placebo. This ensured increase of study power.

There were three global amendments to the original protocol and several country-specific protocol amendments.

- The first global amendment was made on October 12, 2015, prior to the first patient first visit of June 3, 2016. The interim analysis and sample size sections were revised to meet Written Request requirements.

- The second global amendment was made on January 18, 2016, and included non-substantial changes.

- The third global amendment was made on July 18, 2018. It modified the testing strategy for the primary analysis to increase the power of the study.

- Country-specific amendments for Italy and the Republic of Korea either removed or made blood sampling for gene expression profiling, metabolomics/proteomics, and pharmacogenetics optional. A country-specific amendment for the United Kingdom removed parental informed consent for subjects aged 16 years and above. A country-specific amendment for the United States and Canada revised the protocol for sites covered by the Quorum Institutional Review Board, to allow subjects to switch to open-label treatment with vortioxetine with three additional follow-up visits outside the study with the

same clinician (such that enrollment in the open-label extension Study 12712A was not available for subjects at these sites).

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study-related information were reviewed by an ethics committee or institutional review board before the start of the study. The Applicant attests that the study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

See Appendix 19.2 for details.

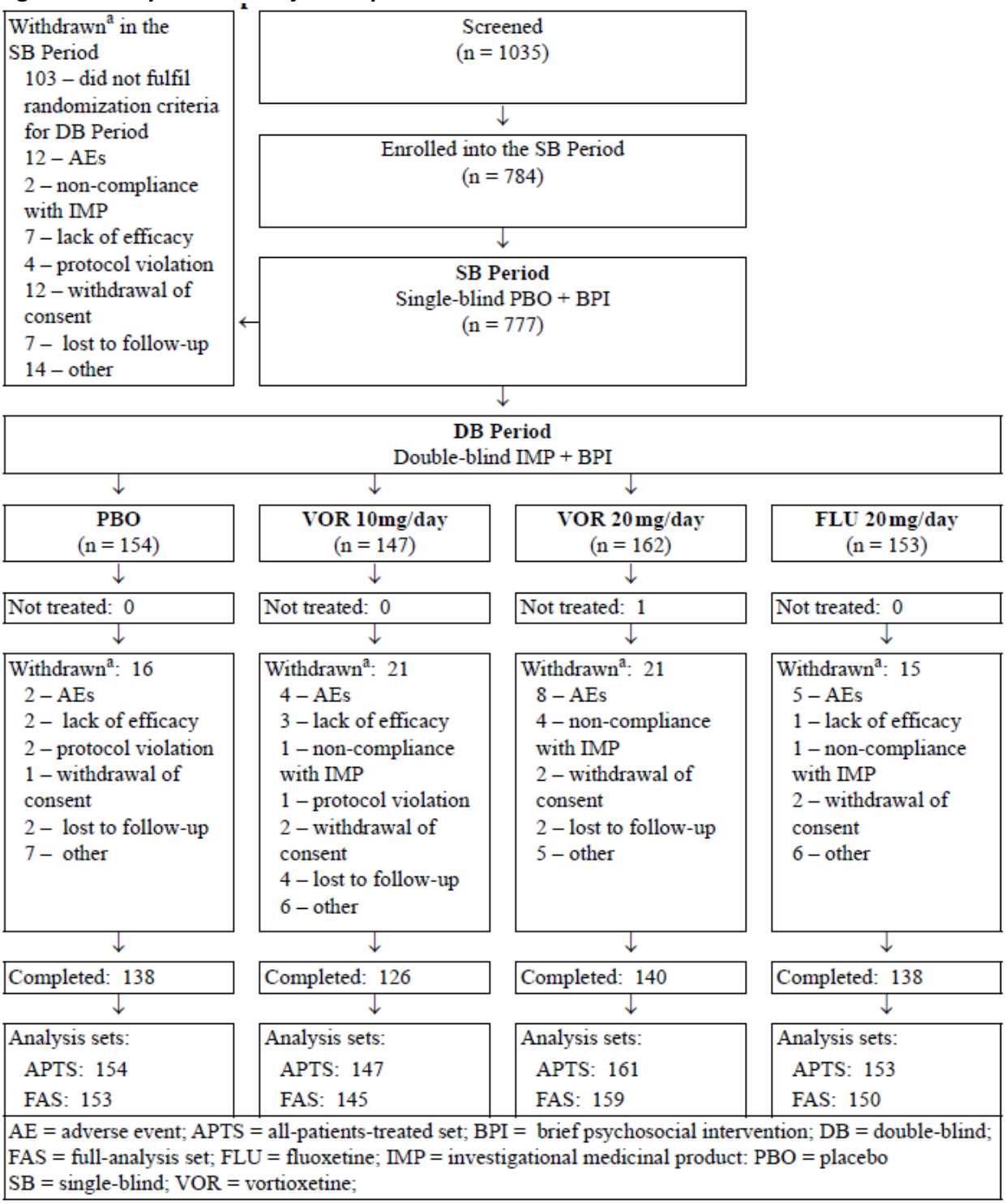
Patient Disposition

Of 1,035 subjects screened, 784 were enrolled into the SB Period, and 616 were randomized into the DB Period. Of the 161 subjects who withdrew during the SB Period, 103 (64.0%) did so for failure to meet randomization criteria. Of the randomized subjects, 138/154 subjects (89.6%) in the placebo group, 126/147 subjects (85.7%) in the vortioxetine 10 mg group, 140/162 subjects (86.4%) in the vortioxetine 20 mg group, and 138/153 subjects (90.2%) in the fluoxetine group completed the study.

The overall withdrawal rate in the DB Period was 12% and similar across treatment groups. The most common primary reasons for withdrawal were “other” (3.9%) and AE (3.1%). “Other” included primarily unwillingness/inability to attend visits or meeting withdrawal criteria; however, one patient was withdrawn for “other” because of suicidal thoughts. Per the Applicant, this is reflected in the C-SSRS at Week 7 but had not been reported as an AE by the investigator. The proportion of patients who withdrew for AEs was lowest in the placebo group (1.3%) and highest in the vortioxetine 20 mg group (5.0%).

See Figure 2 for the Applicant’s diagram of subject disposition and Table 18 for primary reasons for withdrawal during the DB Period for the all patients treated set (APTS) in Study 12710A.

Figure 2. Study 12710A Subject Disposition



a Primary reason

Source: Study 12710A Clinical Study Report, Panel 10, p. 55

Table 18. Study 12710A Double-Blind Period: Withdrawals by Primary Reason (APTS)

Primary Reason	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
All withdrawals	16 (10.4%)	21 (14.3%)	21 (13.0%)	15 (9.8%)
Adverse event	2 (1.3%)	4 (2.7%)	8 (5.0%)	5 (3.3%)
Other	7 (4.5%)	6 (4.1%)	5 (3.1%)	6 (3.9%)
Non-compliance with study drug	0	1 (0.7%)	4 (2.5%)	1 (0.7%)
Lost to follow-up	2 (1.3%)	4 (2.7%)	2 (1.2%)	0
Lack of efficacy	2 (1.3%)	3 (2.0%)	0	1 (0.7%)
Withdrawal of consent	1 (0.6%)	2 (1.4%)	2 (1.2%)	2 (1.3%)
Protocol violation	2 (1.3%)	1 (0.7%)	0	0

Source: Study 12710A Clinical Study Report, Panel 12, p. 57
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, PBO = placebo, VOR = vortioxetine

Clinical Reviewer's Comment: Overall, there was a relatively low rate of withdrawals from the study, roughly balanced among treatment arms. As expected, there were slightly more withdrawals for AEs in the active study drug groups than placebo, with a suggestion of dose-response in vortioxetine (though difficult to conclude with small numbers overall, but noncompliance with study drug was highest in the vortioxetine 20 mg arm as well). The Applicant notes that one "other" withdrawal reported suicidal thoughts (without being reported as an AE).

See Table 19 for Study 12710A DB Period analysis sets. According to the Applicant, the one subject ([(b) (6)]) who was excluded from the all patients randomized set (APRS) in the APTS did not take any study drug in the DB Period. The eight subjects across treatment arms who were excluded from the APTS in the full analysis set (FAS) did not have any valid post-randomization assessments (Subjects [(b) (6)]).

Table 19. Study 12710A Double-Blind Period: Analysis Sets

Analysis Set	PBO n (%)	VOR 10 mg n (%)	VOR 20 mg n (%)	FLU n (%)
All patients randomized set	154 (100%)	147 (100%)	162 (100%)	153 (100%)
All patients treated set	154 (100%)	147 (100%)	161 (99%)	153 (100%)
Full analysis set	153 (99%)	145 (99%)	159 (98%)	150 (98%)
Patients completed treatment	138 (90%)	126 (86%)	140 (87%)	138 (90%)

Source: Study 12710A Clinical Study Report, Panel 11, p. 56
Abbreviations: FLU = fluoxetine, PBO = placebo, VOR = vortioxetine

Protocol Violations/Deviations

According to the Applicant, there were no protocol deviations related to selection criteria, subject management, conduct of the study, or subject assessment that had consequences for including subject or data in any analysis set.

> *Clinical Reviewer's Comment: I reviewed the major protocol deviations related to informed consent; eligibility and withdrawal criteria; disallowed medications; treatment compliance; and efficacy, safety, or PK assessments. Among disallowed medication deviations, almost all that were related to psychiatric medications involved subjects who had recently stopped study drug (and were withdrawn) given suicidal ideation or worsening of depression. Treatment compliance errors mostly involved inadvertently taking an extra capsule or taking the titration capsules in the wrong order; five subjects received the wrong study drug kits (one placebo subject had gastroenteritis and hyperesthesia AEs after receiving fluoxetine and withdrew from the study). Many of the eligibility criteria deviations related to small errors regarding laboratory assessments; a few had CDRS-R scores of 40 at screening (rather than ≥45) because of a programming error (one withdrew at Visit 5). Among efficacy assessment deviations, 12 subjects had assessments completed by uncertified raters (mainly the CDRS-R); ten of these subjects were at site RU1010 in Russia. Overall, I agree with the Applicant's assessment, especially given the small numbers of any particular deviation.*

Table of Demographic and Other Baseline Characteristics

See Table 20 for the DB Period APTS demographic and other baseline characteristics; APTS characteristics were generally similar between the SB Period (not listed) and the DB Period. Subjects were approximately two-thirds female, with demographic characteristics balanced across treatment arms. Ethnicity (not in table) ranged from 20% to 24% Hispanic or Latino across treatment arms in the DB Period. Mean duration of current major depressive episode (MDE) was similar across the vortioxetine and fluoxetine arms at approximately 43 weeks; the placebo arm mean duration was shorter at 34.6 weeks. There was a large range in duration of current MDEs, from approximately 2 weeks to 626 weeks. Somewhat fewer placebo subjects had previously received pharmacotherapy than in the active study drug groups (33.1% versus 36.6 to 38.5%). Baseline CDRS-R scores were similar across treatment arms.

Table 20. Study 12710A All Patients Treated Set Demographic and Baseline Characteristics

Demographic Parameter or Disease Characteristic	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
Sex				
Female	105 (68.2%)	93 (63.3%)	96 (59.6%)	103 (67.3%)
Male	49 (31.8%)	54 (36.7%)	65 (40.4%)	50 (32.7%)
Age (years)				
Mean (SD)	14.6 (1.6)	14.8 (1.7)	14.5 (1.6)	14.8 (1.6)
Median	15	15	15	15
Range	12, 17	12, 17	12, 17	12, 17
Race				
White	106 (68.8%)	108 (73.5%)	109 (67.7%)	112 (73.2%)
Black	22 (14.3%)	19 (12.9%)	19 (11.8%)	20 (13.1%)
Other	21 (13.6%)	17 (11.6%)	25 (15.5%)	17 (11.1%)
Asian	4 (2.6%)	0	4 (2.5%)	2 (1.3%)
Not known	1 (0.6%)	3 (2.0%)	4 (2.5%)	1 (1.3%)
BMI (kg/m^2) - females				
Mean (SD)	22.9 (5.5)	23.3 (5.8)	23.1 (6.6)	23.6 (6.5)
Median	21.6	21.3	21.3	21.9
Range	13.1, 43.2	14.8, 44.9	14.1, 52.3	12.3, 56.7
BMI (kg/m^2) - males				
Mean (SD)	23.0 (5.2)	22.2 (6.0)	22.8 (6.3)	22.5 (4.6)
Median	22.2	20.2	20.9	21.1
Range	16.1, 41.5	14.5, 43.3	15.1, 52.3	14.4, 36.9
Number of previous MDEs				
Mean (SD)	0.6 (0.9)	0.6 (0.8)	0.6 (0.8)	0.4 (0.7)
Median	0	0	0	0
Range	0, 4	0, 4	0, 3	0, 3
Duration of current MDE (weeks)				
Mean (SD)	34.6 (37.0)	43.1 (55.9)	43.2 (57.6)	42.8 (66.8)
Median	22.9	25.4	23.9	24.6
Range	2.4, 222.9	2.7, 463.9	1.7, 473.6	3.3, 626.4
History of pharmacotherapy				
Yes	51 (33.1%)	56 (38.1%)	62 (38.5%)	56 (36.6%)
No	103 (66.9%)	91 (61.9%)	99 (61.5%)	97 (63.4%)
Baseline B CDRS-R total score				
N (Full Analysis Set)	153	145	159	150
Mean (SD)	60.6 (9.1)	61.2 (9.4)	62.5 (9.8)	61.8 (8.9)
Median	60	61	62	62
Range	41, 81	40, 86	42, 87	40, 83

Source: Adapted from Study 12710A Clinical Study Report, Panel 14, p. 59, Table 18, p. 167, Panel 15, p. 60, and Panel 16, p. 61

Abbreviations: BMI = body mass index, CDRS-R = Children's Depression Rating Scale-Revised version, FLU = fluoxetine, MDE = major depressive episode, PBO = placebo, SD = standard deviation, VOR = vortioxetine

Clinical Reviewer's Comment: Overall, baseline demographic and disease characteristics were generally balanced across treatment arms (and generally consistent with the SB Period, not listed). The placebo group did exhibit some small differences as noted, but small enough that it seems unlikely to have affected results. One might have expected a degree of SB Period enrichment for more ill subjects in the DB Period, and it is possible to read the data that way, but any differences are small or inconsistent to draw conclusions. (For example, the mean duration of the current MDE was generally slightly longer in the DB Period groups compared to the SB Period 39.7 weeks (except placebo), although the median for the SB Period at 24.3 weeks was squarely within the DB Period group range. The percentage of SB Period subjects having received prior pharmacotherapy (35.1%) is somewhat lower than the DB Period group range (except placebo).

Race and ethnicity demographic characteristics appear adequately similar to the U.S. general population. Only one subject reported a current MDE duration <2 weeks (i.e., 1.7 weeks); it is unclear how that subject qualified for the study given the inclusion requirement for meeting DSM diagnostic criteria, which specify 2 weeks' duration. The baseline mean and the maximum duration of the current MDE were lower in the placebo group, but the median duration was similar to other groups, and mean Baseline B CDRS-R scores were similar across all groups.

Other Baseline Characteristics (i.e., important prior medications of special interest)

For the DB Period APTS, the most common prior medication of special interest was antidepressant use, which was roughly balanced across DB Period treatment arms (i.e., 16.2% use in placebo, 24.5% use in vortioxetine 10 mg, 21.7% use in vortioxetine 20 mg, and 23.5% use in fluoxetine arms). Prior antipsychotic, anxiolytic, and stimulant use was low and similar between treatment arms (between 1% to 3%, between 2% to 4%, and between 1% to 5%, respectively, across arms). Prior sedative/hypnotic use was slightly lower in the placebo group (3.2%) than the other arms (roughly 8% for each). Generally, prior medication of special interest use was similar between the SB Period and the DB Period APTSs; sedative/hypnotic use was closer to the DB placebo group at 3.9%.

Clinical Reviewer's Comment: Overall, numbers were low for prior medications other than antidepressants, so it is difficult to draw any conclusion regarding the slightly lower sedative/hypnotic use in the placebo arm. The placebo arm did have slightly lower prior use of antidepressants compared to other arms, ranging from a 5.5% to 8.3% difference.

Concomitant or Rescue Medication Use and Treatment Compliance

Concomitant Medication Use

The Applicant did not specify rescue medication use for the study. For the DB Period APTS, the most common therapeutic classes of medication taken by ≥5% of the subjects in any treatment

group that continued after the first dose of study drug were (in order of: placebo; vortioxetine 10 mg; vortioxetine 20 mg; fluoxetine):

- Stimulants, agents used for ADHD and nootropics (6%; 7%; 5%; 4%)
- Hormonal contraceptives for systemic use (5%; 2%; 4%; 7%)

The most common therapeutic classes of medication taken by ≥5% of the subjects in any treatment arm in the DB Period that started at or after the first dose of study drug were (in order of: placebo; vortioxetine 10 mg; vortioxetine 20 mg; fluoxetine):

- Antiinflammatory and antirheumatic producs, non-steroids (11%; 10%; 11%; 11%)
- Other analgesics and antipyretics (8%; 8%; 12%; 9%)
- Stimulants, agents used for ADHD and nootropics (6%; 7%; 5%; 5%)
- Hormonal contraceptives for systemic use (5%; 3%; 4%; 7%)
- Antihistamines for systemic use (2%; 3%; 7%; 5%)
- Adrenergics, inhalants (3%; 2%; 2%; 6%)

Per the Applicant, "approximately 6% of the patients in each treatment group started treatment with psychostimulants, agents used for ADHD and nootropics at or after the first dose" of study drug.

> *<u>Clinical Reviewer's Comment</u>: The protocol stated that stimulant use was permitted if doses had been stable for 4 weeks prior to enrollment but otherwise prohibited, so it is unclear what to make of the 6% of subjects who started ADHD treatment "at or after" the first dose of study drug. Only one subject (Subject* (b) (6) *in the vortioxetine 20 mg arm) was listed as having a major protocol deviation for use of methylphenidate (for the indication of MDD, along with sertraline, both started the day after discontinuation of study drug when hospitalized for suicidal ideation). However, this ADHD treatment use was balanced across treatment arms, so it appears unlikely to have impacted the efficacy findings.*

<u>Treatment Compliance</u>

As noted by the Applicant, for the DB Period APTS and FAS, 88 to 93% of the subjects across treatment groups received study drug for at least 43 days. The mean number of days of exposure to study drug ranged from 52 to 54 days across treatment groups. Based on tablet counts, the proportion of APTS subjects with >80% compliance with study drug was approximately 99% in each treatment group. The majority of the subjects in the APTS (91 to 95% across treatment group) did not have a dose reduction for tolerability.

According to the Applicant, vortioxetine steady-state exposures in adolescents were similar to those previously reported for adults for both 10 and 20 mg. PK sampling estimated compliance based on the plasma concentration data, the estimated CL/F values, and the frequency of the PK samples below the LLOQ. A maximum of two samples were collected from each subject.

According to PK data, in the vortioxetine groups, a total of 16% (48 subjects: 16 subjects (11%) in the 10 mg group and 32 subjects (20%) in the 20 mg group) were considered non-compliant. In the fluoxetine group, 14% (20 subjects) were considered non-compliant.

> *Clinical Reviewer's Comment: The Applicant does not correlate the subjects' compliance by tablet-count with their compliance by PK data, so it is difficult to know if the non-compliant subjects are the same ones based on each method. It is likely that a portion of subjects reporting tablet compliance did not meet PK criteria for compliance, based on the differing numbers. However, as PK non-compliance was similar between vortioxetine and fluoxetine, that allows for some comparison between the two drugs' potential noncompliance impact on efficacy.*

Efficacy Results – Primary Endpoint

The primary endpoint, the mean change from baseline in CDRS-R total score at Week 8, average of the two vortioxetine doses (Avg. VOR), was not statistically significantly different versus placebo (Table 36. Study 12710A Double-Blind Period Columbia Suicide Severity Rating Scale Scores, All Patients Treated SetTable 36). Because the hypothesis testing strategy starts with Avg. VOR, the testing strategy was stopped at this first hypothesis step. At Week 8, the Avg. VOR had a difference of 0.2 points from placebo and the difference was not statistically significant (95% CI: -2.41 to 2.82; p = 0.9). For analyses of the individual vortioxetine doses (10 and 20mg) versus placebo, the results for neither dose were nominally statistically significant. However, the result for fluoxetine (20 mg) dose group compared to placebo was nominally statistically significant in the mean change from randomization to Week 8 in CDRS-R total score (difference= -3.7 points; 95% CI -6.74 to -0.72; p=0.015).

Table 21. Primary Efficacy Analysis in Double-Blind Period: Change from Randomization to Week 8 in the Children's Depression Rating Scale-Revised Total Score (FAS MMRM)

					Comparison to PBO			
						95% CI		
Treatment Group	Week	N	Mean	SE	Diff.	SE	Lower	Upper	p-value
PBO	2	153	-8.83	0.98					
	4	149	-13.71	1.09					
	6	142	-16.71	1.19					
	8	137	-18.22	1.22					
Avg. VOR	2		-9.87	0.82	-1.04	0.99	-2.98	0.91	0.2951
	4		-14.67	0.89	-0.97	1.15	-3.23	1.30	0.4031
	6		-16.61	0.96	0.10	1.29	-2.43	2.63	0.9388
	8		-18.01	0.98	0.21	1.33	-2.41	2.82	0.8778
VOR 10 mg	2	145	-9.58	1.02	-0.75	1.16	-3.02	1.52	0.5154
	4	137	-14.32	1.14	-0.61	1.35	-3.27	2.04	0.6494
	6	127	-15.43	1.24	1.27	1.51	-1.69	4.24	0.3985
	8	126	-17.09	1.27	1.13	1.56	-1.94	4.20	0.4702
VOR 20 mg	2	158	-10.15	0.99	-1.32	1.13	-3.54	0.90	0.2422
	4	153	-15.03	1.10	-1.32	1.32	-3.90	1.27	0.3178
	6	145	-17.78	1.19	-1.08	1.47	-3.96	1.81	0.4637
	8	139	-18.94	1.22	-0.72	1.52	-3.71	2.27	0.6373
FLU 20 mg	2	150	-10.34	1.00	-1.51	1.14	-3.76	0.73	0.1856
	4	145	-16.25	1.11	-2.54	1.33	-5.16	0.07	0.0567
	6	143	-19.20	1.20	-2.49	1.48	-5.40	0.42	0.0929
	8	137	-21.95	1.23	-3.73	1.53	-6.74	-0.72	0.0152

Source: Clinical study report for Study 12710A, Table 47, page 268
FAS (full analysis set): all patients randomized to the double-blind, 8-week treatment period (Phase B) who took at least one dose of double blind investigational medical product, who had a valid Baseline B assessment and at least one valid post-Baseline B assessment of the CDRS-R total score.

Data Quality and Integrity

The reviewers found the quality and integrity of the submitted data satisfying and acceptable for the review analysis.

Efficacy Results – Secondary and other relevant endpoints

As noted by the Applicant, the results of the secondary efficacy analyses were generally consistent with the primary results (i.e., no significance for vortioxetine and nominal significance for fluoxetine). According to the Applicant, there were nominally significant ($p < 0.05$) improvements on the CGI-S score versus placebo at Weeks 1, 3, 4, and 6 in the vortioxetine 20 mg group.

> *Clinical Reviewer's Comment: Given the failure on the primary endpoint and lack of significance at Week 8 on the CGI-S for the vortioxetine 20 mg group, the nominally significant CGI-S results at earlier weeks for the 20 mg group does not appear clinically meaningful.*

Dose/Dose Response

As described above, neither the vortioxetine 10 nor the 20 mg dose separated from placebo on the primary endpoint.

Durability of Response

As described above, neither the vortioxetine 10 nor the 20 mg dose separated from placebo on the primary endpoint.

Persistence of Effect

As described above, neither the vortioxetine 10 nor the 20 mg dose separated from placebo on the primary endpoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Overall the analysis results of COA outcomes were similar between each vortioxetine dose group and placebo. For the fluoxetine arm compared to placebo, the Applicant noted a nominally statistically significant result for PQ-LES-Q total score (items 1 to 14) with a difference of 2.20 (95% CI: 0.04, 4.36; nominal p=0.046—Table 80, p 321 of the clinical study report), but the result for PQ-LES-Q overall evaluation score (item 15) was neutral.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

Not applicable given that Study 12710A was the singular efficacy trial.

Primary Endpoints

See above.

Secondary and Other Endpoints

See above.

Subpopulations

According to the Applicant, primary efficacy results analyzed by age, sex, race, and baseline disease severity were generally similar to the results for the general population for vortioxetine. According to the Applicant, there was a trend toward a larger effect in subjects with more severe baseline depression (baseline CDRS-R ≥66) in the fluoxetine arm (i.e., this subgroup nominally separated from placebo whereas the <55 and ≥55 to <65 groups did not).

Clinical Reviewer's Comment: The Black and "Other" race subgroups appear too small to

draw any conclusions.

Additional Efficacy Considerations

Not applicable.

8.2.2. Integrated Assessment of Effectiveness

As described above, the phase 3, randomized, double-blind, placebo-controlled, active-reference (fluoxetine 20 mg), fixed-dose (vortioxetine 10 and 20 mg), parallel-group Study 12710A was designed to assess the efficacy of vortioxetine for the treatment of MDD in pediatric subjects ages 12 to 17 years. The primary endpoint was change from randomization (baseline B) to Week 8 on the CDRS-R total score. Although there was numerical improvement in all groups, the average vortioxetine did not separate from placebo (see Table 21). Nominally, neither vortioxetine dose group separated from placebo, but the fluoxetine group did separate from placebo. Although this study fulfills the PREA PMR 2084-8, the results do not support the use of vortioxetine for the treatment of MDD in pediatric patients ages 12 to 17 years.

8.3. Review of Safety

8.3.1. Safety Review Approach

The safety data supporting this application are based on the Applicant's Summary of Clinical Safety. The summary presents an analysis of safety data from:

- Two completed studies: the phase 3 interventional Study 12710A in subjects ages 12 to 17 (hereafter referred to as adolescents) and the clinical pharmacology Study 12708A in both adolescents and subjects ages 7 to 11 years (hereafter referred to as children). Study 12708A consisted of a 14 to 21 day main treatment study, with an optional 6-month extension.

- Three ongoing studies: the phase 3 interventional Study 12709A in children, the 6-month open-label extension Study 12712A in children and adolescents, and the 18-month open-label extension Study 12712B in children and adolescents (interim data as of the cutoff date of September 29, 2019).

See Section 8.1 for a discussion of Study 12710A and Table 17 for a tabular description of all of the studies.

8.3.2. Review of the Safety Database

Overall Exposure

See Table 22 for the total safety population (APTS) for the completed studies 12708A and 12710A. In Study 12708A, each dose cohort included six children and six adolescents. In the

open-label extension studies, 523 subjects in Study 12712A (ongoing) and 94 subjects in Study 12712B (completed) had received vortioxetine 5, 10, 15, or 20 mg (not sorted into separate arms) as of the cutoff date (note that subjects from Study 12712A rollover into Study 12712B and should not be counted twice). In ongoing Study 12709A in children, 316 subjects had received blinded study drug (placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine) as of the cutoff date.

Table 22. Total Completed Study Safety Population Size

Study	PBO (N=154)	VOR 5 mg (N=12)	VOR 10 mg (N=159)	VOR 15 mg (N=12)	VOR 20 mg (N=173)	FLU (N=153)
12708A	N/A	12	12	12	12	N/A
12710A	154	N/A	147	N/A	161	153

Source: Adapted from Study 12708A Clinical Study Report, Panel 7, p. 58, and Study 12710A Clinical Study Report, Panel 11, p. 56
Abbreviations: FLU = fluoxetine, N/A = not applicable, PBO = placebo, VOR = vortioxetine
Note: Study 12708A included six children (ages 7 to 11 years) and six adolescents (ages 12 to 17 years) per dose cohort

See Table 23 for Study 12710A safety population (APTS) extent of drug exposure. The majority of subjects across all treatment arms (roughly 88% to 92%) were exposed for ≥43 days.

Table 23. Study 12710A Safety Population (APTS) Extent of Drug Exposure

Duration of Exposure (days)	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
Mean (SD)	54.0 (11.4)	52.4 (12.3)	52.8 (10.9)	53.2 (10.5)
Median	56	56	56	56
Range	7, 130	3, 82	1, 106	4, 86

Source: Adapted from Study 12710A Clinical Study Report, Table 43, p. 263
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, PBO = placebo, SD = standard deviation, VOR = vortioxetine

See Table 24 for Study 12708A safety population extent of drug exposure, including all subjects from the main study and the extension. (In the main study, 48 subjects were treated, and one subject withdrew; 41 subjects continued in the extension.)

Table 24. Study 12708A Safety Population Extent of Drug Exposure

Duration of Exposure (days)	AC 5 mg	AC 10 mg	AC 15 mg	AC 20 mg	CC 5 mg	CC 10 mg	CC 15 mg	CC 20 mg
Main period								
N	6	6	6	6	6	6	6	6
Mean	12.0	16.0	18.0	19.3	14.0	16.0	18.0	20.0
SD	4.9	0	0	1.6	0	0	0	0
Median	14	16	18	20	14	16	18	20
Minimum	2	16	18	16	14	16	18	20
Maximum	14	16	18	20	14	16	18	20
Extension								
N	4	6	6	6	4	5	5	5
Mean	100	141	114	141	144	148	130	146
SD	57	54	64	76	86	61	57	61
Median	78	149	97	187	187	183	123	184
Minimum	59	45	42	25	15	51	49	61
Maximum	184	191	189	194	188	192	187	192

Source: Adapted from Study 12708A Clinical Study Report, Panel 13, p. 64, and Study 12708A Clinical Study Report – Addendum 1, Panel 3, p. 20
Abbreviations: AC = adolescent cohort (ages 12 to 17 years), CC = children cohort (ages 7 to 11 years)

Clinical Reviewer's Comment: The Applicant did not provide information regarding duration of exposure thus far in the ongoing studies.

Adequacy of the safety database:

The safety population included all subjects who received at least one dose of study medication. The Applicant presented data from the individual studies separately given the differences in design. The demographic characteristics of Study 12710A were previously discussed (see Table 20). Study 12708A included a two-thirds female population (similar to 12710A), with roughly two-thirds white and one-quarter black subjects. The results of the studies appear sufficiently generalizable for the purpose of the safety assessment.

Clinical Reviewer's Comment: Long-term exposure was addressed in the adult development program. Long-term in the pediatric population is not an issue given the negative efficacy results.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data were of sufficient integrity and quality for review. OSI inspections were waived given the nature of the submission as a negative trial without obvious issues upon filing review.

Categorization of Adverse Events

The Applicant coded AEs using the lowest level term (LLT), with AEs presented using the preferred term (PT) corresponding to the LLT, according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 16.1 for Study 12708A and Version 21.0 for Study 12710A). AEs, severity of AEs, and serious AEs (SAEs) were appropriately defined. AE assessment included spontaneous reporting in response to a non-leading question (e.g., "how do you feel?") at each visit, and related to results of relevant tests (e.g., laboratory tests, vital signs, and ECGs). The C-SSRS was used to capture events of suicidal ideation and behavior at all visits, and the GBI 10-item mania subscale was used to capture events of mania periodically throughout the studies.

For Study 12708A, the Applicant counted AEs that started in the main study period and continued in the extension period only during the main period. In Studies 12710A and 12709A, AEs that started in the SB Period and continued in the DB Period were only counted in the SB Period, unless the AEs increased in severity during the DB Period, in which case they were counted in both periods. In the open-label extension (OLE) Studies 12712A and 12712B, AEs that started in a previous lead-in study were assigned to that previous study (i.e., coded as starting during the lead-in study and continuing).

Per the Applicant, AEs of special interest were examined separately and grouped in the following categories, determined based on risks potentially associated with antidepressants in the adult population, AEs of specific interest in the pediatric population, general drug safety issues, and/or nonclinical findings. Those AEs were searched using the following standardized MedDRA queries (SMQs) or clusters of PTs:

- AEs potentially associated with antidepressants or of specific interest in pediatric populations:
    - Suicidal ideation and self-injurious behavior: SMQ suicide/self-injury (narrow scope); PTs of overdose and intentional overdose were queried for suicidal intent and reported as suicide attempt if intent was present
    - Mania: PTs mania and hypomania
    - Seizures: SMQ convulsions (broad scope)
    - Serotonin syndrome: PT serotonin syndrome
    - Hyponatremia/syndrome of inappropriate antidiuretic hormone secretion (SIADH): SMQ hyponatremia/SIADH (broad scope)
    - Abnormal bleeding: SMQ hemorrhage (broad scope)

  - Insomnia: PTs hyposomnia, initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia, dyssomnia

  - Somnolence: PT somnolence

  - Hostility and aggression: SMQ hostility/aggression (broad scope)

  - Growth and sexual maturation: high level term (HLT) endocrine abnormalities of puberty

  - Sexual dysfunction: HLTs orgasmic disorders and disturbances, paraphilias and paraphilic disorders, sexual and gender identity disorders not elsewhere classified (NEC), sexual arousal disorders, sexual desire disorders, erection and ejaculation conditions and disorders, sexual function and fertility disorders NEC; PTs genital hypoaesthesia, loss of libido, libido decreased, female sexual arousal disorder, anorgasmia, female orgasmic disorder, male orgasmic disorder, orgasm abnormal, orgasmic sensation decreased, premature ejaculation, vulvovaginal dryness, ejaculation failure, ejaculation delayed, persistent genital arousal disorder; LLT nipple hypoesthesia

  - Nausea/vomiting: HLT nausea and vomiting symptoms

  - Constipation: PTs constipation and post-procedural constipation

  - Closed-angle glaucoma: SMQ glaucoma (broad scope)

- General drug safety issues:

  - Abuse liability: SMQ drug abuse and dependence (broad scope)

  - QT prolongation: SMQ Torsade de Pointes/QT prolongation (broad scope)

- Nonclinical findings (target organ toxicity):

  - Kidney toxicity: SMQ acute renal failure (broad scope)

  - Liver toxicity: SMQ drug related hepatic disorders – comprehensive search (broad scope)

I additionally grouped the following PTs upon examination of the ADAE datasets for AEs of special interest or if multiple occurrences of separate PTs, if grouping made a noteworthy difference in frequency:

- Abdominal pain: and abdominal discomfort, abdominal pain lower, abdominal pain upper
- Anxiety: added generalized anxiety disorder, panic attack
- Depression: added depressed mood, depressive symptom, major depression
- Headache: added tension headache, migraine
- Somnolence: added sedation

> *Clinical Reviewer's Comment: The Applicant's S/AE definitions, and monitoring and severity determinations, appear reasonable. The Applicant's verbatim-to-PT mapping appeared reasonable upon examination, and did not require any recoding prior to grouping.*

Routine Clinical Tests

Blood and urine samples for clinical safety laboratory tests (i.e., hematology, chemistry, urinalysis) were collected. For vital signs, supine and standing blood pressure, and pulse rate were measured. A standard 12-lead ECG was performed. The clinical safety laboratory tests were analysed at a central laboratory. The ECGs were evaluated by a pediatric cardiologist at a central laboratory. See Table 25 and Table 26 for schedules of these assessments in the completed and ongoing OLE studies, respectively. All assessments (original and repeated, if necessary) were used to identify potentially clinically significant (PCS) values.

Table 25. Completed Studies Schedule of Other Safety Assessments

	Screening	Baseline[a]	Treatment Period	Completion/Withdrawal
Clinical Pharmacology Study 12708A				
2-week Main Study Period				
Laboratory tests	√	√		√
Vital signs	√	√	√	√
Weight	√			√
ECGs	√	√		√
6-month Extension Period				
Laboratory tests			√[b]	√
Vital signs			√	√
Weight			√	√
ECGs				√
Efficacy and Safety Study 12710A				
Laboratory tests	√	√[c]	√[d]	√
Vital signs	√	√[c]	√	√
Weight	√	√[c]	√[d]	√
ECGs	√	√[c]	√[d]	√

a In Study 12710A, baseline is the Randomization Visit in the DB Period.
b Visit 15 (Day 84) and Visit 18 (Day 168) of the 6-month Extension Period
c In the DB Period, values from assessments performed at Week 4 of the SB Period were the Randomization Visit values.
d Week 4 of the SB Period, Week 8 of the DB Period, and Week 12 (Completion Visit)

Source: Summary of Clinical Safety, Panel 2, p. 16
Abbreviations: DB = double-blind, ECG = electrocardiogram, SB = single-blind

Table 26. Ongoing Open-Label Extension Studies Schedule of Other Safety Assessments

	Baseline	Treatment Period	Completion/Withdrawal
OLE Study 12712A (6-month Extension Period)			
Laboratory tests	√[a]	√[b]	√
Vital signs	√[a]	√[c]	√
Weight	√[a]	√[d]	√
ECGs	√[a]	√[b]	√
OLE Study 12712B (18-month Extension Period)			
Laboratory tests	√[e]	√[f]	√
Vital signs	√[e]	√[g]	√
Weight	√[e]	√[f]	√
ECGs	√[e]	√[f]	√

a Values from assessments performed at the Completion Visit of Study 12709A or 12710A (Week 12) were the baseline (OLEXA) values of OLE Study 12712A.
b Week 4
c Weeks 1, 2, 4, 8, 12, and 18
d Week 12
e Values from assessments performed at the Completion Visit of OLE Study 12712A (Week 26) were the baseline (OLEXB) values of OLE Study 12712B.

Source: Summary of Clinical Safety, Panel 3, p. 16
Abbreviations: ECG = electrocardiogram, OLE = open-label extension, OLEXA = open-label extension 12712A, OLEXB = open-label extension 12712B

Clinical Reviewer's Comment: The clinical laboratory assessments, additional safety assessments, and collection schedule for labs, vital signs, and ECG were reasonable.

8.3.4. Safety Results

Deaths

Two deaths have occurred in the pediatric development program as of the cutoff date of September 29, 2019, both in Study 12710A; one in a treated subject, and the other in a subject who had been screened. The Applicant reports that no deaths or suspected unexpected serious adverse reactions had been reported in treated subjects in the pediatric program through January 31, 2020.

- Subject (b) (6), a 15-year-old boy at a U.S. site in the placebo arm, completed suicide approximately 1 year following completion of Study 12710A. The subject had a history of MDD, intentional self-injury and insomnia, and had taken sertraline prior to enrollment. At screening, on the C-SSRS for lifetime history, the subject answered "yes" to "wish to be dead," "non-specific active suicidal thoughts," "active suicidal ideation with specific plan and intent," "preparatory acts or behavior," "aborted attempt or self-interrupted attempt," "interrupted attempt," and "actual attempt." For past 12 months, he answered "yes" to "wish to be dead" and "non-specific active suicidal thoughts." At all visits, the subject answered "yes" to "wish to be dead" except for Day 7 and Day 42.

Nearly a year after completing the study, the subject completed suicide. He wrote a suicide note 7 months prior to the suicide.

- Subject (b) (6), a 17-year-old girl at a Russian site, completed suicide 1 day after her screening visit. The subject had a history of MDD and ADHD; she received her last dose of fluvoxamine and carbamazepine for MDD at the screening visit. One day after, she drank an unspecified amount of alcohol, and took 20 tablets of carbamazepine, 10 tablets of fluvoxamine, and spasmalgon. She had written a suicide note. She was found unconscious by her mother and hospitalized. Ten days after the screening visit, the subject died from multi-organ failure, exotoxic shock, and disseminated intravascular coagulation.

  Clinical Reviewer's Comment: Although the first subject had a significant lifetime history of suicidal behavior, he did not within the past 12 months, allowing inclusion in the trial. His death occurred long after study completion, and no information was provided regarding any treatment he had following the study. The second subject completed suicide before actual enrollment in the study.

Serious Adverse Events

In the Study 12710A SB Period, 13 subjects (out of 777 APTS, 1.7%) experienced SAEs: including suicidal ideation (six subjects (0.8%)); suicide attempt (two subjects (0.3%)); and suicidal behavior, generalized anxiety disorder, appendicitis, dysmenorrhea, and influenza (one subject (0.1%) each). One subject experienced two SAEs in the SB follow-up period after withdrawal from the study (intentional overdose and suicide attempt). The Applicant considered all psychiatric SAEs related to study drug (placebo).

In the Study 12710A DB Period, 15 subjects experienced SAEs; see Table 27. The vortioxetine groups included a larger number of SAEs overall, and specifically the 20 mg group more than fluoxetine; all active drug groups more than placebo. The placebo group had no psychiatric SAEs. The Applicant did not include an additional three subjects who experienced SAEs in the DB follow-up period (intentional self-injury, suicidal ideation, and completed suicide).

Table 27. Study 12710A Double-Blind Period Serious Adverse Events (APTS)

MedDRA Preferred Term	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
Any serious adverse event	1 (0.6%)	4 (2.7%)	7 (4.3%)[1]	3 (2.0%)
Suicidal ideation	0	1 (0.7%)	3 (1.9%)[2]	2 (1.3%)
Depression	0	0	1 (0.6%)	0
Suicide attempt	0	0	1 (0.6%)	0
Meningitis	0	0	1 (0.6%)	0
Pneumonia bacterial	0	0	1 (0.6%)	0
Viral UR tract infection	0	0	1 (0.6%)	0
Appendicitis	0	1 (0.7%)	0	0
Bronchitis viral	0	1 (0.7%)	0	0
Gastroenteritis, gastrointestinal viral infection	1 (0.6%)	1 (0.7%)	0	0
Head injury	0	0	0	1 (0.7%)

Source: Adapted from Study 12710A Clinical Study Report, Panel 25, p. 78
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, UR = upper respiratory, VOR = vortioxetine
[1] If including Subject (b) (6) given hospitalization for suicidal ideation on study drug, entry should be 8 (5.0%)
[2] If including Subject (b) (6) given hospitalization for suicidal ideation on study drug, entry should be 4 (2.5%)

Clinical Reviewer's Comment: The Study 12710A DB Period is the most informative for direct placebo-controlled comparison. Of note, SIB-related SAEs occurred only in the active drug groups compared to placebo, which would be consistent with the antidepressant boxed warning. See Section 8.3.5 for a discussion of all SIB-related AEs, including SAEs.

Of the subjects coded to the DB follow-up period, two SAEs appear appropriately coded to the follow-up period and unlikely related to study drug: Subject (b) (6) of the completed suicide was discussed above. Subject (b) (6), a 17-year-old boy at a U.S. site in the fluoxetine arm, experienced intentional self-injury on Day 70 (after completing the DB treatment period on Day 56; he had also started citalopram on Day 57, which would appear to preclude a withdrawal effect, although withdrawal is uncommon given fluoxetine's long half-life). However, the third subject appears to be erroneously coded. Per the narrative, Subject (b) (6), a 15-year-old girl at a U.S. site in the vortioxetine 20 mg arm, experienced suicidal ideation that was rated as not serious on Day 52, and was admitted to the hospital (which should make the suicidal ideation an SAE by definition). She received her last dose of vortioxetine 20 mg on Day 53 and had the completion visit "as planned" on Day 57. On Day 69, the suicidal ideation intensity increased from moderate to severe (and appears to have been coded as an SAE at this point) Her narrative did not clarify the length of the hospitalization.

In Study 12708A, three subjects (all adolescents) experienced SAEs, all of which occurred during

the 6-month extension. In the vortioxetine 20 mg group, one subject (2.4% of total N = 41 all doses) experienced intentional overdose and suicide attempt, and another subject (2.4%) experienced appendicitis. In the vortioxetine 15 mg group, one subject (2.4%) experienced suicidal ideation.

In the OLE studies (as with Study 12708A), there is no comparator, but AEs may inform what a picture of long-term use might show. In Study 12712A, 17 subjects (3.3%) experienced 21 SAEs as of the cutoff date; see Table 28 for a listing of SAEs by lead-in study (12710A versus 12709A), and see Table 29 for a listing of SAEs by lead-in treatment from Study 12710A. No SAEs occurred in Study 12712B. Two subjects in ongoing blinded Study 12709A have reported SAEs in the DB Period (major depression and forearm fracture).

Table 28. Study 12712A Serious Adverse Events by Lead-In Study

MedDRA Preferred Term	Study 12709A (N=188) n (%)	Study 12710A (N=335) n (%)	Total (N=523) n (%)
Any serious adverse event	5 (2.7%)	12 (3.6%)	17 (3.3%)
Suicidal ideation	2 (1.1%)	3 (0.9%)	5 (1.0%)
Suicide attempt	1 (0.5%)	3 (0.9%)	4 (0.8%)
Intentional overdose	0	2 (0.6%)	2 (0.4%)
Depression[1]	0	2 (0.6%)	2 (0.4%)
Lymphadenitis	1 (0.5%)	0	1 (0.2%)
Mania	0	1 (0.3%)	1 (0.2%)
Osteitis	0	1 (0.3%)	1 (0.2%)
Psychogenic seizure	0	1 (0.3%)	1 (0.2%)
Psychomotor hyperactivity	1 (0.5%)	0	1 (0.2%)
Schizophrenia	0	1 (0.3%)	1 (0.2%)
Suicidal behavior	1 (0.5%)	0	1 (0.2%)
Suicide threat	1 (0.5%)	0	1 (0.2%)

Source: Adapted from Summary of Clinical Safety, Panel 5, p. 23
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities
[1] Grouping includes depression and major depression

Table 29. Study 12712A Serious Adverse Events by Study 12710A Lead-In Treatment

MedDRA Preferred Term	PBO (N=82) n (%)	VOR 10 mg (N=78) n (%)	VOR 20 mg (N=93) n (%)	FLU (N=82) n (%)
Any serious adverse event	1 (1.2%)	2 (2.6%)	4 (4.3%)	5 (6.1%)
Suicidal ideation	1 (1.2%)	0	1 (1.1%)	1 (1.2%)
Suicide attempt	1 (1.2%)	0	0	2 (2.4%)
Intentional overdose	0	0	1 (1.1%)	1 (1.2%)
Depression[1]	0	1 (1.3%)	1 (1.1%)	0
Mania	0	1 (1.3%)	0	0
Osteitis	0	0	0	1 (1.2%)
Psychogenic seizure	0	0	1 (1.1%)	0
Schizophrenia	0	0	0	1 (1.2%)

Source: Adapted from Summary of Clinical Safety, Table 18, p. 90
Abbreviations: APRS = all patients randomized set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine
[1] Grouping includes depression and major depression

Clinical Reviewer's Comment: In Study 12712A, somewhat more adolescents than children have experienced SAEs. Among adolescents, subjects who were taking active study drug at lead-in have reported slightly more SAEs than subjects taking placebo at lead-in. However, the numbers are low enough overall that it is difficult to draw any conclusion from the differences. To assess the possibility of grouping SIB-related terms, I reviewed the narrative of Subject (b) (6) (SAE suicidal behavior and suicidal ideation), which specified that the suicidal ideation SAE resulted from C-SSRS answers, but did not specifiy anything regarding the suicidal behavior, so it is unclear for potential grouping if this was an actual attempt, self-injurious behavior, or resulted from C-SSRS answers. For Subject (b) (6) (SAE suicide threat), the narrative does not specify the nature of the event, so it is unclear if that should be grouped with suicidal ideation. For Subject (b) (6) (SAE intentional overdose), the narrative stated it was without suicidal intention and was "to feel better," so that does not appear appropriate for grouping with suicidal behavior. For Subject (b) (6) (SAE intentional overdose and suicide attempt), the overdose of 11 fluoxetine pills was with intent, but if grouped, that subject would only count once given the other SAE of suicide attempt.

Regarding the SAE of schizophrenia, late adolescence does overlap with the at-risk period for the onset of schizophrenia, so that is not unusual.

Adverse Events Leading to Withdrawal

In the Study 12710A SB Period, 14 subjects (1.8%) experienced AEs leading to withdrawal, including: suicidal ideation (six subjects (0.8%)); depression and suicide attempt (two subjects (0.3%) each); and anger, headache, intentional overdose, irritability, major depression, nausea, and tremor (one subject (0.1%) each).

In the Study 12710A DB Period, 20 subjects experienced AEs leading to withdrawal; see Table 30. The vortioxetine groups included a larger number of AEs leading to withdrawal overall, and specifically the 20 mg group more than fluoxetine; all active drug groups more than placebo.

Table 30. Study 12710A Double-Blind Period Adverse Events Leading to Withdrawal (APTS)

MedDRA Preferred Term	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
Any adverse event leading to withdrawal	2 (1.3%)	4 (2.7%)	9 (5.6%)	5 (3.3%)
Suicidal ideation	0	1 (0.7%)	3 (1.9%)	2 (1.3%)
Nausea	0	1 (0.7%)	2 (1.2%)	0
Vomiting	0	0	2 (1.2%)	0
Depression	0	0	1 (0.6%)	1 (0.7%)
ALT increased	0	0	1 (0.6%)	0
Headache	0	1 (0.7%)	1 (0.6%)	0
Meningitis	0	0	1 (0.6%)	0
Anxiety	0	0	0	1 (0.7%)
Dry mouth	1 (0.6%)	0	0	0
Gastroenteritis	1 (0.6%)	0	0	0
Hyperesthesia	1 (0.6%)	0	0	0
Insomnia	1 (0.6%)	0	0	0
Pregnancy	0	1 (0.7%)	0	0
WBC count decreased	0	0	0	1 (0.7%)

Source: Adapted from Study 12710A Clinical Study Report, Panel 25, p. 78
Abbreviations: ALT = alanine aminotransferase, APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine, WBC = white blood cell

> *Clinical Reviewer's Comment: Similar to SAEs, SI-related AEs leading to withdrawal occurred only in the active drug groups compared to placebo, which would be consistent with the antidepressant boxed warning. See Section 8.3.5 for a discussion of SIB-related AEs. Overall, rates were low and appear unlikely to impact efficacy results.*

In Study 12708A, four subjects (all adolescents) experienced an AE leading to withdrawal, all of which occurred during the 6-month extension. One subject (2.4% of total N = 41 all doses) each experienced suicide attempt, nausea, headache, and irritability, in the vortioxetine 20, 15, 10, and 5 mg dose groups, respectively.

In the OLE studies (as with Study 12708A), there is no comparator, but AEs may inform what a picture of long-term use might show. In Study 12712A, 36 subjects (6.9%) experienced an AE leading to withdrawal as of the cutoff date; see Table 31 for a listing of AEs leading to withdrawal by lead-in study (12710A versus 12709A), and see Table 32 for a listing of AEs leading to withdrawal by lead-in treatment from Study 12710A. No AEs leading to withdrawal occurred in Study 12712B. The Applicant did not report if any have occurred in ongoing blinded Study 12709A.

Table 31. Study 12712A Adverse Events Leading to Withdrawal by Lead-In Study

MedDRA Preferred Term	Study 12709A (N=188) n (%)	Study 12710A (N=335) n (%)	Total (N=523) n (%)
Any serious adverse event	15 (8.0%)	21 (6.3%)	36 (6.9%)
Nausea	3 (1.6%)	8 (2.4%)	11 (2.1%)
Suicidal ideation	2 (1.1%)	2 (0.6%)	4 (0.8%)
Suicide attempt	1 (0.5%)	3 (0.9%)	4 (0.8%)
Intentional overdose	0	2 (0.6%)	2 (0.4%)
Major depression	1 (0.5%)	1 (0.3%)	2 (0.4%)
Mania	1 (0.5%)	1 (0.3%)	2 (0.4%)
Dizziness	1 (0.5%)	1 (0.3%)	2 (0.4%)
Vomiting	0	2 (0.6%)	2 (0.4%)
Agitation	1 (0.5%)	0	1 (0.2%)
Anxiety	1 (0.5%)	0	1 (0.2%)
Blood pressure decreased	1 (0.5%)	0	1 (0.2%)
Decreased appetite	0	1 (0.3%)	1 (0.2%)
Dermatitis	1 (0.5%)	0	1 (0.2%)
Headache	0	1 (0.3%)	1 (0.2%)
Hepatitis viral	1 (0.5%)	0	1 (0.2%)
Irritability	0	1 (0.3%)	1 (0.2%)
Non-cardiac chest pain	1 (0.5%)	0	1 (0.2%)
Pruritis	1 (0.5%)	0	1 (0.2%)
Psychogenic seizure	0	1 (0.3%)	1 (0.2%)
Psychomotor hyperactivity	1 (0.5%)	0	1 (0.2%)
Rash	1 (0.5%)	0	1 (0.2%)
Suicidal behavior	1 (0.5%)	0	1 (0.2%)
Tic	1 (0.5%)	0	1 (0.2%)
Tremor	1 (0.5%)	0	1 (0.2%)
Weight decreased	0	1 (0.3%)	1 (0.2%)

Source: Adapted from Summary of Clinical Safety, Panel 7, p. 25
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

Table 32. Study 12712A Adverse Events Leading to Withdrawal by Study 12710A Lead-In Treatment

MedDRA Preferred Term	PBO (N=82) n (%)	VOR 10 mg (N=78) n (%)	VOR 20 mg (N=93) n (%)	FLU (N=82) n (%)
Any serious adverse event	2 (2.4%)	7 (9.0%)	6 (6.5%)	6 (7.3%)
Nausea	1 (1.2%)	4 (5.1%)	2 (2.2%)	1 (1.2%)
Suicide attempt	1 (1.2%)	0	0	2 (2.4%)
Intentional overdose	0	0	1 (1.1%)	1 (1.2%)
Suicidal ideation	1 (1.2%)	0	1 (1.1%)	0
Vomiting	0	2 (2.6%)	0	0
Decreased appetite	0	0	0	1 (1.2%)
Dizziness	0	1 (1.3%)	0	0
Headache	0	1 (1.3%)	0	0
Irritability	0	0	1 (1.1%)	0
Major depression	0	0	0	1 (1.2%)
Mania	0	1 (1.3%)	0	0
Psychogenic seizure	0	0	1 (1.1%)	0
Weight decreased	0	0	0	1 (1.2%)

Source: Adapted from Summary of Clinical Safety, Table 22, p. 97
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine

Clinical Reviewer's Comment: In Study 12712A, somewhat more adolescents than children have experienced SAEs. Among adolescents, subjects who were taking active study drug at lead-in have reported slightly more SAEs than subjects taking placebo at lead-in. However, the numbers are low enough overall that it is difficult to draw any conclusion from the differences.

Significant Adverse Events

Dose Reductions

The Study 12710A clinical study report (CSR) noted that the majority of subjects in the APTS (>90% in any treatment group) did not have a dose reduction because of poor tolerability, but the Applicant did not provide specific dataset information regarding any associated AEs (i.e., the Data Reviewer's Guide stated that a dose reduction for poor tolerability was "derived" without explanation).

Clinical Reviewer's Comment: Given the low numbers involved, dose reductions were unlikely to impact efficacy results. Overall withdrawal rates for AEs were low as well.

Severe Non-Serious Adverse Events

In the Study 12710A SB Period, 15 subjects (1.9%) experienced severe non-serious AEs. These included: headache (four subjects (0.5%)), abdominal pain and abdominal pain upper (grouped, three subjects (0.4%)); irritability (two subjects (0.3%)); and anxiety, back pain, gastroenteritis

viral, initial insomnia, intentional overdose, major depression, nausea, and somnolence (one subject (0.1%) each).

In the Study 12710A DB Period, 15 subjects experienced severe non-serious AEs, almost all in one subject each except as noted. In the placebo group, severe AEs included disturbance in attention and gastroenteritis. In the vortioxetine 10 mg group, severe AEs included headache (two subjects) and arthralgia, asthenia, chronic gastritis, dizziness, dysmenorrhea, fatigue, esophagitis, and vomiting (one subject each). In the vortioxetine 20 mg group, severe AEs included anxiety, nausea, pharyngitis, and suicidal ideation. In the fluoxetine group, severe AEs included breast pain, depression, osteitis, periodontal inflammation, pneumonia viral, and tooth dislocation.

In Study 12708A, five subjects experienced severe non-serious AEs. During the main study period, one child subject experienced a severe AE of headache. During the extension period, one child subject experienced a severe AE of headache; adolescent subjects experienced severe AEs of migraine (two subjects) and depression (one subject).

In the OLE studies (as with Study 12708A), there is no comparator, but AEs may inform what a picture of long-term use might show. In Study 12712A, 15 subjects experienced severe non-serious AEs, including: nausea (four subjects (0.8%)); insomnia and initial insomnia (grouped, two subjects (0.4%)); suicidal ideation, abdominal pain upper, agitation, apathy, arthralgia, decreased appetite, dermatitis, dry mouth, fatigue, headache, hunger, hypoglycemia, micturition urgency, mood swings, pharyngitis, tonsillitis bacterial, vomiting, weight decreased, and weight increased (all one subject (0.2%) each). In Study 12712B, one subject experienced a severe non-serious AE of eosinophil count increased.

> *Clinical Reviewer's Comment: Severe AEs mostly occurred in one subject each in any of the studies. For psychiatric AEs in the Study 12710A DB Period, anxiety and suicidal ideation occurred in the vortioxetine 20 mg arm, and depression occurred in the fluoxetine arm (all in one subject each).*

Treatment Emergent Adverse Events and Adverse Reactions

In the Study 12710A SB Period, the AEs occurring at ≥2% included: headache (66 subjects (8.5%)); abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper (grouped, 38 subjects (4.9%)); nausea (28 subjects (3.6%)); nasopharyngitis (26 subjects (3.3%)); and dizziness (21 subjects (2.7%)).

Table 33 summarizes AEs occurring during the DB Period in ≥2% of subjects in either vortioxetine group and at a greater rater than subjects in the placebo group in Study 12710A. Similar to the adult MDD data in the label, nausea and vomiting were the most commonly observed AEs (i.e., incidence ≥5% and at least twice the rate in placebo).

Table 33. Adverse Events Occurring During the Double-Blind Period in ≥2% of Subjects Treated with Vortioxetine and at a Greater Rate than Subjects Treated with Placebo in Study 12710A (APTS)

MedDRA Preferred Term	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=161) n (%)	FLU (N=153) n (%)
Nausea	7 (4.5%)	21 (14.3%)	31 (19.3%)	10 (6.5%)
Headache	12 (7.8%)	23 (15.6%)	20 (12.4%)	10 (6.5%)
Vomiting	1 (0.6%)	7 (4.8%)	15 (9.3%)	8 (5.2%)
Abdominal pain[1]	6 (3.9%)	10 (6.8%)	13 (8.1%)	11 (7.2%)
Nasopharyngitis	5 (3.2%)	6 (4.1%)	10 (6.2%)	10 (6.5%)
Diarrhea	5 (3.2%)	5 (3.4%)	9 (5.6%)	7 (4.6%)
Dizziness	5 (3.2%)	11 (7.5%)	7 (4.3%)	6 (3.9%)
Suicidal ideation	0	1 (0.7%)	4 (2.5%)	3 (2.0%)
Viral upper respiratory tract infection	1 (0.6%)	3 (2.0%)	3 (1.9%)	5 (3.3%)
Insomnia	2 (1.3%)	3 (2.0%)	2 (1.2%)	2 (1.3%)
Arthralgia	1 (0.6%)	3 (2.0%)	1 (0.6%)	0
Pharyngitis	0	3 (2.0%)	1 (0.6%)	0
Hypersomnia	1 (0.6%)	3 (2.0%)	0	0
Weight decreased	1 (0.6%)	3 (2.0%)	0	5 (3.3%)

Source: Clinical reviewer-created from Study 12710A Clinical Study Report, Panel 24, p. 74, and Study 12710A ADAE dataset
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine
[1] Grouping includes abdominal discomfort, abdominal pain, abdominal pain upper

> *Clinical Reviewer's Comment: Besides nausea and vomiting, in considering the criteria for mostly commonly observed AEs (i.e., ≥5% incidence and at least twice the rate in placebo), headache qualified for the vortioxetine 10 mg group, but was not quite twice the rate in placebo in the 20 mg group. Abdominal pain (grouped with abdominal discomfort and abdominal pain upper) qualified for the vortioxetine 20 mg group, but was not quite twice the rate in placebo in the 10 mg group. Nasopharyngitis, dizziness, and diarrhea were ≥5% and greater than (but less than twice) the rate in placebo. Other AEs listed occurred at <5% frequency; of note, suicidal ideation was more common in the active drug groups, as with SAEs and AEs leading to withdrawal. See Section 8.3.5 for a discussion of SIB-related AEs.*

In the Study 12708A main period, the most commonly reported AEs (≥5%) overall (including all child and adolescent dose groups) included: headache (12 subjects (25%)); nausea and sedation (11 subjects (23%) each); abdominal pain upper (eight subjects (17%)); fatigue and vomiting (six subjects (13%) each); and decreased appetite and irritability (three subjects (6%) each).

In the Study 12708A extension period, the most commonly reported AEs (≥5%) overall (including all child and adolescent dose groups) included: headache (11 subjects (27%)); nausea

(eight subjects (20%)); dysmenorrhea (four female subjects (19% of females)); vomiting (six subjects (15%)); and toothache, upper respiratory tract infection, and weight increased (three subjects (7%) each).

In the OLE studies (as with Study 12708A), there is no comparator, but AEs may inform what a picture of long-term use might show. See Table 34 for AEs occurring in ≥5% of subjects in Study 12712A by Lead-In Study (APTS). Results were similar to the other studies, and generally similar between children and adolescents, except for a higher incidence of nausea in adolescents.

Table 34. Adverse Events Occurring in ≥5% of Subjects in Study 12712A by Lead-In Study (APTS)

MedDRA Preferred Term	Study 12709A (N=188) n (%)	Study 12710A (N=335) n (%)	Total (N=523) n (%)
Subjects with adverse events	61 (32.4%)	137 (40.9%)	198 (37.9%)
Nausea	24 (12.8%)	79 (23.6%)	103 (19.7%)
Headache	27 (14.4%)	66 (19.7%)	93 (17.8%)
Abdominal pain[1]	21 (11.1%)	30 (9.0%)	51 (9.6%)
Vomiting	14 (7.4%)	27 (8.1%)	41 (7.8%)
Dizziness	6 (3.2%)	28 (8.4%)	34 (6.5%)
Nasopharyngitis	10 (5.3%)	21 (6.3%)	31 (5.9%)

Source: Clinical reviewer-created from Summary of Clinical Safety, Panel 9, p. 27, and Study 12712A ADAE dataset
Abbreviations: APTS = all patients treated set, MedDRA = Medical Dictionary for Regulatory Activities
[1] Grouping includes abdominal discomfort, abdominal pain, and abdominal pain upper

> *Clinical Reviewer's Comment: Study 12708A and the ongoing OLE Study 12712A appear to have generally similar patterns of most common AEs to the controlled Study 12710A DB Period.*

In Study 12712B, AEs occurring in ≥5% of subjects include: headache (13 subjects (13.8%)); nausea and abdominal pain (seven subjects each (7.4%) (the latter grouped abdominal discomfort, abdominal pain, and abdominal pain upper)); nasopharyngitis (six subjects (6.4%)); and hyperprolactinemia, respiratory tract infection viral, and vomiting (five subjects (5.3%) each)).

> *Clinical Reviewer's Comment: See Laboratory Findings below for further discussion regarding the AE of hyperprolactinemia in Study 12712B.*

Laboratory Findings

Hematology, Chemistry, and Urinalysis

In the Study 12710A DB period, safety assessments for serum hematology, chemistry, and urinalysis were collected at screening, randomization (baseline B, the start of DB period), Week 8, and Week 12/early termination. The mean changes from randomization during the DB period

did not demonstrate any significant changes or difference between treatment groups. Upon examination of subjects with post-randomization potentially clinically significant (PCS) for >3 subjects in any treatment group, the overall proportions were low and generally similar between treatment groups (and the particular PCS parameters – e.g., low hemoglobin, low or high glucose – were among the most frequently reported PCS parameters in the SB period).

Similarly, examination of shift data in >3 subjects in any treatment group demonstrated low proportions overall and general similarity between treatment groups. Additionally, the majority of post-randomization PCS values in >3 subjects in any treatment group were PCS at baseline.

Regarding hepatic safety, there were no cases that met Hy's Law criteria. Overall, the proportions of subjects with elevated liver enzymes were low. There were two subjects in the vortioxetine 20 mg group who had AST/ALT >3x ULN, one of whose ALT was >10x ULN. That subject (S(b) (6)), a 17 year-old white male in the United States, had also started an over-the-counter weight gain supplement shortly after starting vortioxetine in the DB period. The subject was asymptomatic, was withdrawn from the study, and his ALT improved; given the concomitant supplement, the investigator considered the event not related to study drug.

In Study 12708A, the majority of mean laboratory values were within reference ranges; no PCS laboratory values were reported; and the proportions of subjects with elevated liver enzymes were low, with none that met criteria for Hy's Law.

In the OLE Study 12712A and Study 12712B, mean changes in laboratory values were generally small, except for prolactin in Study 12712B (see below). The proportions of subjects with PCS values was generally low, and upon examination of shift values by lead-in treatments, there were subjects with elevated baseline values in all groups generally similarly. Regarding hepatic safety, no subjects met criteria for Hy's Law. Five subjects in Study 12712A demonstrated elevated ALT and/or AST >3x ULN, including three subjects >5x ULN with one subject's ALT >20x ULN. That subject (S(b) (6)), a 10-year-old girl in Mexico, was apparently treated for viral hepatitis, so the elevations appear unrelated to study drug. The other ALT results >5x ULN were in the low 100s (ULN 25), included one elevation at baseline, and all three normalized in the following measurements.

Prolactin

Prolactin was routinely measured in Studies 12712A and 12712B, but not in Study 12710A or the adult studies. Regarding hyperprolactinemia in Study 12712B and according to the CSR (submitted to IND 112581), an increase in mean prolactin occurred, with change from OLEXB baseline mean 2.28 ± 137.40 (SD) mIU/L at Week 26, to change freom OLEXB baseline mean 169.54 ± 622.26 (SD) mIU/L at Week 52, to change from OLEXB baseline mean 48.23 ± 288.17 (SD) mIU/L at Week 78, to change from OLEXB baseline mean 67.85 ± 329.22 (SD) mIU/L at last measurement (Week 104). Although there was an increase in the mean in child subjects, the larger mean increase appears to have occurred in adolescent subjects. The greatest increase was from 238 mIU/L at OLEXB baseline by 170 mIU/L at 52 weeks of treatment in Study 12712B

(and 78 weeks of treatment counting Study 12712A). Five subjects had AEs of hyperprolactinemia, and one of blood prolactin increased. Five subjects were considered to have PCS prolactin values (≥ 1350 mIU/L) at Week 52. In three of those subjects, the value was PCS at that single time point and returned to within-reference-range by study end. In one of the subjects, the value was still PCS at Week 78 (1513 mIU/L, decreased from peak 2365 mIU/L). In the fifth subject, prolactin was 4075 mIU/L at OLEXB baseline and returned to within-reference-range by study end. An additional subject's prolactin (1323 mIU/L) was above the upper end of reference range (450 mIU/L) but not PCS at Week 78. Those six subjects (four girls ages 14 to 16 years and two boys ages 10 and 12 years) were asymptomatic. The dose of vortioxetine was not changed and the subjects completed the study as planned.

According to the Applicant's Periodic Benefit Risk Evaluation Report submitted December 8, 2020, the Applicant opened a signal for hyperprolactinemia. The PBRER reports ten events of hyperprolactinemia and four events of blood prolactin increased in Study 12712A and Study 12712B, one event of hyperprolactinemia in Studies 12709A and 12710A each (the former still-blinded, the latter in placebo), and one event of blood prolactin increased in the adult Study 12473A. A total of 13 subjects had PCS values ranging from 1366 to 4075 mIU/L. In the seven cases of hyperprolactinemia involving vortioxetine, all subjects were asymptomatic, and one case involved the concomitant medication risperidone as an alternative etiology; none of the others reported relevant medical history or concomitant medications. One of the five cases of blood prolactin increased involves a still-blinded subject in an ongoing study; for the remaining four, all were asymptomatic, and none reported relevant medical history or concomitant medications.

A postmarketing surveillance search found a total of 36 events occurring in 34 cases. Twenty-two cases were reported in adults <65 years of age, with the remaining 12 cases' age unknown. Sixteen events were blood prolactin increased, 13 galactorrhea, and seven hyperprolactinemia. In approximately half of the cases, the time-to-onset was unknown; in the remainder, roughly a third occurred within 1 week to 1 month, and another third within 1 to 3 months. Medical history and concomitant medications were missing for a large portion of cases. A positive de-challenge occurred in seven out of 36 cases; none were identified with a positive re-challenge. In some of the positive de-challenge cases, medical history and concomitant medications were missing; at least one case appeared to have no alternative etiology, although that patient had been seeing an endocrinologist for an unspecified reason for 8 months before starting vortioxetine. The Applicant concluded that considering biological plausibility and cases with positive de-challenge and possible causality in both clinical trials and postmarketing settings, the Company Core Data Sheet would be updated to include hyperprolactinemia in section 4.8 with frequency unknown.

> *Clinical Reviewer's Comment: In the Study 12712B CSR, the Applicant asserts that the lack of signs and symptoms of hyperprolactinemia and the transient temporal course argues against the clinical significance of the findings, and references the results as consistent with a literature review of hyperprolactinemia with antidepressants (Coker*

and Taylor 2010). However, they completed a signal evaluation for the PBRER and added hyperprolactinemia to the CCDS based upon the clinical trial events and postmarketing events (which occurred in adults in 22 cases, and in unknown ages in 12 cases). Based on the postmarketing data, we recommend inclusion of hyperprolactinemia in Section 6.2 Postmarketing Experience; given that the hyperprolactinemia findings were noted in the uncontrolled OLE studies, we do not recommend inclusion in Section 8 with pediatric studies.

Besides the hyperprolactinemia findings, overall, there does not appear to be a new safety signal regarding clinical laboratory assessments compared to the adult population.

Vital Signs

Each study visit included measurements of respiratory rate and supine and standing blood pressure and pulse rate. Height was measured at screening and completion; weight was measured at screening, completion, and periodically (e.g., monthly during Study 12710A, every 6 months during Study 12712B).

In the Study 12710A DB period, mean changes from randomization (DB baseline) for vital sign measurements were small and generally similar between treatment arms. Similarly, the proportions of subjects with post-randomization PCS vital signs were low and generally similar between treatment arms. The only PCS vital sign value in >2 subjects in any treatment arm was high orthostatic pulse rate, but the proportion of subjects was similar across treatment arms (and occurred at randomization as well). In Study 12708A, mean vital signs outside of the reference range were recorded mostly at single time points, with no trends over time; subjects who PCS vital sign values in either the main study period or extension overall had isolated post-baseline PCS values (and occurred at baseline as well). Studies 12712A and 12712B appeared to demonstrate similar results.

Clinical Reviewer's Comment: Given that PCS orthostatic pulse rate values occurred across treatment arms in the Study 12710A DB period including placebo, this does not appear clinically significant despite its (overall low) occurrence in the uncontrolled Studies 12712A and 12712B.

In the Study 12710A DB period, mean changes from randomization (DB baseline) for height, weight, or BMI were small and generally similar between treatment arms. Similarly, the proportions of subjects with post-randomization PCS weights or BMIs were low and generally similar between treatment arms. In Studies 12712A and 12712B, mean weight and BMI changes from OLEXA/OLEXB were small overall; a number of subjects demonstrated PCS changes (of most interest, weight/BMI increases). To assess weight in the context of height, the Applicant assessed BMI changes (according to the World Health Organization BMI-for-age percentiles for girls and boys ages 5 to 19 years). In the majority (82%) of subjects in Study 12712B, there was no shift or a shift of one percentile category in BMI. Three subjects shifted upward above the

normal BMI range; one from normal weight to obese, one from overweight to obese, and one within the obese percentiles.

> *Clinical Reviewer's Comment: Without a control group, it is difficult to draw conclusions from the weight/BMI changes in Studies 12712A and 12712B. Examination of BMI, rather than weight, can factor in to a degree for natural growth, but confounding from MDD or other factors may conflate with any drug-related changes.*

Electrocardiograms (ECGs) and QT

ECGs were collected on the same schedule as clinical laboratory assessments. In Study 12710A, mean changes from randomization in ECG parameters were small and similar across treatment arms. None of the PCS values or shifts from normal to high or low occurred in more than one subject in any treatment arm at any time. One subject in the vortioxetine 20 mg group and two in the fluoxetine group had PCS high QTcB, but none were considered clinically significant.

In Study 12708A mean ECG changes from baseline were small. Several subjects had had isolated PCS low heart rates; baseline values had been low for some. In Studies 12712A and 12712B, mean ECG changes from baseline were small. PCS values were reported in >2 subjects for high RR interval in Study 12712A (five subjects at Week 4, three subjects at Week 26, and four subjects at last assessment), and for high QTcF in Study 12712B for four adolescents in six events (three at Week 52 and three at last assessment). No QTcF was >500 msec.

> *Clinical Reviewer's Comment: Overall, there does not appear to be a safety signal regarding ECG parameters.*

Immunogenicity

In the Study 12710A DB period, one subject in the vortioxetine 10 mg group reported an AE of drug hypersensitivity (skin itch, rash on shoulders and chest); one subject reported an AE of hypersensitivity during the SB period. Small numbers of subjects reported rash or rash pruritic (one placebo, one vortioxetine 10 mg, four vortioxetine 20 mg, two fluoxetine); three subjects reported a rash AE during the SB period. One subject in the vortioxetine 20 mg group reported an AE of urticaria in the DB period; three subjects reported urticaria AEs during the SB period.

> *Clinical Reviewer's Comment: Hypersensitivity reactions are included in the current label Section 6.2 Postmarketing Experience.*

8.3.5. Analysis of Submission-Specific Safety Issues

Suicidal Ideation and Behavior

The Applicant examined SIB-related AEs as described in Section 8.3.3. Besides the two suicides described in Section 8.3.4, the Applicant reports that there have been no suicides reported in

the ongoing OLE studies or blinded Study 12709A through January 31, 2020.

See Table 35 for the results of the Applicant's suicide/self-injury SMQ search in the completed and ongoing OLE studies (note there were no SMQ-related AEs reported in the Study 12708A main study period, only the extension). Of note, there were no SIB-related AEs reported in the placebo arm of Study 12710A during the DB Period, which is lower than the vortioxetine arms in any study or in total, or the fluoxetine arm. In subjects receiving placebo (plus BPI) in the Study 12710A SB Period, any SIB-related AE occurred in 13 subjects (1.7%), which is still lower than the vortioxetine total for all studies or fluoxetine.

Six suicide attempts have occurred in subjects receiving vortioxetine. In the Study 12708A extension period, one adolescent subject (taking vortioxetine 20 mg) attempted suicide via an intentional overdose of 78 acetaminophen tablets 33 days after the first dose of study drug and was withdrawn from the study. During the Study 12710A DB Period, one subject (taking vortioxetine 20 mg) had a suicide attempt 35 days after the first dose of study drug. In the ongoing OLE studies, four subjects attempted suicide (all in Study 12712A), including one child and three adolescent subjects. For the child subject (blinded lead-in study drug), the suicide attempt occurred 2 days after the first dose of vortioxetine study drug. For two adolescent subjects (both fluoxetine lead-in study drug), the suicide attempts occurred 1 and 58 days after the first dose of vortioxetine study drug, and for the third adolescent subject (placebo lead-in study drug), the attempt occurred 91 days after the first dose of vortioxetine study drug.

Of the eight subjects receiving vortioxetine who experienced intentional overdoses, two were reported on the same day as suicide attempt; three specifically noted "no suicidal intention" (e.g., one was reported "for a fast effect"); and the other three were overdoses of one to three tablets. As noted previously, the AEs of suicidal behavior and suicidal threat were difficult to classify as either attempts or ideation based on narrative description. Intentional self-injury AEs were described as cutting and/or non-suicidal self-injurious behavior.

Table 35. Suicide/Self-Injury (SMQ) by Preferred Term by Study, All Patients Treated Sets

	12708A Extension[1]	12710A SB Period	12710A DB Period				12712A	12712B	
MedDRA Preferred Term	VOR 5 to 20 mg	PBO + BPI	PBO	VOR 10 mg	VOR 20 mg	FLU	VOR 5 to 20 mg	VOR 5 to 20 mg	VOR Total
N	41	777	154	147	161	153	523	94	708
Any AE (n (%))	2 (4.9%)	13 (1.7%)	0	2 (1.4%)	6 (3.7%)	6 (3.9%)	17 (3.3%)	1 (1.1%)	28 (4.0%)
Suicidal ideation	1 (2.4%)	7 (0.9%)	0	1 (0.7%)	4 (2.5%)	3 (2.0%)	6 (1.1%)	0	12 (1.7%)
Intentional overdose	1 (2.4%)	3 (0.4%)	0	0	0	1 (0.7%)	7 (1.3%)	0	8 (1.1%)
Intentional self-injury	0	3 (0.4%)	0	1 (0.7%)	2 (1.2%)	1 (0.7%)	3 (0.6%)	0	6 (0.8%)
Suicide attempt	1 (2.4%)	2 (0.3%)	0	0	1 (0.6%)	0	4 (0.8%)	0	6 (0.8%)
Self-injurious ideation	0	0	0	0	0	1 (0.7%)	0	1 (1.1%)	1 (0.1%)
Suicidal behavior	0	1 (0.1%)	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Suicide threat	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)

Source: Clinical reviewer-created from Summary of Clinical Safety, Panel 10, p. 30, and Study 12710A and Study 12708A ADAE datasets
Abbreviations: AE = adverse event, BPI = brief psychosocial intervention, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, SMQ = Standardized MedDRA Query, VOR = vortioxetine
[1] No adverse events captured by the SMQ Suicide/Self-Injury were reported during the Study 12708A main study period

> *Clinical Reviewer's Comment: One caveat with comparison among the studies is the differing length of exposure: Study 12708A extension has completed at 6 months, Study 12710A has completed with a 4-week SB Period and an 8-week DB Period, and OLE Studies 12712A and 12712B are 6- and 18-month durations but are ongoing. However, similar to the results for Study 12710A DB Period SAEs and AEs leading to withdrawal, the overall pattern of increased signal with active study drug is in line with the current labeling boxed warning.*

The Applicant also utilized the C-SSRS to assess suicidal ideation and behavior in the studies. As noted by the Applicant, in Study 12708A, based on the C-SSRS, four subjects (8.3%) had suicidal ideation in the main study period. In the extension period, five subjects (12.2%) had suicidal ideation, two subjects (4.9%) had non-suicidal self-injurious behavior, and one subject (2.4%) had suicidal behavior.

In the Study 12710A DB Period, based on the C-SSRS, the proportion of subjects with suicidal ideation was similar across treatment groups (≤10%); one subject (0.6%) had suicidal behavior (vortioxetine 20 mg group) (see Table 36). On examination, the active drug groups demonstrated a somewhat higher proportion of subjects with active suicidal ideation (i.e., non-specific active suicidal thoughts) or non-suicidal self-injurious behavior, whereas the placebo group included a somewhat higher proportion of subjects reporting passive suicidal ideation (i.e., wish to be dead).

As with AEs, in the OLE studies (as with Study 12708A), there is no comparator, but C-SSRS scores may inform what a picture of long-term use might show. In the OLE studies as of the cutoff date, based on the C-SSRS, 32 subjects (6.2%) had suicidal ideation in Study 12712A and four subjects (4.3%) had suicidal ideation in Study 12712B. Five subjects (1.0%) had suicidal behavior in Study 12712A and none of the subjects had suicidal behavior in Study 12712B.

Table 36. Study 12710A Double-Blind Period Columbia Suicide Severity Rating Scale Scores, All Patients Treated Set

Most Severe Columbia Suicide Severity Rating Scale Score	PBO (N=154) n (%)	VOR 10 mg (N=147) n (%)	VOR 20 mg (N=160) n (%)	FLU (N=153) n (%)
No suicidal ideation or behavior	139 (90.3%)	134 (91.2%)	148 (92.5%)	138 (90.2%)
Non-suicidal self-injurious behavior[1]	1 (0.6%)	4 (2.7%)	4 (2.5%)	5 (3.3%)
Any suicidal ideation	15 (9.7%)	13 (8.8%)	11 (6.9%)	15 (9.8%)
Wish to be dead	13 (8.4%)	7 (4.8%)	6 (3.8%)	8 (5.2%)
Non-specific active suicidal thoughts	1 (0.6%)	5 (3.4%)	4 (2.5%)	3 (2.0%)
Active SI with any methods (not plan) without intent to act	1 (0.6%)	1 (0.7%)	1 (0.6%)	3 (2.0%)
Active SI with some intent to act, without specific plan	0	0	0	0
Active SI with specific plan and intent	0	0	0	1 (0.7%)
Any suicidal behavior	0	0	1 (0.6%)	0
Preparatory acts or behavior	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Non-fatal suicide attempt	0	0	1 (0.6%)	0
Completed suicide	0	0	0	0

Source: Adapted from Study 12710A Clinical Study Report, Table 168, p. 603
Abbreviations: FLU = fluoxetine, PBO = placebo, SI = suicidal ideation, SIB = self-injurious behavior, VOR = vortioxetine
Note: Subjects with any suicidal ideation or behavior are counted for the most severe score
[1] Non-suicidal self-injurious behavior is considered separately

Clinical Reviewer's Comment: Based on C-SSRS scores, the occurrence of any suicidal ideation was generally comparable among treatment arms during the Study 12710A DB Period. This may simply reflect the fact that the C-SSRS does not capture all SIB-related events. The differences noted between placebo versus active study drug groups regarding passive versus active suicidal ideation and non-suicidal self-injurious behavior involve small enough numbers that make it difficult to draw any conclusions.

Other Areas of Interest

In addition to suicidal ideation and behavior, the Applicant examined the following AEs of special interest determined based on risks potentially associated with antidepressants in the adult population, AEs of specific interest in the pediatric population, general drug safety issues, and/or nonclinical findings, using SMQs or clusters of PTs: mania (including use of the GBI), seizures, serotonin syndrome, hyponatremia/SIADH, abnormal bleeding, insomnia and somnolence, hostility and aggression, growth and sexual maturation, sexual dysfunction, nausea/vomiting, constipation, closed-angle glaucoma, abuse liability, QT prolongation, kidney toxicity, and liver toxicity.

No new safety signals were apparent, whether by no reports of related AEs, low and comparable-across-treatment-group-reports in the Study 12710A DB period, or small mean changes from baseline on the GBI regarding mania in the Study 12710A DB period, comparable to placebo. During the Study 12710A DB period, nausea and vomiting occurred at a higher rate in the vortioxetine groups than placebo, similar to the results found with adults. See clinical laboratory assessments in Section 8.3.4 regarding details for hepatic safety. See vital signs in Section 8.3.4 regarding pediatrics and assessment of effects on growth. See Section 8.3.9 regarding abuse liability. See Section 8.3.10 for postmarketing information regarding hostility and aggression.

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

See Section 8.3.5 regarding C-SSRS and GBI results.

8.3.7. Safety Analyses by Demographic Subgroups

In Study 12710A, the incidence of AEs leading to withdrawal and the incidence of overall AEs were generally similar between sexes and races.

Clinical Reviewer's Comment: Given the small numbers of Black, Asian, and Other races among treatment arms, it is difficult to draw any conclusions regarding race.

8.3.8. Specific Safety Studies/Clinical Trials

No new specific safety studies were submitted with this supplement.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity or tumor development studies were submitted with this supplement.

Human Reproduction and Pregnancy

Per the Applicant, one pregnancy was reported in treated subjects in the clinical development program. Subject S(b) (6), a 16-year-old girl in Colombia, was treated with vortioxetine 10 mg for 27 days in the DB period of Study 12710A when she reported that she was pregnant and was withdrawn from the study. The outcome of the pregnancy is not known.

One subject reported a pregnancy in the screening period and was not allowed to enter the study.

Pediatrics and Assessment of Effects on Growth

See vital signs in Section 8.3.4 regarding assessment of height, weight and BMI.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant conducted a search for related PTs and found no apparent safety signal. There were more accidental overdoses in the placebo and fluoxetine groups than vortioxetine. Three subjects reported accidental overdoses in the vortioxetine groups: for taking one additional tablet on one day, one extra tablet on three days, and for two missing tablets per accountability (coded as an overdose).

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See clinical laboratory assessments in Section 8.3.4 regarding the postmarketing hyperprolactinemia signal evaluation in the Applicant's most recent PBRER. Although there was not a signal for hostility and aggression in the SMQ assessment for this supplement, the Applicant had reported a confirmatory signal evaluation in the previous PBRER, and the adverse reaction PTs aggression, agitation, anger, hostility, and irritability have been added to the label Section 6.2 postmarketing experience in the approval of efficacy supplement-20 in November 2020. Lastly, the most recent PBRER confirmed signal evaluations for the adverse reaction PTs headache and hyperhidrosis, which will be added to Section 6.2.

Expectations on Safety in the Postmarket Setting

In addition to current labeling indicated only for adult MDD treatment, the supplement labeling recommendations indicate a lack of efficacy in the adolescent population (see Section 11) to enhance the limitation of any off-label prescribing to pediatric patients.

8.3.11. Integrated Assessment of Safety

The Applicant submitted sufficient information to adequately assess vortioxetine's safety profile in adolescent subjects. The safety profile for this adolescent data base is generally similar to the adult safety data presented in the current vortioxetine label. The adolescent data base included AEs related to suicidal ideation and behavior, which is consistent with the boxed warning in the current labeling. An increased incidence of hyperprolactinemia was noted in the OLE Studies 12712A and 12712B; however, given that that data lacks a control group, and given that the Applicant confirmed a safety signal in postmarketing data involving adults in the most recent PBRER, it appears appropriate for information regarding hyperprolactinemia to be added in Section 6.2, postmarketing experience.

8.4. Conclusions and Recommendations

Study 12710A fulfills the PREA PMR 2084-8. The study results do not support the use of vortioxetine for the treatment of MDD in pediatric patients ages 12 to 17 years, which will be reflected in Section 8.4 of the labeling along with safety information; the Boxed Warning will be retained.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this submission.

10 Pediatrics

Study 12710A fulfills PMR 2084-8 and the amended PWR. Study 12709A in pediatric subjects ages 7 to 11 years (PMR 2084-7) is ongoing.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant is not pursuing an expanded indication based on the negative results from Study 12710A. Section 8.4 of labeling will address the findings of the pediatric clinical studies as follows:

> The safety and effectiveness of TRINTELLIX have not been established in pediatric patients for the treatment of MDD.
>
> Efficacy was not established in an 8-week, randomized, double-blind, placebo-controlled, active-reference study in 615 pediatric patients aged 12 to 17 years with MDD. The primary efficacy endpoint was change from double-blind baseline to Week 8 on the Children's Depression Rating Scale-Revised version. The effect of treatment with vortioxetine was not significantly different from placebo (placebo-subtracted difference of 0.21 (95% CI: -2.41, 2.82; p=0.88)). In this age group, adverse reactions to TRINTELLIX were generally similar to those reported in adults.
>
> Antidepressants, such as TRINTELLIX, increase the risk of suicidal thoughts and behaviors in pediatric patients *[see the Boxed Warning and Warnings and Precautions (5.1)]*.

Additionally, hyperprolactinemia, headache, and hyperhidrosis will be added to Section 6.2 postmarketing experience and Section 7.3, titled "Interference with Urine Enzyme Immunoassays for Methadone" added as proposed under prior approval supplemental NDA S-022.

12 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) does not appear appropriate or indicated based upon this submission.

13 Postmarketing Requirements and Commitment

No new PMRs or PMCs will be issued. Study 12710A fulfills PMR 2084-8.

14 Appendices

14.1. References

Coker F and Taylor D, 2010, Antidepressant-Induced Hyperprolactinemia, CNS Drugs 24(7):563-574.

Uljon S, Kataria Y and Flood JG, 2019, Vortioxetine use may cause false positive immunoassay results for urine methadone, Clinica Chimica Acta 499:1-3.

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 12710A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 118 principal		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Principal Investigator (b) (6) at United States site (b) (6) acted in honoraria for Takeda and acted as a (b) (6) which have a cumulative monetary value in excess of $25,000 USD. The Applicant reports that for ongoing review of medical data, the eligibility of subjects prior to enrollment was to be completed by medical experts from CRO (b) (4) and medical and safety data was to be evaluated by Lundbeck. Ratings consistency was to be evaluated by Lundbeck and CROs (b) (4) and (b) (4)

Clinical Reviewer's Comment: The Applicant's precautionary steps appear appropriate. Further, Site (b) (6) enrolled (b) (6) subjects (of 784 total), which appears unlikely to influence the study findings to any significant extent.

14.3. Clinical Pharmacology

Population PK analysis: A two-compartment PK model with first-order absorption and elimination adequately described the PK of vortioxetine in children and adolescents in Study 12708A. The population PK analysis used in Study 12708A was described in the clinical pharmacology review by Di Zhou (archived 04/04/2017). The population PK analysis was also performed using sparse PK data (two time points) from 248 adolescents with MDD in Study 12710A. The results suggest that a two compartment PK model with first-order absorption and elimination adequately described the PK of vortioxetine in adolescents with MDD. None of the tested covariates (age, gender, weight, body mass index, lean body mass, and creatinine clearance) showed significant influence on the PK of vortioxetine. In Study 12708A, the plasma exposures (Cmax,ss and AUCss) to vortioxetine were found to be similar between children and adults. However, the exposures in adolescents were relatively lower than those observed in adults (Table 37) and the rationale for the lower exposures observed in adolescents (Study 12708A) remain unclear. In Study 12710A, the plasma exposures in adolescents were relatively similar to that for adults and children (Table 37).

Table 37. Model predicted PK parameters of vortioxetine at steady state in children and adolescents with depressive or anxiety disorder, and in healthy adults

PK Parameter	Children (Study 12708A) (N = 24)	Adolescents (Study 12708A) (N = 23)	Adolescents (Study 12710A) (N = 248)	Adults (Pooled popPK) (N = 887)
$C_{max,SS}$ (ng/mL)[a]	17 ± 10	9.3 ± 4.4	13 ± 9.2	14 ± 8.5
AUC_{SS} (ng·h/mL)[a]	302 ± 182	177 ± 84	301 ± 221	294 ± 202
CL/F (L/h)	42 ± 23	62 ± 30	51 ± 39	37 ± 15
Mean values ± standard deviation are presented.				

[a]dose-normalized values equivalent to 10 mg dose; Source: Module 2.7.2. Summary of Clinical Pharmacology Studies

Clinical Pharmacology Reviewer's Comments: The PK characterization of vortioxetine in adolescents with MDD using population PK approach appears to be acceptable. The simulated dose-normalized plasma exposures (Cmax,ss and AUCss) to vortioxetine at

steady state in adolescents with MDD are relatively similar to those observed in adults.

Bioanalysis: Plasma concentrations of vortioxetine (Lu AA21004) and its metabolites, Lu AA34443 and Lu AA39835, were quantified using liquid chromatography with tandem mass spectrometry (LC-MS/MS; Bioanalytical report: 14253, 14900, 10947, 00009). The calibration range for Lu AA21004 is 0.2 ng/mL to 100 ng/mL, for Lu AA34443 is 0.5 ng/mL to 250 ng/mL, and for Lu AA39835 is 0.2 ng/mL to 100 ng/mL. No carryover effect and matrix effect were observed in the bioanalytical studies. The precision and accuracy values of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were within ±15% (±20% at the LLOQ). More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation. The analytes in human plasma were stable over 8 months when stored at -20°C and -80°C. The analytes in human plasma were stable over 6 hours at room temperature, three freeze-thaw cycles following -20°C/-80°C and autosampler stability at 4°C over 72 hours. Up to 10-fold dilution did not affect the precision and accuracy of the measurement of analytes.

Clinical Pharmacology Reviewer's Comments: The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

Interference with urine drug screen for methadone: Uljon et al., 2019, reported that the urine specimens from seven patients on vortioxetine doses (5 mg/day to 20 mg/day) showed the positive results for methadone with the Roche KIMS Methadone II Urine immunoassay (MDN2). However, the urine specimen from these patients tested negative with the confirmatory analytical assay (gas chromatography/ mass spectrometry) and other immunoassay platforms (the Multigent Methadone assay on the Architect Analyzer (Abbott Laboratories) and the Metdox Methadone assay on the MEDTOXScan instrument (Medtox Diagnostics)). Approximately 59% of orally administered dose of [^{14}C]-labeled vortioxetine was reported to be excreted in the urine predominantly as vortioxetine metabolite (Lu AA34443), and negligible amount as vortioxetine (TRINTELLIX United States Package Insert (USPI)). Therefore, the metabolite of vortioxetine (Lu AA34443) is mainly expected to have cross reactivity in the MDN2 assay. The reported cross reactivity of vortioxetine and its metabolite in the MDN2 assay was 3.5 and 14%, respectively, and these values are higher than the cross reactivity limit of 0.5%. Therefore, a confirmatory analytical technique (e.g., chromatographic methods) should be considered to confirm the positive methadone urine drug screen results.

Clinical Pharmacology Reviewer's Comments: Given the use of vortioxetine has been reported to cause false positive results in urine immunoassays for methadone, the review team recommends adding this laboratory test interaction in Section 7 of the TRINTELLIX USPI.

14.4. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

SIMRAN K PARIHAR
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