NDA Multi-Disciplinary Review and Evaluation

Application Type	sNDA; efficacy supplement
Application Number(s)	204447/S-026
Priority or Standard	Priority
Submit Date(s)	February 23, 2023
Received Date(s)	February 23, 2023
PDUFA Goal Date	August 23, 2023
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience (ON)
Review Completion Date	August 23, 2023
Established/Proper Name	Vortioxetine
(Proposed) Trade Name	Trintellix
Pharmacologic Class	Antidepressant
Code name	2020100
Applicant	Takeda Pharmaceuticals USA, Inc
Dosage form	Tablet
Applicant proposed Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	No change to the indicated population is proposed; the Applicant has proposed revisions to the Prescribing Information based upon a study of vortioxetine in pediatric patients ages 7 to 11 years with major depressive disorder (MDD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable
Recommendation on Regulatory Action	The approved age range (adults) will not be expanded; relevant pediatric information will be added to labeling.
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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

Signatures

Please refer to uploaded memos for each discipline in DARRTS.

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
BMI	body mass index
BPI	brief psychosocial intervention
BW	body weight
CDER	Center for Drug Evaluation and Research
CDRS-R	Children's Depression Rating Scale-Revised version
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	Confidence Interval
DB	double-blind
DMC	data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	electrocardiogram
eCTD	electronic common technical document
FAS	full-analysis set
FDA	Food and Drug Administration
FLU	fluoxetine
GBI	General Behavior Inventory
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version
kg	kilogram
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
NDA	new drug application
NME	new molecular entity
OLE	open-label extension
OLEXA	open-label extension baseline A in Study 12712A
OLEXB	open-label extension baseline B in Study 12712B
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PBO	placebo
PCS	potentially clinically significant
PD	pharmacodynamics
PedsQL-VAS	Pediatric Quality of Life
PGA	Parent Global Assessment-Global Improvement
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SB	single-blind
SD	standard deviation
SE	standard error
VAS	visual analogue scale
VOR	vortioxetine
WR	Written Request

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 is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established. It is available as immediate-release tablets for daily administration, in strengths of 5, 10, and 20 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant previously conducted an 8-week, randomized, double-blind, placebo-controlled, active reference study in 616 pediatric subjects ages 12 to 17 years with major depressive disorder (MDD). This study was negative; the study was reviewed under a previous efficacy supplement and relevant pediatric information for the 12 to 17-year-old-age group was added to Section 8.4 of labeling (NDA 20447/S-021). An efficacy and safety study in pediatric subjects ages 7 to 11 years was ongoing at the time of approval of S-021. The Agency noted that the ongoing study would be insufficient on its own to support pediatric MDD labeling; however, the Agency advised the Applicant to submit final clinical study reports from this study (as well as the associated long-term safety extension) to meet the terms of the Pediatric Written Request.

In this supplement (S-026), the Applicant has submitted data from the 8-week, 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 540 pediatric subjects ages 7 to 11 years. This study did not demonstrate a statistically significant difference between vortioxetine and placebo. This supplement also includes updated data from long-term safety extension studies. The safety profile in pediatric subjects was consistent with the known safety profile in the indicated population (adults with MDD). Based on the information in this supplement, the indicated population will not be expanded, but updated pediatric information will be added to labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Major depressive disorder (MDD) is a serious and debilitating illness affecting approximately 4% of U.S. children and adolescents. Additional effective treatments are needed; however, the clinical study presented in this supplement did not demonstrate efficacy for vortioxetine as treatment for pediatric MDD. Relevant pediatric information will be included in labeling, but the indicated population (adults with MDD) will not be expanded.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Symptoms of MDD in pediatric patients include depressed or irritable mood, anhedonia, changes in appetite and weight (including failure to gain weight at the expected rate), difficulties with sleep, psychomotor agitation or retardation, decreased energy level, poor concentration, and feelings of worthlessness or guilt. In severe cases, MDD can result in suicidal ideation and behavior. • MDD is associated with impairments in social, educational, and other functional outcomes. • The most recent National Survey of Children's Health study revealed that the prevalence of pediatric MDD in the United States is 4%.	MDD is a serious and potentially debilitating condition that can disrupt developmental trajectories in affected pediatric patients, causes significant psychological distress, and can lead to poor functional outcomes.
Current Treatment Options	• To date, only two antidepressants (fluoxetine and escitalopram) 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted an 8-week, 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 540 pediatric subjects ages 7 to 11 years (Study 12709A). • The study evaluated two doses of vortioxetine, 10 mg and 20 mg. The primary endpoint assessed the change at Week 8 for the average of the two vortioxetine doses (Avg. VOR) compared to placebo on the Children's Depression Rating Scale – Revised Version (CDRS-R), a validated clinical outcome assessment that the Agency has accepted in other pediatric MDD programs. • The study did not demonstrate a statistically significant difference between Avg. VOR and placebo on the primary efficacy endpoint. Furthermore, neither the 10-mg nor the 20-mg vortioxetine dose separated from placebo.	Neither the previously submitted and reviewed efficacy and safety study (conducted in subjects ages 12 to 17 years) nor the study submitted with this supplement (conducted in subjects ages 7 to 11 years) demonstrated efficacy of vortioxetine for the treatment of pediatric patients. Vortioxetine's indicated population (adults) will not be expanded to include pediatric patients.
Risk and Risk Management	• The treatment-emergent adverse events in Study 12709A that occurred in ≥2% of subjects in either vortioxetine arm and at ≥ twice the frequency as in the placebo arm were nausea and vomiting. Nausea and vomiting are listed (along with constipation) as the most common adverse reactions in the adult development program. There were few serious adverse events, severe adverse events, and adverse events leading to withdrawal in the open-label safety extensions and the long-term safety data appeared consistent with the data from the controlled studies. • The incidence of suicidal ideation and behavior was similar in the vortioxetine and placebo groups in Study 12709A. However, the overall number of subjects exposed to vortioxetine in this study was small compared to the number included in the pooled analysis that supported the class warning for antidepressants.	Safety findings will be reflected in Section 8.4. Based on the data presented with this supplement, the pediatric and adult safety profiles for vortioxetine are largely similar.

1.4. Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

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). Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized, attempt suicide, or die by suicide. MDD is considered the leading cause of disability worldwide and is associated with increased mortality (at a median rate of 10 years of life lost; Walker et al. 2015). An estimated 17.3 million adults in the United States (7.1%) had at least one major depressive episode in 2017, with an estimated incidence of approximately 242 million people worldwide (SAMHSA 2018; GBD 2018). According to the National Survey of Children's Health, the prevalence of pediatric MDD was 4% in 2020 (Lebrun-Harris et al. 2022).

2.2. Analysis of Current Treatment Options

Although the Agency has approved multiple antidepressant medications for the treatment of MDD in the adult population, only two antidepressants (fluoxetine and escitalopram) have demonstrated safety and effectiveness in adequate and well-controlled studies with resultant pediatric indications in product labeling. Fluoxetine is approved for the treatment of MDD in pediatric patients ages 8 to 17 years and escitalopram is approved for MDD in patients ages 12 years and older. Clinical studies of other antidepressants have failed to demonstrate efficacy in pediatric patients despite efficacy in adults (e.g., desvenlafaxine, duloxetine, levomilnacipran, paroxetine, sertraline, venlafaxine, vilazodone). 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 for 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 the Treatment of Major Depressive Disorder in Pediatric Patients

Product Name	Approval Adult / Pediatric	Ages of Pediatric Approval	Formulation/ Recommended Dosage	Efficacy Studies Supporting Labeling	Safety Concerns Noted in Pediatric Studies
Fluoxetine	1987 / 2003	8 to 17 years	Capsule: 10, 20, 40 mg Liquid: 20 mg/5mL Dosage: 10 to 20 mg/day (initial dose) with maximum dose 20 mg	Two 8- to 9-week placebo- controlled clinical trials with pediatric outpatients 8 to ≤18 years with MDD	Mania/hypomania (most common AR associated with discontinuation), decreased weight gain, decrease in alkaline phosphatase Overall similar ARs to adults. ARs with incidence of >2% and >placebo include: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia
Escitalopram	2002 / 2009	12 to 17 years	Tablets: 5, 10, 20 mg Oral solution: 1 mg/mL Dosage: 10 mg once daily with maximum recommended dose of 20 mg (titration after 3 weeks)	One 8-week flexible-dose (10 to 20 mg escitalopram), 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 pediatric AR associated with discontinuation: insomnia Overall similar ARs to adults. ARs with incidence of >2% and >placebo include: back pain, urinary tract infection, vomiting, and nasal congestion

Source: Clinical reviewer-created from fluoxetine and escitalopram U.S. Prescribing Information
Abbreviations: AR = adverse reaction, MDD = major depressive disorder

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- In 2013, vortioxetine (NDA 204447, brand name Brintellix later revised to Trintellix) was approved for the treatment of MDD in adults, with the following Pediatric Research Equity Act (PREA)-related postmarketing requirements (PMRs):

  - PMR 2084-1: Deferred pediatric study under PREA for the treatment of major depressive disorder in children aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing vortioxetine in the relevant pediatric population.

  - PMR 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.

  - PMR 2084-3: Deferred pediatric study under PREA for the treatment of major depressive disorder in adolescents aged 12 to 17 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.

  Studies were waived for subjects ages 0 to 6 years because the necessary studies are impossible or highly impractical. Studies for subjects ages 7 to 17 years were deferred because the product was ready for approval in adults and pediatric studies had not yet been completed.

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; 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.

- In August 2011, the Applicant submitted a proposed pediatric study plan to fulfill PREA requirements. The Agency provided comments on the proposed study plan in November 2011.

- In October 2012, the Applicant submitted NDA 204447 for the treatment of MDD in adults, including a proposed pediatric study plan with a pediatric pharmacokinetic study (Study 12708A) and safety and efficacy studies in pediatric subjects ages 7 to 11 years and 12 to 17 years (Study 12709A and Study 12710A, respectively). The Agency issued the abovementioned PMRs upon NDA approval in September 2013.

- In May 2015, the Applicant submitted a Proposed Pediatric Study Request (PPSR). In September 2015, the Agency issued a pediatric Written Request (WR), including:

  - Study 1: A pediatric pharmacokinetic (PK) study. The Agency acknowledged that the Applicant had submitted the study report for PK Study 12708A and considered it adequate to support studies in pediatric patients.

  - Study 2: An efficacy and safety study for pediatric subjects ages 7 to 11 years old with MDD. Conduct a randomized, double-blind, placebo- and active-controlled, parallel-group, short-term, fixed-dose efficacy and safety study of vortioxetine in the treatment of pediatric patients (ages 7 to 11 years) with a diagnosis of MDD. The trial should be designed in a way that fully evaluates the drug in children, therefore the study must assess at least two fixed doses, and must include an active control (fluoxetine) arm. The selected doses must be agreed upon by the Agency. The fixed-dose design is necessary for assessing potential dose-response relationships for efficacy and safety and to determine the lowest effective dose.

  - Study 3: An efficacy and safety study for pediatric subjects ages 12 to 17 years old with MDD. Conduct a randomized, double-blind, placebo- and active-controlled, parallel-group, short-term, fixed-dose efficacy and safety study of vortioxetine in the treatment of pediatric patients (ages 12 to 17 years) with a diagnosis of MDD. The trial should be designed in a way that fully evaluates the drug in children, therefore the study must assess at least two fixed doses, and must include an active control (fluoxetine) arm. The selected doses must be agreed upon by the Agency. The fixed-dose design is necessary for assessing potential dose-response relationships for efficacy and safety and to determine the lowest effective dose.

  - Study 4: An open-label, long-term pediatric safety study. Collect longer-term safety data for a minimum duration of 6 months of exposure to vortioxetine in pediatric patients (ages 7 to 17 years) with a diagnosis of MDD. The longer-term safety data could be obtained from open-label studies, e.g., a longer-term open-label extension of the controlled efficacy studies, or from separate longer-term open-label safety studies. The long-term safety data must evaluate doses at or above the dose or doses identified as effective in an adequately designed efficacy trial, as described above.

- The Applicant agreed to the WR in December 2015 and submitted protocol amendments and statistical analysis plans (SAPs) for Studies 2 (Study 12709A) and 3 (Study 12710A; both

protocols had been originally submitted in August 2015), and a protocol for Study 4 (Study 12712A) to meet the WR requirements.

- In April 2017, the Agency notified the Applicant that PMR 2084-1 had been fulfilled upon review of PK Study 12708A.

- In March, May, and June 2018, the Agency provided feedback on the Applicant's planned interim analysis for Study 12709A.

- In April 2018, the Applicant requested modification of the PMRs including removal of the fluoxetine arms because of Study 12709A and 12710A recruitment difficulties, as well as a deferral extension.

- In June 2018, following discussions between the Division and the Pediatric Review Committee (PeRC), the Agency agreed with removal of the fluoxetine arms and PMRs 2084-2 and 2084-3 were released and replaced by, respectively:

  - 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 to 17 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.

- In September 2018, the Agency granted another deferral extension request for Studies 12709A and 12710A because of delays involving study participants, sites, and/or management.

- In February 2019, the Agency issued an amended WR with removal of the fluoxetine arms from Studies 2 and 3.

- In July 2019, the Agency provided feedback on the blinded sample size reassessment for Study 12709A based on the prespecified interim analysis results, which confirmed that the study did not meet efficacy or futility criteria. The study continued with a revised sample size.

- In September 2019, the Agency granted a deferral extension request for Study 12709A because of delays involving study participants, sites, and/or management.

- In July 2020, the Applicant submitted efficacy supplemental NDA (sNDA) 21 (S-021) with the negative results of Study 12710A (as well as available safety and efficacy datasets for ongoing Study 12712A and 12712B. Study 12712B was an 18-month open-label extension study of Study 12712A. Conduction of Study 12712B was required by the terms of the European Medicines Agency (EMA) Pediatric Investigation Plan).

- In November 2020, the Applicant submitted a request to amend the WR with revised timelines given study delays (partly related to COVID-19) for Study 12709A and 12712A.

- In November 2020, the Applicant submitted the final clinical study report (CSR) for Study 12712B to IND 112581.

- In January 2021, the Agency approved S-021, which provided for the addition of labeling safety information in pediatric patients ages 12 to 17 years with MDD, based on the negative results of Study 12710A; the Agency notified the Applicant that PMR 2084-8 had been fulfilled. (Concurrently, the Agency approved prior approval labeling supplement 022, which added the adverse reactions hyperprolactinemia, headache, and hyperhidrosis to Section 6.2 postmarketing experience.)

- In February 2021, following discussions between the Division and PeRC, the Agency released the Applicant from PMR 2084-7. The Agency noted that, given that Study 12710A was negative, a positive result in Study 12709A would be insufficient on its own to support pediatric MDD labeling. As such, there was not a path forward for pediatric MDD labeling based on negative Study 12710A and ongoing Study 12709A. However, should the Applicant wish to complete the WR and pursue pediatric exclusivity, the Agency advised the Applicant to submit a request to amend the WR with a proposal for a second adequate and well-controlled study in children aged 7 to 11 years (in addition to the ongoing Study 12709A).

- In March 2021, following further discussion between the Division and PeRC, the Agency issued an amended WR that removed Studies 2 and 4. To meet the terms of the WR and possibly qualify for pediatric exclusivity extension, reports of the Studies 1 and 3 must be submitted to the Agency on or before December 31, 2023. In addition, the Applicant must submit clinical study reports (with access to subject-level datasets at Agency request) upon early termination or completion of Study 12709A and Study 12712A (i.e., Studies 2 and 4) no later than December 31, 2023.

  Of note, the Applicant had indicated in discussions with the Agency that completion of Study 12709A was required under the terms of the EMA Pediatric Investigation Plan, so they intended to complete the study.

- In June 2022, the Agency agreed that the Applicant's pediatric sNDA submission plans, including CSRs with subject-level datasets, appeared adequate.

- In December 2022, the Applicant submitted the clinical study report (CSR) for Study 12709A to IND 112581.

- On February 23, 2023, the Applicant submitted S-026 with the results of Study 12709A and 12712A to fulfill the terms of the WR.

- On April 24, 2023, the Agency notified the Applicant that the filing review found no issues precluding review and the supplement was granted Priority Review status.

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

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were conducted for this efficacy supplement.

4.2. Product Quality

No new product quality information was submitted with this efficacy supplement.

4.3. Clinical Microbiology

No clinical microbiology data were included in this efficacy supplement.

4.4. Devices and Companion Diagnostic Issues

This application does not include data related to any devices or companion diagnostics.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data were submitted with this supplement. A juvenile animal study was submitted and reviewed previously, under NDA 204447 Supplement 21 (see Unireview dated 01/22/2021).

6 Clinical Pharmacology

6.1. Executive Summary

In this efficacy supplement, the Applicant did not propose any changes to sections of the TRINTELLIX label that are relevant to clinical pharmacology. No new clinical pharmacology studies were included in this submission.

The Applicant submitted the results of three studies: 1) Study 12709A: An interventional, randomized, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in pediatric patients ages 7 to 11 years, with MDD; 2) Study 12712A: Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with MDD from 7 to 18 years of age; 3) Study 12712B: Long-term, open-label, flexible-dose, continuation extension study with vortioxetine in child and adolescents. Sparse PK samples were collected in Study 12709A and the PK of vortioxetine was characterized in pediatric subjects ages 7 to 11 years with MDD using population PK modeling analysis.

Population PK analyses suggest that the simulated dose-normalized mean peak plasma exposures (Cmax,ss) and area under the plasma concentration-time curve (AUCss) at steady state in pediatric subjects ages 7 to 11 years with MDD from Study 12709A are comparable to those observed in adolescents and adults. No apparent relationship between efficacy variables – Children's Depression Rating Scale-Revised Version (CDRS-R), General Behavior Inventory (GBI), Parent Global Assessment-Global Improvement (PGA), Clinical Global Improvement – Severity (CGI-S), and Children's Global Assessment Scale (CGAS)–and plasma exposures (Cavg) to vortioxetine was observed. Please refer to Section **Error! Reference source not found.**4 for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

See Table 2 for a listing of clinical trials relevant to this NDA efficacy supplement. Controlled efficacy and safety data for the 7-to-11 year-old population consists of results from Study 12709A. Additional new safety information comes from the completion of the 6-month open-label extension Study 12712A and updated data since the S-021 data cutoff for the 18-month open-label extension Study 12712B. Additional pediatric safety information that was previously reviewed for the S-021 submission comes from the PK Study 12708A (including its open-label extension). Study 12710A, which was reviewed for the S-021 submission, is included for reference as a source of overall pediatric safety data (in the 12-to-17-year-old population, including as a lead-in to Study 12712A (and hence 12712B)).

Table 2. Listing of Clinical Trials Relevant to NDA 204447-S026

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								
12709A Completed	027096 55	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	683 SB enrolled 540 DB randomized	Ages 7 to 11 with MDD	United States (27), Russia (13), Mexico (eight), Poland, Serbia (five each), Colombia, Ukraine (four each), France, Italy (three each), Bulgaria, Germany, Hungary, Latvia, Spain (two each), Canada, Estonia, Israel, South Africa (one each)
Studies to Support Safety								
12712A Terminated[2]	028712 97	Open-label, flexible-dose, multicenter, long-term extension	Oral vortioxetine 5, 10, 15, or 20 mg once daily	Safety	6 months	662 treated[3], 526 completed	Ages 7 to 18 with MDD, completed 12709A or 12710A	Russia (15), Mexico, Poland (seven each), Italy (six), Serbia (five), Colombia, Germany, Latvia, Ukraine, United States (four each), France, Spain (three each), Bulgaria, Hungary, Republic of Korea, United Kingdom (two each), Canada, Estonia, Israel, South Africa (one each)
12712B Completed	031086 25	Open-label, flexible-dose, multicenter, long-term extension	Oral vortioxetine 5, 10, 15, or 20 mg once daily	Safety	18 months	94 treated[4], 58 completed	Ages 7 to 17 with MDD, completed 12712A	Russia (9), Poland (six), Bulgaria, Hungary, Italy, Serbia, Spain (two each), Estonia, France, Germany, Latvia, South Africa, United

Trial/ Status	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Endpoint	Duration/ Follow Up	Patients enrolled	Study Population	Countries (Number of Sites)
								Kingdom (one each)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
12710A Completed	027 097 46	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 years with MDD	United States (41), Russia (16), Mexico, Poland (seven each), Germany, Italy, Serbia, Spain (five each), Colombia, Latvia, Ukraine (four each), France, Republic of Korea (three each), Bulgaria, Hungary, United Kingdom (two each), Canada, Estonia, South Africa (one each)
12708A Completed	014 910 35	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 years with DSM-IV-TR depressive or anxiety disorder	United States (6) and Germany (1)

Source: Clinical reviewer-created from Tabular Listing of All Clinical Studies; Study 127091A, 12712A, 12712B, 12710A, and 12708A 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 was amended to remove the active reference (fluoxetine) arm because of recruitment difficulty.

[2] Study 12712A was terminated in line with recommendation from the Data Monitoring Committee following the negative efficacy results of Study 12709A.

[3] Including 327 subjects from Study 12709A and 335 subjects from Study 12710A.

[4] Including 25 subjects from Study 12709A and 69 subjects from Study 12710A.

7.2. Review Strategy

The efficacy review focuses on the phase 3 study, 12709A, a randomized, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose, multicenter trial. The study is described in more detail in Section 8.1. Agency statistician Kelly Yang, PhD, reviewed the Applicant's statistical analysis.

The safety review includes data from Study 12709A as well as data from the previously reviewed Study 12710A in pediatric subjects ages 12 to 17 years, the open-label extensions Study 12712A (6 months) and Study 12712B (18 months, completed and previously reviewed), and the clinical pharmacology Study 12708A, which included a 14-to-20-day main treatment period, followed by a 6-month open-label extension (previously reviewed).

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

8.1. Study 12709A

8.1.1. Study Design

Trial Design

Study 12709A 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 ages 7 to 11 years. The study was conducted at 86 sites in 18 countries internationally, including 27 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 required to have a CDRS-R total score ≥45 and a CGI-S score ≥4 (moderately ill) at screening and enrollment (Baseline A), and to use adequate contraception if sexually active (and of childbearing potential if female). Female subjects ages ≥10 years (or younger at the discretion of the investigator if subjects were deemed to be of reproductive potential) 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 **Error! Reference source not found.**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

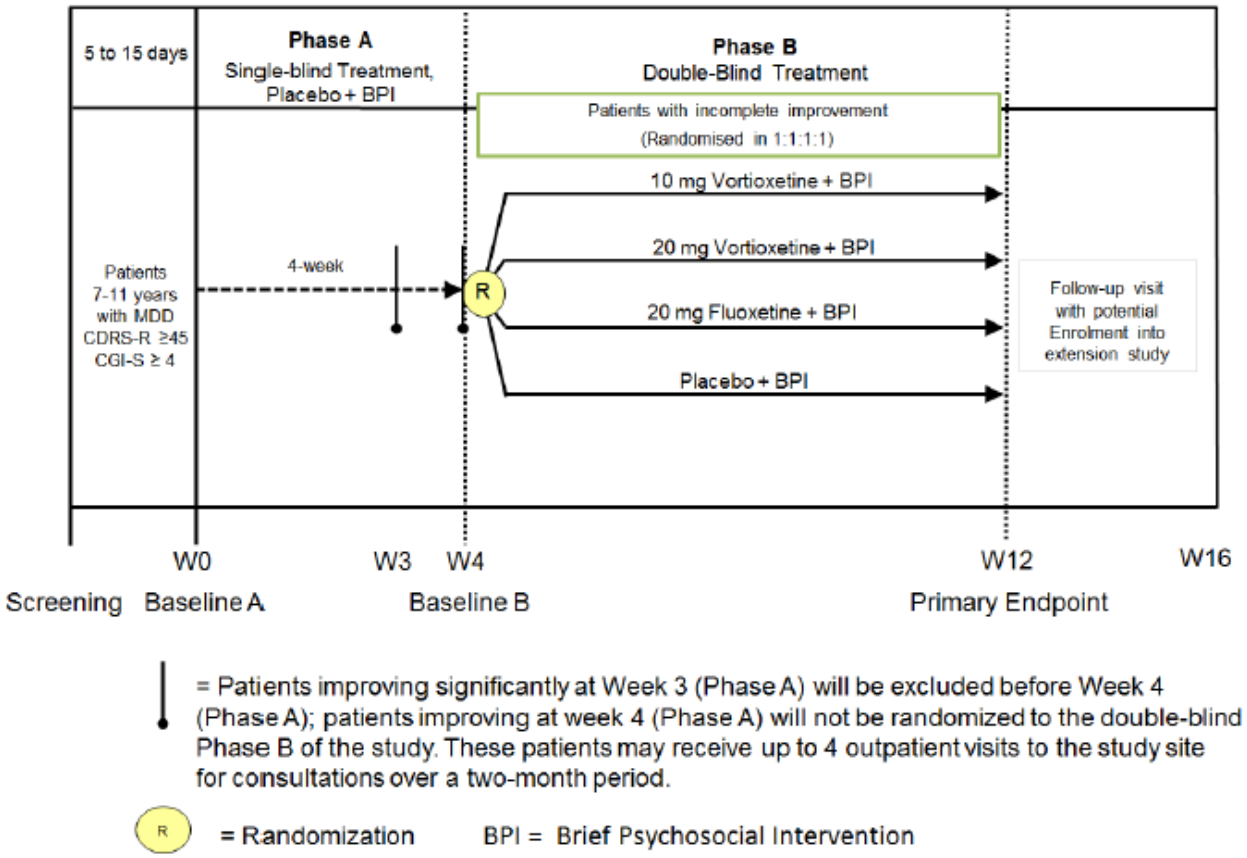
    - A <40% decrease in CDRS-R total score (subtracted by 17 to avoid a flooring effect) compared to enrollment (Baseline A)

    - PGA score >2 (i.e., at best minimally improved)

    Prior to the interim analysis and subsequent amendment, 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. Following the interim analysis, the fluoxetine arm was removed because of recruitment difficulties (see Section 3.2 for presubmission regulatory history) and subjects were randomized 1:1:1 to the remaining arms.

- 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 12709A Original Study Design Schematic



Source: Study 12709A Protocol, Panel 1, p. 13
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
Note: Following the interim analysis, the fluoxetine arm was removed because of recruitment difficulties and subjects were randomized 1:1:1 to the remaining arms.

> *<u>Clinical Reviewer's Comment</u>: The study design 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 (four items), somatic (six items), subjective (four items), and behavior (three 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 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 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 six domains during the 8-week treatment period
    - Change from Baseline B in the PedsQL average score in each of six 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

The efficacy analyses were based on the full analysis set (FAS) population, which consisted of all patients randomized to the double-blind, 8-week treatment period (Phase B) who took at least one dose of double-blind investigational medicinal product (IMP), had a valid Baseline assessment and at least one valid post-randomization assessment of the CDRS-R total score.

The primary efficacy parameter was the change from Baseline B in the CDRS-R total score after 8 weeks of treatment, which was analyzed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed effects of treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo), country, and week and Baseline B CDRS-R total score, treatment-by-week interaction, and Baseline B CDRS-R-by-Week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. An unstructured covariance matrix was used to model the covariance of within-patient scores.

The Applicant pre-specified a closed testing procedure to compare treatment groups to placebo, starting with the comparison of the average effect of the two vortioxetine doses versus placebo at a one-sided 2.5% significance level. If the result was statistically significant, each vortioxetine dose was tested separately versus placebo at a one-sided 2.5% significance level. Statistical significance could be claimed on the individual doses only if significance was claimed for the average vortioxetine dose.

The planned sample size before the pre-specified interim analysis was 480 patients (120 per treatment group). This was derived based on the following assumptions:

- A primary MMRM (Mixed Model for Repeated Measurements) analysis based on the average effect of the two doses of vortioxetine versus placebo at Week 8 on the CDRS-R
- Both vortioxetine doses have an effect of 4 points each versus placebo
- A standard deviation (SD) of 11 for the primary endpoint: change in CDRS-R at Week 8
- A power of 85%, with a one-sided significance level of 2.5%
- A drop-out rate of 15%

Moreover, to maintain the power at 85%, the Applicant increased the sample size by a factor of 1.045 to correct for the loss of power due to the sequential approach. Thus, 378 randomized patients were required in the final analysis in addition to 68 patients who were randomized to the fluoxetine group (prior to interim analysis), which gives a total sample size of 446 randomized subjects.

To ensure that the study is adequately powered, the Applicant performed a blinded sample size reassessment prior to the interim analysis, which was conducted based on 271 randomized subjects who were to be included in the interim analysis as of July 15, 2019. The Applicant reported that the SD estimate stabilized after approximately 160 subjects had been included. The mean value of the SD observed after n=160 was 12.67, and the observed withdrawal rate among the 271 subjects was 9.2%. With the updated SD and withdrawal rate, n=150 subjects would need to be randomized per group to meet the target 85% power.

The Applicant subsequently conducted the interim analysis for 271 randomized subjects on July 18, 2019. The interim analysis was based on a sequential approach, including an interim analysis with stopping rules for efficacy and futility, and an error-spending approach based on the Kim & DeMets method with rho=2 applied on the outcome from the MMRM model. After the efficacy analysis results were reviewed by the Independent Statistical Group (ISG), because the efficacy/futility criteria were not met, it was determined that this study would continue with adjusting the overall sample size to n=157 per group. Thus, the Applicant increased the total sample size from 446 subjects to 539 subjects to maintain the 85% power.

> *Statistical Reviewer's Comment: In the Protocol Amendment 2 and corresponding SAP Version 2.0 (August 21, 2018), the Applicant proposed to include an additional unblinded comparative interim analysis to evaluate efficacy or futility after a blinded sample size reassessment. The Division advised the Applicant that, although they may abort the trial based on futility, the sample size would still need to be adjusted according to the blinded reassessment to ensure 85% power if the interim analysis results look promising but the projected power for the final analysis appears to be below the targeted power.*

Protocol Amendments

There were three global amendments to the original protocol and several country-specific protocol amendments. As described above, there were two statistically relevant global protocol amendments. The first amendment (October 12, 2015), before the study started, added a blinded sample size re-assessment to ensure that the study was sufficiently powered to meet

the requirements of the WR. The third amendment (August 21, 2018), after the study commenced, changed the testing strategy for the primary endpoint by first testing the averaged effect of the two, fixed vortioxetine doses versus placebo, followed by the comparison of the individual vortioxetine doses versus placebo, to allow for a smaller sample size. The amendment also added an interim analysis for efficacy or futility; if the study was to continue following the interim analysis, recruitment to the fluoxetine arm would be stopped given recruitment difficulties.

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 (GCP).

The Applicant submitted a letter to the Agency on July 15, 2021, regarding a suspected serious GCP breach and closure of study site BG1023. Per the letter, Dr. Veselka Vasileva was a Principal Investigator (PI) in Study 12709A. The site enrolled a total of 17 subjects, all of whom completed Study 12709A (and further participation in Study 12712A; at the time of the letter, three subjects were ongoing in Study 12712A and since completed). Per the Applicant:

> During a regular review of site's efficacy scales data in 12709A study, a scale reviewer at (b) (4) [Contract Research Organization] CRO identified unusual patterns in CDRS-R, CGI-S, and CGI-I scales which were significantly different to data generated at other sites participating in the study. Specific concerns were based on the increased tendency in CDRS-R total scores and an absence of noticeable change in CGI-S and CGI-I scores recorded at this site for the duration of the study. Lundbeck's review of additional assessments such as Vital Signs showed minimal to no variation in blood pressure values collected by the site. Systolic Blood Pressure values were repetitive across patients and across visits.
>
> The Lundbeck study team received comprehensive analyses of ECGs, Vital Signs and Scales data from the eCOA Vendor ((b) (4)). Results of the analyses were suggestive of possible misconduct at site BG1023. Lundbeck conducted an audit of the investigator site in attempt to determine the cause of the data anomalies and to assess the impact on the site, subjects, study and systems. The audit did not identify any confirmatory evidence of misconduct or potential risk to patients' safety. However, the audit concluded that the unusual data patterns observed with CDRS-R, CGI-S, CGI-I and systolic blood pressure values were likely to be attributed to Principal Investigator's bias in scoring of efficacy scales and lack of adequate oversight based on the observed nonconformances.

On June 24, 2021, Lundbeck concluded a remote audit of the site BG1023 to attempt to determine the cause of the data anomalies, assess impact on study and potential risks to the study subjects. The audit resulted in the nonconformances described below. The data collected by the site to support efficacy assessments lacked evidence of robustness and adequate PI oversight. Specifically,

1. CDRS-R scales demonstrated identical patterns in total scores across 12 of 17 patients for period beginning September 30, 2018. The observed upward trend was indicative of worsening of MDD symptoms; however, the PI was unable to explain the rationale for the upward trend nor provide evidence supporting such clinical judgement.

2. There was no change in mean CGI-S score during the duration of the study for all patients. An absence of change in the mean CGI-S score was contradictory to the increase in scores observed with CDRS-R scales. The PI was unable to explain the contradiction between CGI-S and CDRS-R scores.

3. CGI-I scales remained constant at a score of "4" for 16 of 17 patients, resulting in no variation. This absence of variability in the CGI-I scores was contradictory to the increase observed in the CDRS-R scales. Upon inquiry to explain identical scores across visits and patients, the Principal Investigator indicated she did not review previous visit data prior to beginning a new visit with a patient and had failed to recognize repetitions in the scoring. The PI was unable to provide rationale for lack of variability in CGI-I scores.

4. Systolic Blood Pressure measured for 6 of 17 patients across various visits was not reflective of the actual measurement conducted in clinical setting. For example, Systolic blood pressure for (b) (6) remained 112 mmHg from Visit 1 through Visit 11. Due to general concerns with the robustness of data collection by this site, there was a lack of confidence from Lundbeck that identical blood pressure readings were likely in 11 consecutive visits. Upon inquiry to explain repetitions in blood pressure values, the Principal Investigator indicated she did not review previous visit data prior to beginning a new visit with a patient and had failed to recognize repeated values. The Principal Investigator was unable to explain the cause of the identical systolic blood pressure recorded for these patients.

Upon conclusion of the audit and based on the above nonconformances, Lundbeck made the decision to terminate the site from participation (b) (4). Site BG1023 was notified to stop enrollment in ADVANCE 12709A study and subsequent extension study 12712A. The site will be closed immediately for the 12709A study.

As noted, three subjects were allowed to finish Study 12712A, after which the site was closed for that study.

Clinical Reviewer's Comment: Of the 17 site subjects (out of 540 randomized subjects in the Study 12709A DB period), six (1.1%) were randomized to vortioxetine 10 mg; five (0.9%) to vortioxetine 20 mg; four (0.7%) to placebo; and two (0.4%) to fluoxetine. Thus, it appears unlikely for these subjects' results to have impacted the overall efficacy conclusions.

Financial Disclosure

See Appendix 0 for details.

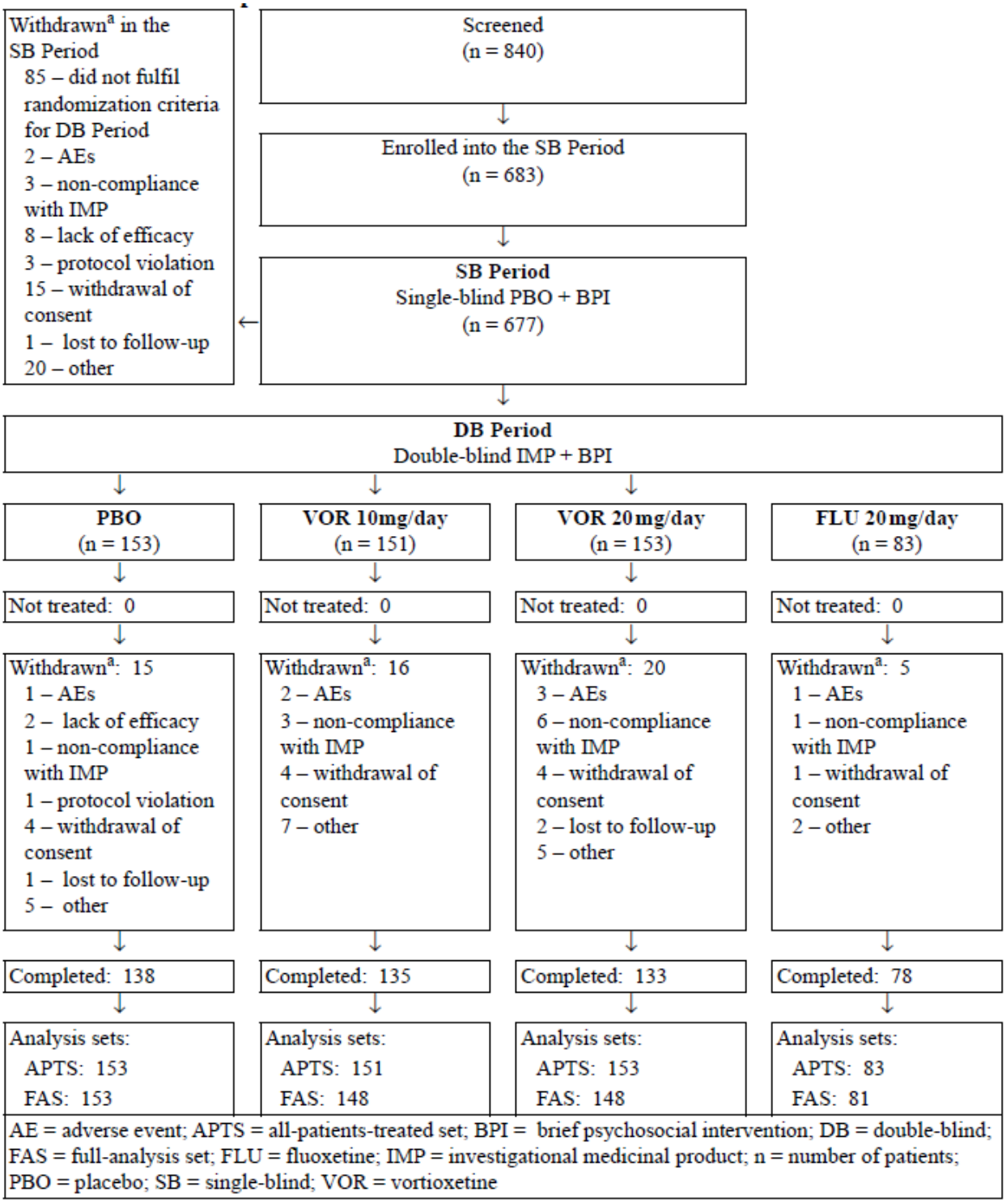
Patient Disposition

Of 840 subjects screened, 683 were enrolled into the SB Period, and 540 were randomized into the DB Period. Of the 137 subjects who withdrew during the SB Period, 85 (62.0%) did so for failure to meet randomization criteria. Of the randomized subjects, 138/153 subjects (90.2%) in the placebo group, 135/151 subjects (89.4%) in the vortioxetine 10 mg group, 133/153 subjects (86.9%) in the vortioxetine 20 mg group, and 78/83 subjects (94.0%) in the fluoxetine group completed the study.

The overall withdrawal rate in the DB Period was 10.4%, with the lowest rate for fluoxetine (6.0%) compared to the other three arms (9.8% to 13.1%, highest for vortioxetine 20 mg). The most common primary reasons for withdrawal were "other" (3.5%), withdrawal of consent (2.4%), and non-compliance with study drug (2.0%). The proportion of patients who withdrew for AEs was lowest in the placebo group (0.7%) and highest in the vortioxetine 20 mg group (2.0%).

See Figure 2 for the Applicant's diagram of subject disposition and Table 3 for primary reasons for withdrawal during the DB Period for the all patients treated set (APTS) in Study 12709A.

Figure 2. Study 12709A Subject Disposition



a Primary reason

Source: Study 12709A Clinical Study Report, Panel 10, p. 61

Table 3. Study 12709A Double-Blind Period: Withdrawals by Primary Reason (APTS)

Primary Reason	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
All withdrawals	16 (10.6%)	20 (13.1%)	15 (9.8%)	5 (6.0%)
Adverse event	2 (1.3%)	3 (2.0%)	1 (0.7%)	--
Other	7 (4.6%)	5 (3.3%)	5 (3.3%)	2 (2.4%)
Non-compliance with study drug	3 (2.0%)	6 (3.9%)	1 (0.7%)	1 (1.2%)
Lost to follow-up	--	2 (1.3%)	1 (0.7%)	--
Lack of efficacy	--	--	2 (1.3%)	1 (1.2%)
Withdrawal of consent	4 (2.6%)	4 (2.6%)	4 (2.6%)	1 (1.2%)
Protocol violation	--	--	1 (0.7%)	--

Source: Study 12709A Clinical Study Report, Panel 12, p. 63
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 except for fluoxetine, which was slightly lower than the other three arms. Noncompliance with study drug was highest in the vortioxetine 20 mg arm. Numbers in individual reason categories are low enough to make comparison difficult.*

See Table 4 for Study 12709A DB Period analysis sets. All subjects in the all patients randomized set (APRS) were included in the APTS DB Period. Ten subjects (1.9%) from the APTS were not included in the full analysis set (FAS) because of a lack of valid post-randomization assessments.

Table 4. Study 12709A Double-Blind Period: Analysis Sets

Analysis Set	VOR 10 mg n (%)	VOR 20 mg n (%)	PBO n (%)	FLU n (%)
All patients randomized set	151 (100%)	153 (100%)	153 (100%)	83 (100%)
All patients treated set	151 (100%)	153 (100%)	153 (100%)	83 (100%)
Full analysis set	148 (98%)	148 (97%)	153 (100%)	81 (98%)
Patients completed treatment	135 (89%)	133 (87%)	138 (90%)	78 (94%)

Source: Study 12709A Clinical Study Report, Panel 11, p. 62
Abbreviations: FLU = fluoxetine, PBO = placebo, VOR = vortioxetine

Protocol Violations/Deviations

See the Compliance with Good Clinical Practices section above for a discussion of site irregularities at Site BG1023.

A CRO identified a security incident that involved unauthorized access to and the deployment of ransomware on certain ERT systems on September 20, 2020. The Applicant conducted a review of the impact of the cyber-attack and concluded it did not constitute a serious breach.

Study data from one subject were processed outside the standard workflow as a result of server disconnection.

The Applicant provided a listing of important protocol deviations, including those involving informed consent; eligibility and withdrawal criteria; efficacy, PK, and safety assessments; treatment compliance; disallowed medications; and other issues.

Table 5. Study 12709A Double-Blind Period: Protocol Deviations (APTS)

Deviation Category	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
Subjects with deviation				
Visit outside scheduled window	24 (15.9%)	26 (17.0%)	31 (20.3%)	14 (16.9%)
Dosing non-compliance	18 (11.9%)	16 (10.5%)	17 (11.1%)	7 (8.4%)
Other deviation due to COVID-19 pandemic	17 (11.3%)	16 (10.5%)	17 (11.1%)	--
Other	11 (7.3%)	16 (10.5%)	5 (3.3%)	7 (8.4%)
Safety labs not collected/lost, or not suitable	13 (8.6%)	11 (7.2%)	13 (8.5%)	4 (4.8%)

Source: Clinical Reviewer-created from Study 12709A ADSL and DV datasets
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, PBO = placebo, VOR = vortioxetine
Note: Subjects may have had multiple occurrences of each deviation and in more than one category

> *Clinical Reviewer's Comment: Overall, the incidence of deviations was generally balanced across treatment arms, does not appear excessive for a trial of this nature, and does not raise significant concerns about study conduct. I reviewed the Applicant's listing for details of deviations. Generally, visits outside the scheduled window appeared to be close to the window period. See below for further discussion of non-compliance. Other deviations due to the COVID-19 pandemic were local processing of hematology samples (note that the pandemic occurred after the fluoxetine arm had been discontinued in 2018). Other deviations were varied and appeared to be deviations that could have been included in another category (e.g., regarding sample collection timing, incorrect informed consent versions used, assessment and visit window variations). Safety lab issues also appeared varied and were generally balanced across arms.*

Table of Demographic Characteristics

See Table 6 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. Demographic characteristics were generally balanced across treatment arms. Ethnicity (not in table) ranged from 41% to 47% Hispanic or Latino across treatment arms in the DB Period. (Enrollment at Colombian sites ranged from 13% to 24% across arms, and enrollment at Mexican sites ranged from 16% to 19% across arms.) Mean duration of current major

depressive episode (MDE) was generally similar across arms. There was a large range in duration of current MDEs, from approximately 2 weeks to 287 weeks. Generally similar numbers of subjects had previously received pharmacotherapy across arms at 11% to 20%. Baseline CDRS-R scores were similar across treatment arms.

Table 6. Study 12710A All Patients Treated Set Demographic and Baseline Characteristics

Demographic Parameter or Disease Characteristic	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
Sex				
Female	72 (47.7%)	70 (45.8%)	62 (40.5%)	39 (47.0%)
Male	79 (52.3%)	83 (54.2%)	91 (59.5%)	44 (53.0%)
Age (years)				
Mean (SD)	9.4 (1.5)	9.3 (1.4)	9.3 (1.4)	9.3 (1.4)
Median	10	9	10	9
Range	7, 11	7, 11	7, 11	7, 11
Race				
White	74 (49.0%)	76 (49.7%)	70 (45.8%)	45 (54.2%)
Black	20 (13.2%)	21 (13.7%)	21 (13.7%)	13 (15.7%)
Other	56 (37.1%)	52 (34.0%)	60 (39.2%)	22 (26.5%)
Asian	--	2 (1.3%)	--	--
Not reported	1 (0.7%)	2 (1.3%)	2 (1.3%)	3 (3.6%)
BMI (kg/m^2)				
N	149	153	153	83
Mean (SD)	18.9 (4.3)	19.0 (3.8)	19.2 (4.5)	19.2 (4.3)
Median	17.8	18.1	18.5	18.3
Range	13.5, 36.4	13.5, 32.2	12.5, 37.8	13.4, 33.0
Number of previous MDEs				
Mean (SD)	0.3 (0.5)	0.2 (0.5)	0.3 (0.5)	0.3 (0.5)
Median	0	0	0	0
Range	0, 2	0, 4	0, 3	0, 2
Duration of current MDE (weeks)				
Mean (SD)	32.8 (36.9)	30.9 (36.8)	29.3 (33.0)	35.3 (40.6)
Median	23.0	21.0	20.1	25.7
Range	2.6, 287.7	2.7, 263.3	2.3, 270.9	3.7, 262.1
Received pharmacotherapy				
Yes	23 (15.2%)	17 (11.1%)	30 (19.6%)	11 (13.3%)
No	128 (84.8%)	136 (88.9%)	123 (80.4%)	72 (86.7%)
Baseline B CDRS-R total score				
N (Full Analysis Set)	148	148	153	81
Mean (SD)	60.7 (9.3)	60.4 (9.4)	60.1 (10.2)	61.1 (9.5)
Median	60	59	59	59
Range	42, 83	41, 86	41, 92	43, 88

Source: Adapted from Study 12709A Clinical Study Report, Panel 14, p. 66, Table 13, p. 162, Panel 15, p. 66, and Panel 16, p. 68, and Panel 17, p. 69

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). In comparison to the U.S. general population, Asian subjects were underrepresented. And of note, the proportion of subjects identifying as Hispanic or Latino in the DB period ranged from 41% to 47% across arms, which is higher than the U.S. general population (for comparison, the proportion ranged from 21% to 24% across treatment arms in the previously reviewed adolescent Study 12710A). An examination of enrollment by country appears to explain the study differences: the DB population enrolled in Colombia and Mexico ranged from 31% to 42% in Study 12709A, versus 11% to 21% in Study 12710A across treatment arms. The Applicant did not comment (i.e., ethnicity data were not summarized in the CSR). Overall, the U.S. proportion of subjects was lower in Study 12709A than 12710A, at 21% versus 35%. It is unclear if these differences could have impacted the study results or generalizability to the U.S. population.

Other Baseline Characteristics (e.g., other medical conditions)

For the DB Period APTS, the most common relevant concurrent condition was attention deficit/hyperactivity disorder (ADHD), generally similar across treatment arms ranging from 9% to 15%.

Concomitant Medications and Treatment Compliance

Concomitant Medication Use

During the DB Period, the most common therapeutic class of medications (i.e., taken by ≥5% of subjects) continued by subjects in any arm was psychostimulants, agents used for ADHD and nootropics, ranging from 5% to 8% across arms. ADHD medication was permitted if the subject required pharmacological therapy and could not be maintained on a stable dose of psychostimulant for 4 weeks prior to enrollment; psychostimulants were permitted with a 4-week stable dosing period prior to enrollment. Other classes of medications started during the DB Period included anti-inflammatory and antirheumatic products (non-steroids) and other analgesics and antipyretics, at generally similar rates across arms (3% to 7%).

Treatment Compliance

According to the Applicant, by tablet count the proportion of subjects with ≥80% compliance during the DB Period ranged from 95% to 100% across arms. However, based on PK data from a maximum of two samples per subject, 77/273 (28%) of the subjects treated with vortioxetine were considered non-compliant.

Clinical Reviewer's Comment: It is unclear how to interpret the difference in compliance reports between tablet counts and PK data. If the PK data are more reliable, that could certainly impact efficacy. However, it was limited to a maximum of two samples per

subject.

Efficacy Results – Primary Endpoint

The primary endpoint, the mean change from Baseline B in CDRS-R total score at Week 8, average of the two vortioxetine doses (Avg. VOR), was not statistically significantly different versus placebo (Table 7). 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 -2.09 points from placebo and the difference was not statistically significant (95% CI: -4.54 to 0.36; p=0.094). (To correct for alpha spending in the interim analysis, the two-sided alpha level for the final analysis was 0.045.) For analyses of the individual vortioxetine doses (10 and 20 mg) versus placebo, the results for neither dose were nominally statistically significant. The result for fluoxetine compared to placebo was closer to nominal statistical significance in mean change from randomization to Week 8 in CDRS-R total score with a difference of -3.30 points (95% CI -6.65 to 0.04; nominal p=0.053).

Table 7. Study 12709A Primary Efficacy Analysis in the Double-Blind Period: Change from Randomization to Week 8 on the Children's Depression Rating Scale-Revised Total Score (FAS MMRM)

Primary Endpoint	PBO (N=153)	Avg. VOR	VOR 10 mg (N=148)	VOR 20 mg (N=148)	FLU 20 mg (N=81)
CDRS-R Total Score at Baseline (SD)	60.1 (10.19)		60.7 (9.34)	60.4 (9.41)	61.1 (9.52)
LSM Change from Baseline (SE)	-17.48 (1.35)	-19.57 (1.16)	-19.20 (1.37)	-19.94 (1.37)	-20.78 (1.60)
Placebo-subtracted difference (95% CI)		-2.09 (-4.54, 0.36)	-1.72 (-4.56, 1.11)	-2.46 (-5.29, 0.37)	-3.30 (-6.65, 0.04)
P-value (two-sided)		0.094	0.234	0.088	0.053

Source: Statistical reviewer-adapted from Study 12709A Clinical Study Report, Panel 17, p.69, Panel 18, p. 72
Abbreviations: Avg. = average, CDRS-R = Children's Depression Rating Scale-Revised version, FAS = full analysis set, FLU = fluoxetine, MMRM = mixed model for repeated measurements, SD = standard deviation, SE = standard error, 95% CI = unadjusted 95% confidence interval (p-value also unadjusted), PBO = placebo, VOR = vortioxetine
Note: The p-values should be compared with the significance level of 0.045 due to an unblinded interim analysis conducted.

<u>Clinical Reviewer's Comment</u>: Although not significant, the Avg. VOR (apparently driven by the 20 mg dose) came closer to significance in Study 12709A than Study 12710A (previously reviewed, in subjects ages 12 to 17 years), where for the change from randomization to Week 8 on the CDRS-R total score, the Avg. VOR had a difference of +0.2 points from placebo (95% CI: -2.41 to 2.82; p=0.878). In Study 12710A, fluoxetine did nominally separate from placebo with a difference of -3.7 points (95% CI: -6.74 to -0.72; p=0.015). It is unclear why the studies had different nominal results; the following issues were considered in the review:

- *Design and conduct of the studies: The studies were identically designed; although the fluoxetine arm was removed before completion of Study 12709A enrollment, it is unclear how that could have affected differences in the results in*

the vortioxetine arms. It is possible that the enrollment difficulties differed between studies, but study conduct generally appeared to be similar. (The irregularities at one Bulgarian site as described above do not appear likely to have impacted the overall study results).

- *Geographic differences: The adult efficacy data suggested a potential difference based on geography. In the non-elderly adult efficacy study results as described in the vortioxetine label, the two U.S. study primary endpoints separated from placebo at the 20 mg dose (but not at 10 or 15 mg), compared to the three non-U.S. studies where doses as low as 5 mg separated from placebo (at least in one of the two with a 5 mg dose). (In an additional elderly U.S. and non-U.S. study, 5 mg separated from placebo.) So, it is of note that the 20 mg dose in Study 12709A appeared to get closer to separation; however, Study 12709A had a smaller U.S. population than Study 12710A (21% versus 35% as noted above), which does not support an alignment with the adult data generally. However, there was a larger proportion of subjects from Colombia and Mexico in Study 12709A than 12710A as noted; it is unclear what, if any, impact that could have had.*

- *Dose reductions: Both studies had similar numbers of dose reductions across the vortioxetine arms (5 to 8%), which does not support a difference.*

- *Compliance: Based on PK data, Study 12709A had a higher proportion of subjects on vortioxetine who were considered non-compliant than Study 12710A (28% versus 16%), which if anything would support the opposite outcome. However, compliance based on tablet counts was similar between studies.*

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 endpoint results. Differences relative to placebo were not nominally statistically significant, except for a few exceptions (i.e., the change from Baseline B to Week 8 on the PedsQL VAS total average score and emotional distress summary score for Avg. VOR; and the change from Baseline B to Week 8 on the CDRS-R behavior subscore and on the CGAS score, and for the proportions of responders (≥50% decrease on CDRS-R total score) and remitters (CDRS-R total score ≤28), for the fluoxetine arm).

Dose/Dose Response

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

the primary endpoint. The 20 mg dose did separate numerically from placebo to a larger extent than 10 mg (i.e., -2.46 versus -1.72).

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

As noted by the Applicant, no relevant differences for Avg. VOR or individual doses versus placebo were generally observed for the CDRS-R item scores or the Multidimensional Anxiety Scale for Children – Short Version (MASC-10) scores.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

Not applicable given that Study 12709A was the single efficacy trial in subjects ages 7 to 11 years. See above for comment regarding comparison to Study 12710A in subjects ages 12 to 17 years.

Primary Endpoints

See above.

Secondary and Other Endpoints

See above.

Subpopulations

According to the Applicant, the primary efficacy analysis (MMRM) was applied for a number of subgroups, and generally a large heterogeneity in the estimated treatment effects across age, sex, race, country, and region were observed. Per the Applicant, no consistent findings were observed, but greater treatment differences to placebo were observed within the group of male subjects, White subjects, and subjects from the European region.

Clinical Reviewer's Comment: Given the overall negative findings, smaller size of subpopulations, and lack of control for multiplicity, it is difficult to interpret any observations of treatment differences between subgroups.

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 12709A was designed to assess the efficacy of vortioxetine for the treatment of MDD in pediatric subjects ages 7 to 12 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, average vortioxetine did not separate from placebo (Table 7). Nominally, neither vortioxetine dose group separated from placebo; the fluoxetine group came closer to nominal separation from placebo. The results do not support the use of vortioxetine for the treatment of MDD in pediatric patients ages 7 to 12 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 referring to:

- Two completed studies:
    - The completed phase 3 interventional Study 12709A in subjects ages 7 to 11 years (also referred to hereafter as children)
    - The terminated 6-month open-label extension (OLE) Study 12712A in subjects ages 7 to 18 years.
- The 18-month open-label extension Study 12712B in subjects ages 7 to 17 years (reviewed for S-021), with updated information from the previous data cutoff of September 19, 2019, through study completion on April 16, 2020.

Two other completed and previously reviewed studies (see January 21, 2021, S-021 unireview for full details) contributed to the overall pediatric safety database:

- The phase 3 interventional Study 12710A in subjects ages 12 to 17 years (also referred to hereafter as adolescents).

- The clinical pharmacology Study 12708A in subjects ages 7 to 17 years. Study 12708A consisted of a 14-to-21-day main treatment study, with an optional 6-month extension.

See Section 8.1 for a discussion of Study 12709A and Table 2 for a tabular description of all the studies. This review will not repeat data analyses from the S-021 review.

8.3.2. Review of the Safety Database

Overall Exposure

See Table 4 for the total safety population (APTS) in Study 12709A. In the open-label extension studies, Study 12712A included 662 subjects (i.e., 139 more subjects than at the S-021 submission data cutoff; with 327 subjects from Study 12709A and 335 subjects from Study 12710A). The final report for Study 12712B included the same number of subjects (i.e., 94) as at the S-021 data cutoff. See the S-021 unireview for details regarding Study 12708A. In total, 964 unique subjects were exposed to vortioxetine over the five studies.

In Study 12709A, the mean number of days of exposure to study drug (DB Period) ranged from 52 to 54 days across arms (median 56 for all arms; range 2 to 73 days). In Study 12712A, the mean number of days of exposure to vortioxetine was 160 days (median 182; range 1 to 216 days). Vortioxetine dosing was flexible from 5 to 20 mg/day, with a mean dose of 12 mg/day for children and 13 mg/day for adolescents. In Study 12712B, the mean number of days of exposure to vortioxetine was 459 days (median 544; range 20 to 561 days). See the S-021 unireview for details regarding Study 12708A.

> *Clinical Reviewer's Comment: Exposure to study drug appears adequate based on study design. As described in the prescribing information, vortioxetine was evaluated for safety in 5852 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-and postmarketing clinical studies and the program has met the 6-month and 1-year ICH recommendations for safety exposure for chronically administered drugs. The safety data for pediatric subjects alone aligns with the ICH recommendations for numbers of subjects exposed for at least 6 months and 12 months.*

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 12709A were previously discussed (see Table 6). The results of the studies appear sufficiently generalizable for the purpose of the safety assessment.

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.

> *Clinical Reviewer's Comment: The single Bulgarian site issues as described above appear to have been adequately addressed by the Applicant.*

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 24.0 for Study 12709A and Version 22.0 for Study 12712A and 12712B). 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.

In Study 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 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 hypoesthesia, 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)

The clinical reviewer 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: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
- Blood triglycerides increased: blood triglycerides increased, hypertriglyceridemia
- Chest pain: chest pain, non-cardiac chest pain
- Depression: depression, depressive symptom, major depressive disorder
- Fatigue: asthenia, fatigue
- Headache: headache, tension headache
- Hyperbilirubinemia: blood bilirubin increased, hyperbilirubinemia
- Hyperprolactinemia blood prolactin increased, hyperprolactinemia
- Insomnia: initial insomnia, insomnia
- Leukopenia: leukopenia, white blood cell count decreased
- Neutropenia: neutropenia, neutrophil count decreased
- Somnolence: sedation, somnolence
- Tachycardia: heart rate increased, tachycardia, sinus tachycardia

> *Clinical Reviewer's Comment: The Applicant's (S)AE definitions, 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; prolactin was collected in the OLE studies. Height and weight 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 analyzed at a central laboratory. The ECGs were evaluated by a pediatric cardiologist at a central laboratory. See the S-021 review for schedules of these assessments in the short-term efficacy studies and OLEs. All assessments (original and repeated, if necessary) were used to identify potentially clinically significant (PCS) values. The Applicant did not describe how PCS cutoff values were set.

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

8.3.4. Safety Results

Deaths

No deaths occurred in Study 12709A or the OLE studies.

Serious Adverse Events

In the Study 12709A SB Period (on placebo), six subjects (out of SB 677 APTS, 0.9%) experienced seven SAEs: tachycardia, gastroenteritis, viral pharyngitis, intentional self-injury, suicidal ideation, intentional overdose, and suicide attempt (one subject (0.1%) each, with the last two in the same subject).

In the Study 12709A DB Period, seven subjects experienced SAEs (Table 8). The placebo group included the most SAEs, including one suicide attempt; the vortioxetine 20 mg group included the other two psychiatric SAEs, major depression and mania.

Table 8. Study 12709A Double-Blind Period Serious Adverse Events (APTS)

MedDRA Preferred Term	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
Subjects with serious adverse events	1 (0.7%)	2 (1.3%)	3 (2.0%)	1 (1.2%)
Major depression	--	1 (0.7%)	--	--
Mania	--	1 (0.7%)	--	--
Tracheitis	1 (0.7%)	--	--	--
Forearm fracture	--	--	--	1 (1.2%)
Cellulitis	--	--	1 (0.7%)	--
Pneumonia	--	--	1 (0.7%)	--
Suicide attempt	--	--	1 (0.7%)	--

Source: Adapted from Study 12709A Clinical Study Report, Panel 26, p. 85
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine

> *Clinical Reviewer's Comment: The Study 12709A DB Period is the most informative for direct placebo-controlled comparison. Overall, the numbers of SAEs are small, with psychiatric SAEs for both vortioxetine and placebo that are labeled (i.e., mania) or expected in a population with MDD (i.e., major depression, suicide attempt). See Section 8.3.5 for a discussion of all SIB-related AEs, including SAEs.*

During the Study 12712A treatment period, 14 subjects (2.1%) experienced SAEs: three subjects with five SAEs from lead-in Study 12709A, and 11 subjects with 13 SAEs from lead-in Study 12710A. See Table 9 for a listing of SAEs by lead-in study. No SAEs occurred in Study 12712B.

Table 9. Study 12712A Treatment Period Serious Adverse Events by Lead-In Study (APTS)

MedDRA Preferred Term	Lead-In 12709A (N=327) n (%)	Lead-In 12710A (N=335) n (%)	Total (N=662) n (%)
Subjects with serious adverse events	3 (0.9%)	11 (3.3%)	14 (2.1%)
Suicidal ideation	2 (0.6%)	2 (0.6%)	4 (0.6%)
Suicide attempt	1 (0.3%)	3 (0.9%)	4 (0.6%)
Intentional overdose	--	3 (0.9%)	3 (0.5%)
Major depression	--	1 (0.3%)	1 (0.2%)
Mania	--	1 (0.3%)	1 (0.2%)
Suicidal behavior	1 (0.3%)	--	1 (0.2%)
Psychogenic seizure	--	1 (0.3%)	1 (0.2%)
Arthropathy	--	1 (0.3%)	1 (0.2%)
Osteitis	--	1 (0.3%)	1 (0.2%)
Psychomotor hyperactivity	1 (0.5%)	--	1 (0.2%)
Torticollis	--	1 (0.3%)	1 (0.2%)

Source: Clinical reviewer-adapted from Study 12712A Clinical Study Report, Table 167, p. 410
Abbreviations: APTS = all patients treated set, MedDRA = Medical Dictionary for Regulatory Activities
Note: Subjects may have had more than one serious adverse event for the same or different preferred terms.

During the Study 12712A 4-week safety follow-up period (following medication discontinuation, for subjects who did not enroll in Study 12712B), five subjects reported six SAEs, including suicide threat and lymphadenitis bacterial (the latter twice for one subject) for subjects from lead-in Study 12709A, and suicidal ideation, depression, and schizophrenia (the latter twice for one subject) for subjects from lead-in Study 12710A.

> *Clinical Reviewer's Comment: In the OLE studies, there is no comparator, but AEs may inform what a picture of long-term use might show. The overall number of SAEs is low, and lower for subjects from Study 12709A than Study 12710A. Psychiatric SAEs are labeled (e.g., suicidal ideation or behavior-related, or mania) or expected in a population with MDD (i.e., major depression).*

Adverse Events Leading to Withdrawal

In the Study 12709A SB Period, four subjects (0.6%) experienced five AEs leading to withdrawal, including: suicidal ideation, suicide attempt, intentional overdose, intentional self-injury, and nausea (one subject (0.1%) each).

In the Study 12709A DB Period, six subjects experienced AEs leading to withdrawal (Table 10). The vortioxetine groups included a larger number of AEs leading to withdrawal overall.

Table 10. Study 12709A Double-Blind Period Adverse Events Leading to Withdrawal (APTS)

MedDRA Preferred Term	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
Subjects with any adverse event leading to withdrawal	2 (1.3%)	3 (2.0%)	1 (0.7%)	--
Major depression	--	1 (0.7%)	--	--
Mania	--	1 (0.7%)	--	--
Vomiting	--	1 (0.7%)	--	--
Blood thyroid stimulating hormone increased	1 (0.7%)	--	--	--
Nausea	1 (0.7%)	--	--	--
Suicide attempt	--	--	1 (0.7%)	--

Source: Clinical reviewer-adapted from Study 12709A Clinical Study Report, Panel 27, p. 87
Abbreviations: APTS = all patients treated set, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, VOR = vortioxetine

> *Clinical Reviewer's Comment: Similar to SAEs, psychiatric AEs leading to withdrawal for both vortioxetine and placebo are labeled (i.e., mania, nausea/vomiting) or expected in a population with MDD (i.e., major depression, suicide attempt). 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 12712A, 40 subjects (6.0%) experienced an AE leading to withdrawal: 18 subjects (5.5%) from lead-in Study 12709A, and 22 subjects (6.6%) from lead-in Study 12710A. See Table 11 for a listing of AEs leading to withdrawal by lead-in study. No AEs leading to withdrawal occurred in Study 12712B.

Table 11. Study 12712A Adverse Events Leading to Withdrawal by Lead-In Study (APTS)

MedDRA Preferred Term	Lead-In 12709A (N=327) n (%)	Lead-In 12710A (N=335) n (%)	Total (N=662) n (%)
Subjects with any adverse event leading to withdrawal	18 (5.5%)	22 (6.6%)	40 (6.0%)
Nausea	3 (0.9%)	8 (2.4%)	11 (1.7%)
Suicidal ideation	2 (0.6%)	2 (0.6%)	4 (0.6%)
Suicide attempt	1 (0.3%)	3 (0.9%)	4 (0.6%)
Intentional overdose	--	3 (0.9%)	3 (0.5%)
Vomiting	1 (0.3%)	2 (0.6%)	3 (0.5%)
Major depression	1 (0.3%)	1 (0.3%)	2 (0.4%)
Mania	1 (0.3%)	1 (0.3%)	2 (0.4%)
Irritability	1 (0.3%)	1 (0.3%)	2 (0.4%)
Dizziness	1 (0.3%)	1 (0.3%)	2 (0.4%)
Agitation	1 (0.3%)	0	1 (0.2%)
Anxiety	1 (0.3%)	0	1 (0.2%)
Blood pressure decreased	1 (0.3%)	0	1 (0.2%)
Decreased appetite	--	1 (0.3%)	1 (0.2%)
Dermatitis	1 (0.3%)	0	1 (0.2%)
Headache	--	1 (0.3%)	1 (0.2%)
Hepatitis viral	1 (0.3%)	0	1 (0.2%)
Neutropenia	1 (0.3%)		1 (0.2%)
Non-cardiac chest pain	1 (0.3%)	0	1 (0.2%)
Pruritis	1 (0.3%)	0	1 (0.2%)
Psychogenic seizure	--	1 (0.3%)	1 (0.2%)
Psychomotor hyperactivity	1 (0.3%)	0	1 (0.2%)
Rash	1 (0.3%)	0	1 (0.2%)
Suicidal behavior	1 (0.3%)	0	1 (0.2%)
Tic	1 (0.3%)	0	1 (0.2%)
Torticollis	--	1 (0.3%)	1 (0.2%)
Tremor	1 (0.3%)	0	1 (0.2%)
Weight decreased	--	1 (0.3%)	1 (0.2%)

Source: Clinical reviewer-adapted from Study 12712A Clinical Study Report, Table 181, p. 426
Abbreviations: APTS = all patients treated set, MedDRA = Medical Dictionary for Regulatory Activities

Clinical Reviewer's Comment: As noted, in the OLE studies, there is no comparator, but AEs may inform what a picture of long-term use might show. Similar to SAEs, the overall number of AEs leading to withdrawal is low, and lower for subjects from Study 12709A than Study 12710A. The most common reasons (including most psychiatric SAEs) are labeled (e.g., nausea/vomiting, suicidal ideation or behavior-related, mania, irritability, dizziness) or expected in a population with MDD (i.e., major depression).

Significant Adverse Events

Dose Reductions

The Study 12709A 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 Adverse Events

In the Study 12709A SB Period, five subjects (0.7%) experienced severe AEs. These included gastroenteritis, hypertriglyceridemia, dizziness, initial insomnia, and intentional self-injury (one subject (0.1%) each).

In the Study 12709A DB Period, eight subjects (1.5%) experienced seven severe AEs. In the vortioxetine 10 mg group, three subjects (2.0%) experienced severe AEs: insomnia (two subjects) and product dispensing error (one subject; the wrong study drug kit was given). In the vortioxetine 20 mg group, two subjects (1.3%) experienced one severe AE each: headache and hyperthermia. In the placebo group, two subjects (1.3%) experienced one severe AE each: suicide attempt and diarrhea. In the fluoxetine group, one subject (1.2%) experienced a severe AE of decreased appetite.

In Study 12712A, 26 subjects (3.9%) experienced 41 severe AEs, including: nausea (five subjects (0.8%)); suicidal ideation (four subjects (0.6%)); suicide attempt (three subjects (0.5%)); insomnia (two subjects (0.3%)); and agitation, anxiety, apathy, depression, irritability, intentional overdose, mania, mood swings, suicidal behavior, abdominal pain, arthralgia, decreased appetite, dermatitis, dizziness, dry mouth, fatigue, headache, hunger, hypoglycemia, micturition urgency, osteitis, pharyngitis, psychogenic seizure, tonsillitis bacterial, vomiting, and weight increased (all one subject (0.2%) each). In Study 12712B, one subject experienced a severe AE of eosinophil count increased.

> *Clinical Reviewer's Comment: In the Study 12709A DB Period, severe AEs occurred at a low and similar frequency between treatment arms. In the OLE studies, there is no comparator, but AEs may inform what a picture of long-term use might show. The overall number of severe AEs was low in the OLEs. Severe AEs mostly occurred in one subject each in any of the studies. As with SAEs and AEs leading to withdrawal, the most common severe AEs were labeled or expected.*

Treatment Emergent Adverse Events and Adverse Reactions

In the Study 12709A SB Period, the AEs occurring at ≥2% incidence included: headache (39 subjects (5.8%)); abdominal discomfort, abdominal pain, abdominal pain upper (grouped, 26 subjects (3.8%)); and nausea (23 subjects (3.4%)).

Table 12 summarizes AEs occurring during the Study 12709A DB Period in ≥2% of subjects in either vortioxetine group and at a greater rate than subjects in the placebo group. 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 12. Study 12709A 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 (APTS)

MedDRA Preferred Term	VOR 10 mg (N=151) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=83) n (%)
Nausea	19 (12.6%)	17 (11.1%)	7 (4.6%)	5 (6.0%)
Vomiting	14 (9.3%)	10 (6.5%)	3 (2.0%)	3 (3.6%)
Abdominal pain[1]	14 (9.3%)	11 (7.2%)	8 (5.2%)	5 (6.0%)
Dizziness	7 (4.6%)	5 (3.3%)	5 (3.3%)	3 (3.6%)
Illness	--	5 (3.3%)	--	--
Nasopharyngitis	6 (4.0%)	4 (2.6%)	5 (3.3%)	10 (6.5%)
Diarrhea	5 (3.3%)	1 (0.7%)	4 (2.6%)	3 (3.6%)

Source: Clinical reviewer-created from Study 12709A Clinical Study Report, Panel 25, p. 82, and Study 12709A 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 lower, abdominal pain upper.

> *<u>Clinical Reviewer's Comment</u>: Abdominal pain (grouped) occurred at ≥5% in all groups, but not at twice the rate in placebo for the vortioxetine arms. This was similar to the results of Study 12710A.*

See Table 13 for AEs occurring in ≥2% of total subjects in Study 12712A by lead-in study, and Table 14 for AEs occurring in ≥3% of total subjects (i.e., >2 subjects) of total subjects in Study 12712B by lead-in study. Results were generally similar to the lead-in placebo-controlled studies, and generally similar between children and adolescents. Note that prolactin was only measured in the OLE studies (see Laboratory Findings below).

Table 13. Study 12712A Adverse Events Occurring in ≥2% of Total Subjects by Lead-In Study (APTS)

MedDRA Preferred Term	Lead-In 12709A (N=327) n (%)	Lead-In 12710A (N=335) n (%)	Total (N=662) n (%)
Nausea	60 (18.3%)	78 (23.3%)	138 (20.8%)
Headache	49 (15.0%)	67 (20.0%)	116 (17.5%)
Abdominal pain[1]	43 (13.1%)	31 (9.3%)	74 (11.2%)
Vomiting	41 (12.5%)	28 (8.4%)	69 (10.4%)
Nasopharyngitis	24 (7.3%)	22 (6.6%)	46 (6.9%)
Dizziness	10 (3.1%)	28 (8.4%)	38 (5.7%)
Diarrhea	20 (6.1%)	8 (2.4%)	31 (5.9%)
Insomnia[2]	8 (2.4%)	14 (4.2%)	22 (3.3%)
Weight increased	5 (1.5%)	16 (4.8%)	21 (3.2%)

Source: Clinical reviewer-created from Summary of Clinical Safety, Table 3.c, p. 23, Study 12712A Clinical Study Report, Table 158, p. 400, 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
[2] Grouping includes initial insomnia, insomnia

Table 14. Study 12712B Adverse Events Occurring in ≥3% of Total Subjects by Lead-In Study (APTS)

MedDRA Preferred Term	Lead-In 12709A (N=25) n (%)	Lead-In 12710A (N=69) n (%)	Total (N=94) n (%)
Headache	4 (16.0%)	9 (13.0%)	13 (13.8%)
Abdominal pain[1]	1 (4.0%)	6 (8.7%)	7 (7.4%)
Nausea	2 (8.0%)	5 (7.2%)	7 (7.4%)
Hyperprolactinemia[2]	2 (8.0%)	4 (5.8%)	6 (6.4%)
Respiratory tract infection viral	3 (12.0%)	2 (2.9%)	5 (5.3%)
Vomiting	--	5 (7.2%)	5 (5.3%)
Accidental overdose	1 (4.0%)	3 (4.3%)	4 (4.3%)
Diarrhea	--	3 (4.3%)	3 (3.2%)
Influenza	--	3 (4.3%)	3 (3.2%)
Viral infection	--	3 (4.3%)	3 (3.2%)
Weight increased	--	3 (4.3%)	3 (3.2%)

Source: Clinical reviewer-created from Summary of Clinical Safety, Table 3.d, p. 24, Study 12712B Clinical Study Report, Table 110, p. 266, and Study 12712B 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
[2] Grouping includes blood prolactin increased, hyperprolactinemia

Clinical Reviewer's Comment: As noted, in the OLE studies, there is no comparator, but AEs may inform what a picture of long-term use might show. (Note the Study 12712B subpopulation from lead-in Study 12709A is small, limiting interpretation.) The OLE studies appeared to have generally similar patterns of most common AEs to the

controlled study DB Periods. See Laboratory Findings below for further discussion regarding the AEs of hyperprolactinemia in Study 12712B.

Laboratory Findings

Hematology, Chemistry, and Urinalysis

In Study 12709A, safety assessments for serum hematology, chemistry, and urinalysis were collected at screening, randomization (Week 4/Baseline B, the start of the 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 differences between treatment groups. Upon examination of subjects with post-randomization potentially clinically significant (PCS) results 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 (from normal to high or low) for results 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.

Overall, laboratory-related AEs did not occur in >1 subject in any treatment group except for leukopenia (reported in two subjects each in the vortioxetine arms). One subject in the vortioxetine 10 mg group was withdrawn during the DB Period for a non-serious moderate AE of blood thyroid stimulating hormone increased (Table 10). The subject ((b) (6)) was an 11-year-old male at a Mexican study site without relevant medical history or concomitant medications. On Day 21 following randomization, his TSH was elevated (results not reported). He was withdrawn from the study and had not recovered at the safety follow-up visit on Day 63.

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 was one subject in the vortioxetine 20 mg group who had ALT >3x ULN. Hepatic laboratory-related AEs did not occur in >1 subject in any treatment group.

Clinical Reviewer's Comment: The laboratory results in the Study 12709A DB Period do not suggest a new safety signal.

In OLE Study 12712A, clinical laboratory assessments were collected at OLE extension A baseline (OLEXA, i.e., the end of the lead-in Study 12709A/12710A), Week 4, and Week 26/early termination. In Study 12712B, assessments were collected at OLE extension B baseline (OLEXB, i.e., the end of lead-in Study 12712A), Week 52, Week 78, and Week 104/early termination. In 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 were generally low, and upon examination of shift values by lead-in treatments, there were

subjects with elevated baseline values in all groups generally similarly. Overall, laboratory-related AEs occurred in generally low numbers of subjects. One subject, an 8-year-old female from lead-in Study 12709A at a study site in Poland, was withdrawn for an AE of neutropenia (Table 11). The subject received placebo during Study 12709A and had no relevant concomitant medical history or medications. On Day 29 of Study 12712A, the subject had a low neutrophil/leukocyte ratio of 15.5%, and vortioxetine was stopped on Day 31. On Day 34, the results had returned to within range.

Regarding hepatic safety, no subjects met criteria for Hy's Law. Six subjects in Study 12712A demonstrated elevated ALT and/or AST >3x ULN. One subject ((b) (6)), a 10-year-old female at a Mexican study site, was apparently treated for viral hepatitis, so the elevations appear unrelated to study drug. Other elevated results included elevation at baseline and normalization in the following measurements. Overall, hepatic laboratory-related AEs were low in number.

Prolactin

Prolactin was routinely measured in OLE Studies 12712A and 12712B, but not in the placebo-controlled studies 12709A or 12710A or the adult studies. No new related data was presented for Study 12712B (see the S-021 review for full details). As noted, an increase in mean prolactin occurred in Study 12712B (with a larger mean increase in adolescent subjects), with five subjects (5.3%) who had PCS high prolactin values and six subjects (6.4%) who had AEs of hyperprolactinemia or blood prolactin increased (two of the subjects with related AEs were also counted in Study 12712A). Since the cutoff date for S-021, total subjects with related PCS values or related AEs in Study 12712A were reported, including seven subjects (1.1%) who had PCS high prolactin at Week 4 and four subjects (0.6%) who did at the last assessment. Nine subjects (1.3%) had AEs of hyperprolactinemia or blood prolactin increased; however, one subject was taking concomitant risperidone, and one subject had a previously elevated baseline while on placebo in the lead-in study. As previously reported for Study 12712B, all subjects were asymptomatic, the dose was not changed for any subject, and all subjects completed the studies as planned.

> *Clinical Reviewer's Comment: As noted, in the OLE studies, there is no comparator, but safety results may inform what a picture of long-term use might show. Overall, the laboratory results from the now-finished OLE studies do not suggest a new safety signal, as hyperprolactinemia was added to the label with approval of S-022 at the same time as S-021 (see Section 3.2). As previously described in the S-021 review, the Applicant asserted that the lack of signs and symptoms of hyperprolactinemia and the transient temporal course argues against the clinical significance of the findings and referenced the results as consistent with a literature review of hyperprolactinemia with antidepressants (Coker and Taylor 2010). However, the Applicant completed a signal evaluation for the Periodic Benefit Risk Evaluation Report (PBRER) based on postmarketing reports and added hyperprolactinemia to the Company Core Data Sheet*

based on the OLE clinical trial events and postmarketing events (which occurred in adults in 22 cases, and in unknown ages in 12 cases).

Vital Signs

Each study visit included measurements of supine and standing blood pressure and pulse rate. Height (by stadiometer) and weight were measured at screening, completion, and periodically (i.e., monthly during Study 12709A, every 3 months during Study 12712A, every 6 months during Study 12712B).

Blood Pressure and Pulse Rate

In the Study 12709A 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 >3 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). A small number of AEs of tachycardia were reported across all treatment arms.

In Studies 12712A and 12712B, mean changes from baseline for vital sign measurements were also small, and the proportions of subjects with post-randomization PCS vital signs were low. The only PCS vital sign value in >3 subjects in Study 12712A or >2 subjects in Study 12712B was high orthostatic pulse rate, and the proportion was similar to the range demonstrated across all treatment groups in Study 12709A, including placebo. In Study 12712A, one subject discontinued for an AE of blood pressure decreased, and a small number of AEs of blood pressure decreased and tachycardia were reported.

Clinical Reviewer's Comment: Given that PCS orthostatic pulse rate values occurred across treatment arms in the Study 12709A DB period including placebo, and the proportions were similar in the OLE studies, the data do not appear to suggest a drug-related effect.

Weight and Body Mass Index

In the Study 12709A DB period, mean changes from randomization (DB baseline) for 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. There were slightly more subjects with PCS low weight or low BMI in the vortioxetine 20 mg group at the last assessment compared to the other groups (e.g., five and eight subjects with PCS low weight or low BMI, respectively, versus one and two subjects for vortioxetine 10 mg, respectively, and two subjects each for placebo). Comparatively, a higher number of subjects had PCS high weight or high BMI in the placebo arm (e.g., 11 and eight subjects in the placebo arm, versus three subjects each in the vortioxetine 20 mg arm, at last

assessment). A small number of AEs of weight decreased and weight increased were reported across all treatment arms.

> *Clinical Reviewer's Comment: In the short term, the differences in PCS low versus high weight or BMI could imply a dose-response effect of nausea potentially affecting appetite or food intake (i.e., between vortioxetine 20 mg and placebo), but the numbers are low enough overall and the differences comparatively small such that it is difficult to draw conclusions. The Applicant did not set PCS values for height.*

In Study 12712A, mean weight and BMI changes from OLEXA were small overall. PCS high weight was observed in an increasing proportion of subjects from Week 12 to Week 26, but the proportion with PCS high BMI was lower, per the Applicant reflecting the overall growth in the study population. Weight increased was reported as an AE in 21 subjects (3.2%), with a few AEs of weight decreased also reported.

In Study 12712B, the Applicant assessed weight in the context of BMI changes; measurements were available at OLEXB and Week 78 for 67 subjects. As noted by the Applicant, in the majority (55, 82%) of subjects, there was no shift or a shift of one percentile category in BMI. Three subjects shifted three percentile categories, and three subjects shifted upward above the normal weight BMI range: one from normal weight to obese, one from overweight to obese, and one within the obese percentiles. Five subjects (5.3%) reported AEs of weight increased.

> *Clinical Reviewer's Comment: Without a control group, it is difficult to draw conclusions from the weight/BMI changes in Studies 12712A and 12712B, which would ideally provide long-term weight impact data compared to the short-term efficacy studies. Examination of BMI, rather than weight, can account for natural growth to a degree, but confounding from MDD or other factors may obscure any drug-related changes.*

Electrocardiograms (ECGs) and QT

ECGs were collected on the same schedule as clinical laboratory assessments. In Study 12709A, 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 each arm had PCS high QTcB and the subject in the vortioxetine arm also had a PCS high QTcF (434 msec, change from baseline 65 msec); none were considered clinically significant or considered AEs. One AE of bundle branch block right was reported in the placebo group and a small number of AEs of tachycardia were reported across all treatment arms.

In Studies 12712A and 12712B, mean ECG changes from baseline were small. In Study 12712A, PCS values were reported in at total of six subjects for high RR interval in Study 12712A (at Week 4 (five subjects) and/or Week 26 (four subjects), and in a total of four subjects for PCS high QTcB (at Week 4 (two subjects) and/or Week 26 (three subjects); the QTcB increases were >60 msec, but none had QTcF >500 msec. None of the subjects had ECG-related AEs; four AEs of

electrocardiogram QT prolonged were reported in other subjects. A small number of AEs of tachycardia were reported.

In Study 12712B, no PCS values were reported in >2 subjects except for QTcF: four subjects had high QTcF (at Week 52 (three subjects) and at last assessment (three subjects)), all for QTcF increase >60 msec, but none had QTcF >500 msec. None of these subjects had ECG-related AEs; one AE of electrocardiogram QT prolonged was reported in another subject. One AE each of sinus bradycardia and sinus tachycardia was reported.

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

Immunogenicity

In the Study 12709A DB period, small numbers of subjects reported potentially related AEs: two subjects with rash (both vortioxetine 10 mg) and pruritis allergic (one each vortioxetine arm) and one subject each with drug eruption (vortioxetine 20 mg), drug hypersensitivity (vortioxetine 10 mg), and hypersensitivity (fluoxetine).

> *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. There were no suicides reported in Study 12709A or the OLE studies.

See Table 15 for the results of the Applicant's suicide/self-injury SMQ search in Study 12709A and the OLE studies. During the Study 12709A SB Period while receiving placebo plus BPI, any SIB-related AE occurred in three subjects (0.4%). During the DB Period, there were two SIB-related AEs reported in one subject each: suicidal ideation (on vortioxetine 10 mg, 0.7%) and suicide attempt (on placebo, 0.7%). For the subject on vortioxetine 10 mg, the AE of suicidal ideation was considered non-serious.

During Study 12712A, eighteen subjects (2.7%) reported SIB-related AEs: four subjects (1.1%) from lead-in Study 12709A and 16 subjects (4.8%) from lead-in Study 12710A. The one subject reporting an SIB-related AE in Study 12712B was from lead-in Study 12710A.

Table 15. Suicide/Self-Injury (SMQ) by Preferred Term by Study, All Patients Treated Sets

	12709A					12712A			12712B		
	SB Period	DB Period									
MedDRA Preferred Term	PBO + BPI	VOR 10 mg	VOR 20 mg	PBO	FLU	Lead-In 12709A	Lead-In 12710A	Total	Lead-In 12709A	Lead-In 12710A	Total
N	677	151	153	153	83	327	335	662	25	69	94
Subjects with any related AE (n (%))[1]	3 (0.4%)	1 (0.7%)	--	1 (0.7%)	--	4 (1.1%)	16 (4.8%)	18 (2.7%)	--	1 (1.4%)	1 (1.1%)
Suicidal ideation	1 (0.1%)	1 (0.7%)	--	--	--	2 (0.6%)	4 (1.2%)	6 (0.9%)	--	--	--
Intentional overdose	1 (0.1%)	--	--	--	--	--	8 (2.4%)	8 (1.2%)	--	--	--
Intentional self-injury	1 (0.1%)	--	--	--	--	1 (0.3%)	2 (0.6%)	3 (0.5%)	--	--	--
Suicide attempt	1 (0.1%)	--	--	1 (0.7%)	--	1 (0.3%)	3 (0.9%)	4 (0.6%)	--	--	--
Self-injurious ideation	--	--	--	--	--	--	--	--	--	1 (1.4%)	1 (1.1%)
Suicidal behavior	--	--	--	--	--	1 (0.3%)	--	1 (0.2%)	--	--	--
Suicide threat	--	--	--	--	--	1 (0.3%)	--	1 (0.2%)	--	--	--

Source: Clinical reviewer-created from Summary of Clinical Safety, Table 3.e, p. 26, Study 12709A, Study 12712A, and Study 12712B ADAE datasets
Abbreviations: AE = adverse event, BPI = brief psychosocial intervention, DB = double-blind, FLU = fluoxetine, MedDRA = Medical Dictionary for Regulatory Activities, PBO = placebo, SB = single-blind, SMQ = Standardized MedDRA Query, VOR = vortioxetine
[1] Subjects who had more than one suicide/self-injury-related AE were counted once for the total

> *Clinical Reviewer's Comment: The controlled DB Period data from Study 12709A do not demonstrate a higher incidence of SI/B-related AEs for vortioxetine versus placebo (in contrast to the results of Study 12710A, where the active drug arms had higher incidence than placebo). In the OLE studies, adolescents had a higher incidence of SI/B-related AEs than children. Given that the boxed warning for SI/B applies to pediatric patients and young adults, it is unclear why there appear to be differences between children and adolescents in this development program. However, overall, the numbers are small compared to the pooled analyses for the boxed warning.*

The Applicant also assessed suicidal ideation and behavior with the C-SSRS in the studies. In the Study 12709A DB Period, based on the C-SSRS, the proportion of subjects reporting any suicidal ideation was similar across treatment groups (≤4%); one subject (0.7%) reported suicidal behavior in the placebo group (Table 16). No subjects reported non-suicidal self-injurious behavior on the C-SSRS.

In the OLE studies, based on the C-SSRS, 37 subjects (5.6%) reported suicidal ideation in Study 12712A and four subjects (4.2%) reported suicidal ideation in Study 12712B. Five subjects (0.8%) reported suicidal behavior in Study 12712A and none in Study 12712B. Eleven subjects (1.7%) reported non-suicidal self-injurious behavior in Study 12712A and none in Study 12712B.

Table 16. Study 12709A Double-Blind Period Columbia-Suicide Severity Rating Scale Scores, All Patients Treated Set

Most Severe Columbia Suicide Severity Rating Scale Score	VOR 10 mg (N=149) n (%)	VOR 20 mg (N=153) n (%)	PBO (N=153) n (%)	FLU (N=82) n (%)
Any suicidal ideation or behavior	2 (1.3%)	3 (2.0%)	4 (2.7%)	3 (3.7%)
Any suicidal ideation	2 (1.3%)	3 (2.0%)	3 (2.0%)	3 (3.7%)
Wish to be dead	1 (0.7%)	2 (1.3%)	2 (1.3%)	--
Non-specific active suicidal thoughts	--	1 (0.7%)	1 (0.7%)	3 (3.7%)
Active SI with any methods (not plan) without intent to act	1 (0.7%)	--	--	--
Active SI with some intent to act, without specific plan	--	--	--	--
Active SI with specific plan and intent	--	--	--	--
Any suicidal behavior	--	--	1 (0.7%)	--
Preparatory acts or behavior	--	--	--	--
Aborted attempt	--	--	--	--
Interrupted attempt	--	--	--	--
Non-fatal suicide attempt	--	--	1 (0.7%)	--
Completed suicide	--	--	--	--
Non-suicidal self-injurious behavior	--	--	--	--

Source: Clinical reviewer-adapted from Study 12709A Clinical Study Report, Table 172, p. 556
Abbreviations: FLU = fluoxetine, PBO = placebo, SI = suicidal ideation, SIB = self-injurious behavior, VOR = vortioxetine
Note: Subjects with any suicidal ideation or behavior are counted once for the most severe score

Clinical Reviewer's Comment: As with SIB-related AEs, the controlled DB Period C-SSRS data from Study 12709A do not demonstrate higher C-SSRS reports of SIB for vortioxetine versus placebo.

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 considered by report of no or few related AEs, low and comparable-across-treatment-group AEs in the Study 12709A DB period, or small mean changes from baseline on the GBI regarding mania in the Study 12709A DB period, comparable to placebo. During the Study 12709A DB period, nausea and vomiting occurred at a higher rate in the vortioxetine groups than placebo, similar to the results found with adults (Table 12). Insomnia occurred in two subjects (1.3%) in the vortioxetine arm alone. See Section 8.3.4 subsections regarding details for hepatic safety (clinical laboratory assessments), for assessment of effects on growth (vital signs), and for QT prolongation (ECGs). See Section 8.3.9 regarding abuse liability.

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 the Study 12709A DB Period, the incidence of overall AEs was generally similar between sexes and between White and Black subjects across treatment arms.

Clinical Reviewer's Comment: Given the small numbers of subjects in racial categories other that White 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

No pregnancies were reported in Study 12709A or the OLE studies.

Pediatrics and Assessment of Effects on Growth

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

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the Study 12709A SB Period, one subject took an intentional overdose of placebo. During the DB Period, two subjects (1.3%) in the vortioxetine 20 mg arm and one subject each in the vortioxetine 10 mg arm (0.7%) and fluoxetine arm (1.2%) were reported to have taken accidental overdoses. Accidental overdose cases appeared to be generally of one extra tablet, e.g., by forgetting that the dose had already been administered.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant reports that from market introduction in 2013 through June 30, 2022, a total of 353 cases of off-label pediatric use of vortioxetine have been reported; where age was reported, the majority (≥90%) concerned use in adolescents. The Applicant reports that more than half of the cases did not co-report an adverse reaction, and the majority (89%) of those co-reported were nonserious and labeled. Nausea, vomiting, pruritis, and headache were the most common reactions (i.e., reported in >10 patients). The Applicant did not identify any new safety concerns.

Expectations on Safety in the Postmarket Setting

In addition to current labeling, which indicates vortioxetine only for adult MDD treatment and includes information about the lack of efficacy in 12-to-17-year-olds in Section 8.4 of the label, information about the lack of efficacy in the 7-to-11-year-old population will be added to Section 8.4 based on the data submitted in this supplement (see Section **Error! Reference source not found.**). Pediatric safety data are also included in Section 8.4. The inclusion of these data will inform healthcare professionals that the efficacy and safety of vortioxetine for

treatment of MDD in pediatric patients ages 7 to 17 years have not been established.

8.3.11. Integrated Assessment of Safety

The Applicant submitted sufficient information to adequately assess vortioxetine's safety profile in subjects ages 7 to 11 years. The safety profile for this population is generally similar to the adult safety data presented in the current vortioxetine label.

8.4. Conclusions and Recommendations

The results of Study 12709A do not support the use of vortioxetine for the treatment of MDD in pediatric patients ages 7 to 11 years, which will be reflected in Section 8.4 of the labeling along with safety information.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this submission.

10 Pediatrics

The Applicant was released from related PMR 2084-7 (see Section 3.2). The completion of Study 12710A and Study 12708A with submission of the CSRs and datasets for Study 12709A and Study 12712A fulfill the amended pediatric WR (see Section 3.2), as adjudicated by the Pediatric Exclusivity Board.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant is not pursuing an expanded indication based on the negative results from Study 12709A. Section 8.4 of labeling will address the findings of the pediatric clinical studies as follows, as discussed in consultation with the Division of Pediatric and Maternal Health:

> The safety and effectiveness of TRINTELLIX have not been established in pediatric patients.
>
> The safety and efficacy of TRINTELLIX were evaluated in two randomized, double-blind, placebo- and active-controlled 8-week studies in pediatric patients with MDD, one in patients 7 to 11 years of age (N=540 randomized) and one in patients 12 to 17 years of age (N=616 randomized). The primary efficacy endpoint for both studies was the change from baseline to week 8 in the Children's Depression Rating Scale-Revised (CDRS-R) total score. The CDRS-R assesses the severity of depression and change in depressive symptoms in children and adolescents with depression. TRINTELLIX was not superior to placebo in either study. Patients from the controlled 8-week studies were eligible to enroll in a 6-month open-label extension study (N=662 treated). Across the three studies, the most commonly observed adverse reactions to TRINTELLIX in pediatric patients 7 to 17 years of age were generally similar to those observed in adults *[see Adverse Reactions (6)]*.
>
> Antidepressants, such as TRINTELLIX, increase the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Hyperprolactinemia was previously added to Section 6.2 with the approval of labeling S-022 with S-021.

12 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is not appropriate or indicated based upon the data from this submission.

13 Postmarketing Requirements and Commitment

No new PMRs or PMCs will be issued. The Applicant was released from related PMR 2084-7 (see Section 3.2).

14 Division Director Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

15 Appendices

15.1. References

American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Arlington (VA): American Psychiatric Association.

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

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018, Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017, Lancet, 392:1789-1858.

Lebrun-Harris LA, Ghandour RM, Kogan MD, and Warren MD, 2022, Five-year Trends in U.S. Children's Health and Well-being, 2016-2020. JAMA Pediatr; 176(7):e220056.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2018, Key Substance Use and Mental Health Indicators in the United States: Results From the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53), Rockville (MD): Center for Behavioral Health Statistics and Quality, SAMHSA, accessed June 1, 2020, https://www.samhsa.gov/data/.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 12709A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: See Applicant listing (Form 3454)		
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: With S-021	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) See Applicant listing		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

As previously noted for Supplement 021, Principal Investigator [redacted] (b) (6) at United States site [redacted] (b) (6) acted in honoraria for Takeda and acted as a [redacted] (b) (6) which resulted in 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 [redacted] (b) (4) and medical and safety data was to be evaluated by Lundbeck. Ratings consistency was to be evaluated by Lundbeck and CROs [redacted] (b) (4) and [redacted] (b) (4)

Clinical Reviewer's Comment: The Applicant's precautionary steps appear appropriate. Further, Site (b) (6) enrolled (b) (6) subjects (of 683 total, with one randomized, of 540 total), which appears unlikely to influence the study findings.

15.3. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this supplement.

15.4. Clinical Pharmacology

Bioanalysis: Plasma concentrations of vortioxetine was quantified using liquid chromatography with tandem mass spectrometry (LC-MS/MS; Bioanalytical report: 16749; Validation Report: 17153 and (b) (4) 22082.001). The calibration range for vortioxetine is 0.2 ng/mL to 50 ng/mL. 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 lower limit of quantitation (LLOQ)). More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation. Carryover effect was observed in the run IDs 19 and QU20 for some zero samples following the highest calibration and quality control (QC) samples. However, this did not affect the study samples. The analytes in human plasma were stable over 19 months when stored at -20°C and -80°C. The analytes in human plasma were stable over 4 hours at room temperature, five freeze-thaw cycles following -20°C/-80°C and autosampler stability at 4°C over 73 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.*

Population PK analysis: Of 273 patients, 502 plasma concentrations were collected. Ninety-six plasma concentrations from 37 patients were below the LLOQ and two samples from a patient were missing sampling date and these samples were removed from the analysis. A total of 404 plasma concentrations from 235 children 7 to 11 years old with MDD were used for the 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 initial structural model used in Study 12708A was applied to data from Study 12709A. The results suggest that a two compartment PK model with first-order absorption and elimination adequately described the PK of vortioxetine in children 7 to 11 years old with MDD. Of the covariates (sex, age, weight, height, body mass index (BMI), lean body mass (LBM) and, creatinine clearance and region) tested, the region was found to be an influential covariate on oral clearance. The final model included only region as a covariate.

The dose-normalized (equivalent to 10 mg) mean plasma exposures (Cmax,ss and AUCss) to vortioxetine at steady-state in children from Study 12709A were found to be relatively similar to those observed in adolescents from Study 12708A but lower (Cmax,ss: 41% and AUCss: 32%) than those observed in children from Study 12708A. The exposures in children from Study 12709A were also lower (Cmaxss: 22 and 28% and AUCSS: 32% and 32%) than those observed in adolescents from Study 12710A and adults from pooled studies, respectively (Table 17). The rationale for the lower exposures observed in children from Study 12709A remain unclear. In Study 12710A, the plasma exposures in adolescents were relatively similar to those observed in adults and children (Table 17**Error! Reference source not found.**). Given the variability in plasma exposures to vortioxetine is high, the plasma exposures to vortioxetine in children from Study 12709A were deemed to be comparable to adolescents and adults.

Table 17. Model predicted PK parameters of vortioxetine at steady state in children and adolescents with depressive or anxiety disorder, and in healthy adults

Parameter	Children (Study 12708A)	Children (Study 12709A)	Adolescents (Study 12708A)	Adolescents (Study 12710A)	Adults (pooled popPK)
$C_{max,SS}$ (ng/mL)[a]	17 ± 10	10.1 ± 7.8	9.3 ± 4.4	13 ± 9.2	14±8.5
AUC_{SS} (ng·h/mL)[a]	302 ± 182	205 ± 95	177 ± 84	301 ± 221	294±202
CL/F (L/h)	42±23	67 ± 49	62±30	51 ± 39	37±15

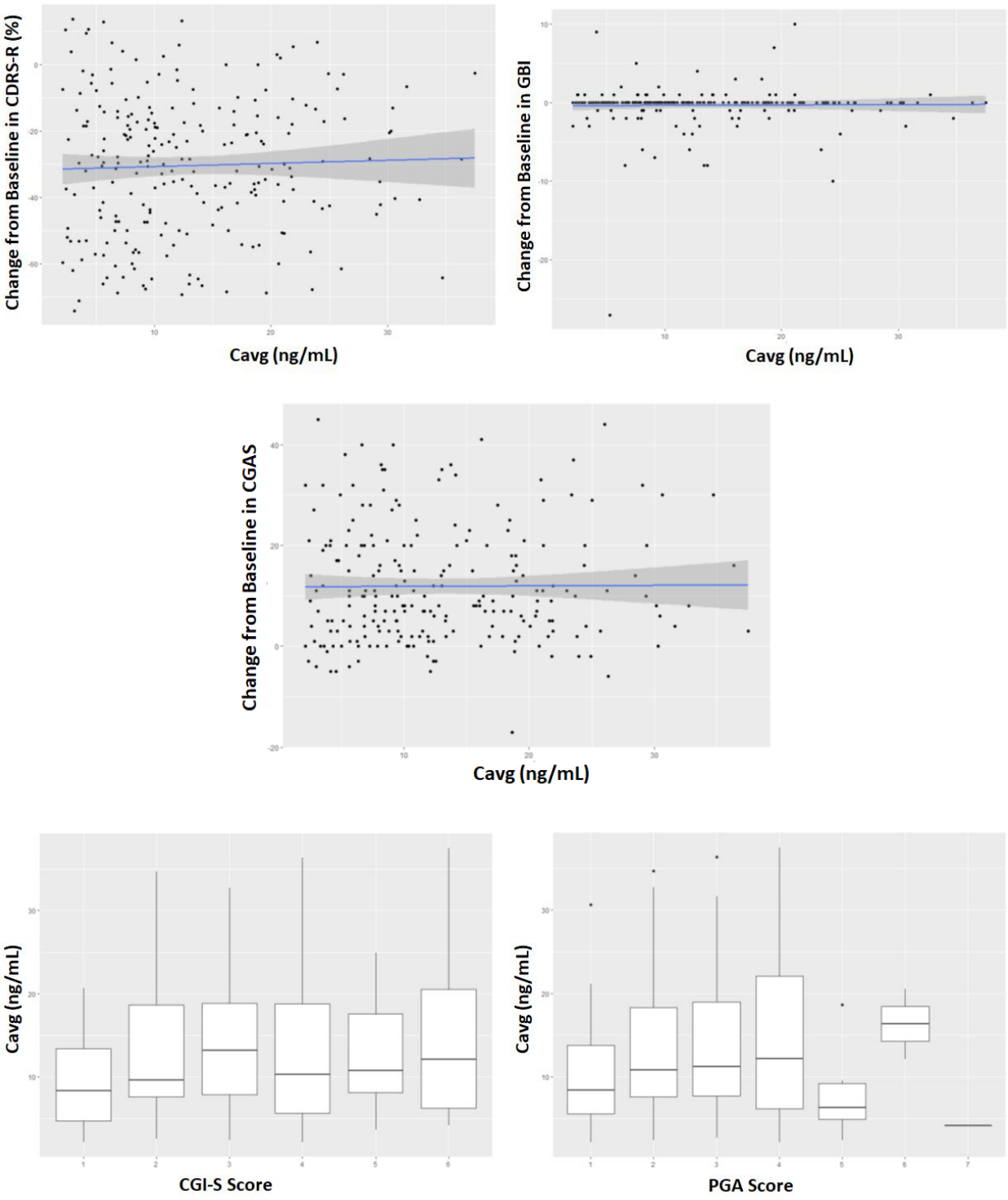
a Simulated values to steady-state and dose-normalised to 10 mg

Source: Panel 10, Study 12709A, Pop PK/PD report

Reviewer's Comments: The PK characterization of vortioxetine in children 7 to 11 years with MDD using population PK approach appears acceptable. The simulated dose-normalized plasma exposures (Cmax,ss and AUCss) to vortioxetine at steady state in children 7 to 11 years with MDD are comparable to those observed in adolescents adults.

The exposure-response relationship between the change in the efficacy parameters (CDRS-R, GBI, CGAS (treated as continuous variables), CGI-S and PGA) from baseline to Week 8, and plasma exposure (Cavg) of vortioxetine was investigated through non-linear and linear regression analyses and the results are shown in Figure 3.

Figure 3. Relationship Between the Efficacy Parameters (CDRS-R, GBI, CGAS, CGI-S and PGA) and Plasma Exposure (Cavg) of Vortioxetine



Source: Panel 8 and Panel 9, Study 12709A, Pop PK/PD report

Reviewer's Comments: There was no apparent relationship between plasma exposures and efficacy parameters observed. This suggests that variability in plasma exposures to vortioxetine observed in Study 12709A is not expected to impact the efficacy.

15.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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

/s/

BERNARD A FISCHER on behalf of TIFFANY R FARCHIONE
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