NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 22567/s021
Priority or Standard	Priority
Submit Date(s)	08/01/2019
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PDUFA Goal Date	02/01/2020
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience
Review Completion Date	1/31/2020
Established/Proper Name	Vilazodone hydrochloride
(Proposed) Trade Name	Viibryd
Pharmacologic Class	Selective Serotonin Reuptake Inhibitor
Code name	N/A
Applicant	Allergan Sales, LLC
Dosage form	10 mg, 20 mg, and 40 mg tablets
Applicant proposed Dosing Regimen	20 mg to 40 mg once daily with food
Applicant Proposed Indication(s)/Population(s)	Major Depressive Disorder (MDD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Major Depressive Disorder (MDD) in adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	370143000
Recommended Dosing Regimen	20 mg to 40 mg once daily with food

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DPMH=Division of Pediatrics and Maternal Health
PLT=Patient Labeling Team
ADL=Associate Director of Labeling (DP)
PE=Pediatric Exclusivity

Glossary

AE	adverse event
CDRS-R	Children's Depression Rating Scale-Revised
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CMC	chemistry, manufacturing, and controls
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-4th Edition Text Revision
ECG	electrocardiogram
HD	high dose
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAS	juvenile animal study
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version
LD	low dose
MedDRA	Medical Dictionary for Regulatory Activities
MD	mid dose
MDD	Major depressive disorder
MMRM	mixed effects model for repeated
NDA	new drug application
NOAEL	No Observed Adverse Effect Level
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	postnatal day
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
PWR	Pediatric Written Request

1 Executive Summary

1.1. Product Introduction

Vilazodone is an antidepressant that selectively inhibits central nervous system serotonin reuptake. It is also a partial agonist at serotonergic 5-HT1A receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown. Vilazodone is available as 10 mg, 20 mg and 40 mg film-coated tablets for oral administration. It was approved for the treatment of Major Depressive Disorder (MDD) in adults in 2011.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The pediatric clinical studies submitted in this supplemental application were negative and the Applicant is not seeking an expansion of the indicated population.

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MDD is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. In severe cases, MDD can result in suicide. • The most recent National Survey of Children's Health study revealed a prevalence of pediatric MDD of 3.2% (approximately 1.9 million US children and adolescents).	MDD is a debilitating and chronic illness, the leading cause of disability worldwide, and a major contributor to the global burden of disease. Although less common than in adults, it is none the less a public health concern among pediatric patients.
Current Treatment Options	• To date, only two antidepressants have been approved for treatment of MDD in pediatric patients. Several other antidepressant clinical trials have failed to demonstrate efficacy in pediatrics.	There is a need for more treatment options for pediatric MDD.
Benefit	• The vilazodone pediatric clinical trails failed to demonstrate efficacy.	The indication will not be expanded to include pediatric patients.
Risk and Risk Management	• This pediatric data base included adverse events related to suicidal ideation and behavior, which is consistent with the boxed warning in current labeling. • The most common AEs include: nausea, vomiting, diarrhea, dizziness, and abdominal pain.	Safety findings will be reflected in Section 8.4, and the Boxed Warning will be retained. Based on the data presented with this supplement, the pediatric and adult safety profiles for vilazodone are largely similar.

1.4. Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

MDD is a serious and life-threatening condition characterized by depressed mood and loss of interest or pleasure coupled with significant weight changes, change in sleep pattern, fatigue, psychomotor agitation or retardation, decreased ability to concentrate and recurrent thoughts of death or suicide. MDD is the leading cause of disability worldwide,[1] and more than 17 million adults in the United States may experience an episode of depression in a given year.[2] The most recent National Survey of Children's Health study revealed a prevalence of pediatric MDD of 3.2% (approximately 1.9 million US children and adolescents).

2.2. Analysis of Current Treatment Options

Although pediatric and adult MDD are symptomatically similar, the response to treatment between these populations is markedly different. To date, only two antidepressants—fluoxetine and escitalopram—have demonstrated safety and effectiveness in adequate and well-controlled studies with resultant pediatric indications in product labeling. Clinical studies of other antidepressants have failed to demonstrate efficacy in pediatric patients despite efficacy in adults (e.g., desvenlafaxine, duloxetine, paroxetine, sertraline, venlafaxine). Fluoxetine is approved for the treatment of MDD in pediatric patients ages 8 to 17 years. However, escitalopram is approved for MDD only in patients age 12 years and older.

Because of the differential response to treatment between adult and pediatric patients, extrapolation of efficacy from adults to pediatrics is not feasible and pediatric clinical studies are required in order to gain a marketing indication. The current supplemental application consists of data from clinical trials evaluating the safety and effectiveness of vilazodone for the treatment of MDD in pediatric patients. These studies were designed to fulfill post-marketing requirements and the terms of a Pediatric Written Request.

[1] https://www.who.int/news-room/fact-sheets/detail/depression. Accessed January 30, 2020.
[2] https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed January 30, 2020.

Table 1. Summary Table of Antidepressants Labeled for MDD in the Pediatric Population

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

Source: Fluoxetine and escitalopram labels

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Vilazodone was approved in January 2011 for the treatment of MDD in adults. All clinical studies in support of the MDD indication were conducted under Investigational New Drug (IND) application 054613.

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of initial approval, the Agency issued the following post-marketing requirements (PMRs) for deferred pediatric studies under the Pediatric Research Equity Act (PREA):

1723-1 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing of vilazodone in the relevant pediatric population.

1723-2 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

1723-3 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a second study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study may be a fixed-dose study.

1723-4 To support the use of vilazodone in children less than 13 years of age, you must conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study.

On January 30, 2012, the Applicant submitted a Proposed Pediatric Study Request (PPSR), and a Pediatric Written Request (PWR) was issued on February 28, 2012. The terms of the PWR reflected the above PREA PMRs.

The Applicant submitted the final study report for the juvenile animal study on September 19, 2013. On April 14, 2014, he Division notified the Applicant that PMR 1723-4 was fulfilled.

On April 9, 2018, the Applicant requested changes to the PWR, including removing the pediatric pharmacokinetic (PK) study, modifying the age groups for the two efficacy studies, modifying the gender distribution, and changing the timing of the interim analysis and timeframe for submitting the final study reports. PMR 1723-1 was formally released on April 21, 2014. In lieu of a standalone PK study in pediatric patients, the Applicant agreed to incorporate sparse sampling in the safety and efficacy study in patients with MDD age 13 to 17 years and use that information to guide dose selection in a second safety and efficacy study in patients with MDD age 7 to 17 years. The revised PWR was issued on July 18, 2018.

Deferral extensions for the PREA PMRs 1723-2 and 1723-3 and were granted on August 28, 2015. On January 17, 2018, the Division released the Applicant from PMR 1723-2 and issued a new PMR:

1723-12 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 12 to 17. Conduct a study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled study. This study must be a fixed-dose study.

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

4.1. Office of Scientific Investigations (OSI)

No site inspections were conducted.

4.2. Product Quality

In Module 3, the Applicant provided CMC information for the new 5 mg pediatric dosage form used in the pediatric studies. Based on the CMC assessment (See NDA-022567-SUPPL-21 product review), the risk associated with using this non-commercial 5 mg pediatric strength in clinical studies is low. This supplement is recommended for APPROVAL from the standpoint of CMC. The 5 mg pediatric dosage form used in the pediatric studies is not to be commercialized.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) with partial agonistic activity at 5HT1A receptors. As noted above, the initial approval letter and PWR required a juvenile animal study (JAS) to support the use of vilazodone in children under 13 years of age. The Applicant submitted a protocol to evaluate neurological/behavioral and reproductive development in juvenile rats on December 29, 2011. The Division provided comments to the protocol on January 31, 2012, and requested that the Applicant conduct the following additional tests:

- Sperm analysis in reproductive assessment
- Measurements of bone length and density.

The final study report was submitted to the NDA (SDN 322) on September 19, 2013, prior to enrolling children ≤12 years of age. The current efficacy supplement did not contain any nonclinical studies but the label will be updated with relevant findings from the JAS.

In the 13-week juvenile animal study, rats were orally gavaged once daily with vilazodone doses of 0, 10, 50, and 200 mg/kg from postnatal day (PND) 21 to 90 followed by a 3-week dose-free period. There was an absence of grooming in open field observations during the treatment period which was accompanied with red/clear material observed up to 3 hours post dose starting at 50 mg/kg in the clinical observations. An irreversible behavioral deficit (a lack of habituation in an acoustic startle test) was observed in males at the highest dose and in females at ≥50 mg/kg both during drug treatment and after recovery period. Drug treatment appeared to have affected habituation in a novel environment. The No Observed Adverse Effect Level (NOAEL) for males was 50 mg/kg/day and for females it was 10 mg/kg/day which were 8.2 times for males and 1.02 times for females compared with the maximum tested pediatric dose of 30 mg. There was a delay in sexual maturation starting at ≥50 mg/kg and a decrease in femur density in females observed at 200 mg/kg. AUC exposures for these findings at the respective NOAELs of 10 mg/kg and 50 mg/kg are 1.02 times and 3.1 times the AUC for the parent drug at a maximum tested pediatric dose of 30 mg/day.

The neurobehavioral deficit, sexual delay and decrease bone density will be described in the label in section 8.4 under Juvenile Animal Studies. See 10, below, for the Division's proposed language excerpted from the label.

Juvenile Animal Toxicity Data

In a juvenile animal study, male and female rats were treated with vilazodone (10, 50, and 200 mg/kg/day) starting on PND 21 through 90. A delay in the age of attainment of vaginal patency (i.e., sexual maturation) was observed in females starting at 50 mg/kg/day with a NOAEL of 10

mg/kg/day. This NOAEL was associated with AUC levels equal to those measured at a maximum dose tested in pediatrics (30 mg). Adverse behavioral effects (lack of habituation in an acoustic startle test) were observed in males at 200 mg/kg and females starting at 50 mg/kg both during drug treatment and the recovery periods. The NOAEL for this finding was 50 mg/kg for males and 10 mg/kg for females, which was associated with AUC levels greater than (males) or equal to (females) those observed with the maximum dose tested in pediatric patients. An 8% decrease in femur mineral density was observed in female rats at 200 mg/kg, compared to the control group. The NOAEL for this finding was 50 mg/kg, which was associated with an AUC level greater than those measured at the maximum dose tested in pediatrics.

5.2. Toxicology

5.2.1. Other Toxicology Studies

Juvenile Animal Study

13-week oral (gavage) toxicity study with recovery in juvenile animals/Study No. 69563:

Key Study Findings

- A drug effect was observed on female sexual maturation. This was reflected by a delay of 1.3 to 2.7 days in vaginal patency at 50 and 200 mg/kg/day. This delay at 50 and 200 mg/kg is occurring despite an increase in body weight of 4% and 11% respectively.
- In the acoustic startle test, there was an indication of failure to habituate in males at 200 mg/kg/day and females starting at ≥50 mg/kg/day, both during drug treatment and after the recovery period. A statistically significant decrease in the overall maximum response values (MAX) was observed in high dose males (HDM; 20%) and high dose females (HDF; 40%) compared with controls on PND 61. This effect continued to be observed in the same dose groups on PND 104.
- A statistically significant decrease in femur density (8%) was noted in female rats at 200 mg/kg.
- The NOAEL for the delay in sexual maturation and the decrease in femur density are 10 mg/kg and 50 mg/kg, respectively in females. The AUC levels at these doses were 1.02 times and 3.1 times the AUC for the parent drug at the maximum dose tested in the pediatric population (30 mg). The NOAEL for irreversible failure to habituate in an acoustic startle test was 50 mg/kg for males and 10 mg/kg for females in this study. The AUC levels at these doses were 8.2 times for males and 1.02 times for females of the AUC levels observed at the maximum dose tested in the pediatric population.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 10 (low dose; LD), 50 (mid dose; MD), and 200 (high dose; HD) mg/kg/day; once daily from PND 21 to 90. All treatment groups received the same volume (10ml/kg)
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous 0.25% hydroxypropyl-methylcellulose
Species/Strain:	Rat/Crl:CD (SD)
Number/Sex/Group:	40/sex/dose for main study group
Age:	PND 21
Satellite groups/ unique design:	TK group had 27/sex/dose Vilazodone was administered to juvenile male and female rats from PND 21 to 90. Beginning on PND 91, up to 20 rats/sex/group assigned to the post-treatment period remained on the study until GD 15 (F) or equivalent postnatal day (M) without treatment. Neurobehavioral assessments were conducted on PND 61 (prior to daily dose administration) and on PND 105 (recovery). For reproductive assessment, males were observed for balanopreputial separation beginning on PND 35 and females were observed for vaginal patency beginning on PND 25. For estrous cycle testing, vaginal smears were taken for each female assigned to the post-treatment period for 10 consecutive days prior to cohabitation and continuing until evidence of mating was observed or until the end of the mating period. Each mating pair was examined daily for the presence of the copulatory plug or the presence of sperm in the vaginal lavage. Animals were a minimum of 113 days old at the start of gestation. When evidence of copulation was not detected after 10 days of cohabitation, the female was placed with another male from a treatment group with previous evidence of mating for an additional 5 days. When evidence of mating was not apparent for a total of 15 days, the females were placed in individual cages with nesting material until necropsy.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results:

Parameters	Major Findings
Mortality	No test article related mortality.
Clinical signs	Dose-dependent observation of red and/or clear material around the nose and/or mouth starting at MD for males (MDM) and HD for females (HDF) throughout the treatment period following dose administration. This finding was observed up to 3 hours (the last time point for observation post dose) but did not persist to the next morning.
Body weights	Unremarkable
Hematology	Unremarkable
Clinical chemistry	Unremarkable
Gross pathology	Unremarkable
Organ weights	Unremarkable
Histopathology Adequate battery: Yes; 3 brain sections evaluated.	Unremarkable
Special evaluation: Locomotor activity	No remarkable drug related findings that were beyond historical control data.
Special evaluation: Startle response	There was a drug effect on auditory startle responses on both PND 60 and PND 104. Drug treated rats had a decrease in overall MAX values, (20% in HDM and 40% in both MDF and HDF on PND 60 compared to control). For these dose groups, the values were lower than historical control range (see Table 2). The overall MAX values reached a statistical significance at the HDF (p=0.019) and a trend for statistical significance was seen for HDM and MDF (p=0.057). Similarly, on PND 104, the overall MAX values continued to be lower for treatment groups. Mean values were 33%, 27% and 28% lower than controls in HDM, MDF and HDF, respectively during recovery. The overall MAX values reached a statistical significance in HDM (p=0.028) and a trend was observed for HDF (p=0.052) . This apparently irreversible drug effect is likely to be a pharmacological effect based on the established literature finding that 5HT1A agonists block prepulse inhibition of acoustic startle reflex (Rigodon, et al., *J Pharmacol Exp Ther*, 1992).

Parameters	Major Findings
Special evaluation continued: Functional observational battery	In open field observations, an absence of grooming (0.0 counts) was observed in all drug treated groups as compared with controls (0.2 counts) on PND 61. The Applicant states that absence of grooming in a 2-minute observation period is a normal finding in rats and is not considered to be test article-related. However, based on the clinical observations of red/clear staining as a dose-responsive effect observed up to 3 hours postdose (the last time point for daily observations), this Reviewer believes that this finding is drug-mediated, although transient. Decreased grooming is consistent with published literature for rodent models of depression, Alzheimer's and Parkinson's and after administration of D2 receptor antagonists (Kalueff, et al., *Nat Rev Neurosci*, 2016).
Special evaluation continued: Biel water maze	No remarkable drug-related findings that extended beyond the historical control data.
Special evaluation continued: Sexual maturity	No remarkable drug-related effects on the mean age of attainment of balanopreputial separation in males. In females, there appeared to be a delay in the mean age of attainment of vaginal patency in MD (34.1 days) and HD (35.5 days) compared with the concurrent control group (32.8 days) and mean historical control group (32.7 days) (see Table 3). The values for day of attainment at the HD was higher than 3 standard deviations above the range for the historical control values. Specifically, 2, 3, 9, and 19 females in C, LD, MD and HD reached vaginal patency later than PND 35, which is the highest range for historical control values. This delay at the MD and HD, is occurring despite an increase in body weight of 4% and 11%, respectively. Therefore, this reviewer considers the delay in the mean age of attainment of vaginal patency at both the MD and the HD to be drug-related.
Special evaluation: Reproductive toxicity	No remarkable drug-related effects beyond historical control data for reproductive performance, intrauterine parameters or spermatogenesis endpoints.
Special evaluation: Bone density	A statistically significant decrease in femur density (8%) was observed in the proximal femur of HDF (see Table 4). There were no historical control comparisons for bone density parameters.

Parameters	Major Findings
Toxicokinetics	Oral administration of vilazodone resulted in systemic exposure to both parent and M17 metabolite. In general, exposure to both entities increased dose proportionally for AUC and less than dose proportionally for Cmax. There was no consistent gender difference in exposures to vilazodone or for the M17 metabolite. Parent drug accumulation was clearly evident over time, with metabolite following the opposite direction, particularly for females at the MD and HD. Exposure to metabolite ranged from 1% to 9% of the parent drug with a decrease observed on PND 90 compared with PND 21. Tmax for parent drug was 3 to 5 hours post dosing and for M17 it was 3 to 8 hours. Half-life for parent was 2 to 6 hours for parent and shorter for M17 metabolite (2 to 4 hours). See the Pharm/Tox Appendix for tables excerpted from P. 50 to 51 of the study report (seeTable 27 and **Table 28**).

LD: low dose; MD: mid dose; HD: high dose.

Table 2. Summary of Startle Response Data [Mean Overall Maximum Response Values (MAX) on PND 60 and PND 104 in Juvenile Rats]

Parameter	0	10	50	200	Mean HC Range (Min-Max)
PND 60					
MAX in males	0.955	1.163	0.831	0.727+	1.074 (0.87-1.3)
MAX in females	1.063	0.896	0.679+	0.634*	0.840 (0.674-1.056)
PND 104					
MAX in males	1.385	1.196	1.136	0.931*	N/A
MAX in females	1.17	0.933	0.868	0.845+	N/A

The table is created by the Reviewer using the Applicant's data and historical control (HC) data.
*Significantly different from control group, p<0.05; +sTrend for statistical significance from control group, p=0.056; N/A=Not Available

Table 3. Summary of Sexual Maturity Data in Juvenile Animals Treated with Vilazodone PND 21 to 90

Parameter	0	10	50	200	Mean HC Range (Min-Max)
Balanopreputial separation (PND)	45.2	45.7	45.9	46.3	44.6 (42.3-48.2)
Body weight (g) at BP separation	258.7	260.4	255.9	250.2	235.4 (202-273)
Vaginal patency (PND)	32.8	32.9	34.1**	35.5**	32.7 (31.6-34.0)
Body weight (g) at patency	118	118	122.9	131.6**	111.0 (99.3-119)

The table is created by the Reviewer using the Applicant's data and historical control (HC) data.
**Significantly different from control group, p<0.01

Table 4. Bone Densitometry Data for the Proximal Femur in Female Rats

Parameter	0	10	50	200	HC Control Data
Mineral content (g)	0.13	0.13	0.12	0.12	N/A
Bone area (cm^2)	0.55	0.55	0.54	0.55	N/A
Bone mineral density (g/cm^2)	0.24	0.23	0.23	0.22*	N/A

The table is created by the Reviewer using the Applicant's data. No historical control (HC) data were available for bone density parameters.

*Significantly different from control group, $p<0.05$; N/A = Not Available

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant has submitted information on the pharmacokinetics of vilazodone in pediatric patients ages 7 to 17 years. As stipulated by the PWR, the Applicant first conducted an efficacy and safety study in patients 12 to 17 years of age with MDD. This study incorporated sparse PK sampling in order to assess dose-response relationships and guide the selection of doses for the second efficacy study in children and adolescents. The dose selection for the second trial in patients ages 7 to 17 years was informed by the PK data from the first study. Sparse PK samples collected from both efficacy studies were used to elucidate vilazodone PK in children and adolescent patients via a population PK approach. The PK endpoints for vilazodone included clearance and volume of distribution. The study was prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for vilazodone, with at least 80% power. A summary (mean, median) of PK parameters such as half-life was also reported. The Applicant met the terms of the PWR.

6.2. Summary of Clinical Pharmacology Assessment

The Applicant has fulfilled the requirements outlined in the PWR. The study report (VLZ-MS-08) discusses the PK and pharmacokinetic/pharmacodynamic (PK/PD) analysis conducted by the Applicant. The data for the population PK and PK/PD model development originated from two studies in pediatric and adolescent patients with MDD. Based on the results of modeling and simulation, and considering the vilazodone tablet strengths available (5 mg, 10 mg, and 20 mg), the dosing schemes selected were expected to lead to similar titration schedules and steady-state exposures from treatment with 20 mg and 40 mg in adult patients, respectively.

In both studies VLZ-MD-21 and VLZ-MD-22, vilazodone (15 mg/day or 30 mg/day) or placebo was administered for 8 weeks. 480 subjects (median body weight 63.7 kg and median age 15 year), with a total of 2524 observations of vilazodone were included in the PK analysis (Table 5, Table 6).

Table 5. Number of Subjects and Number of Vilazodone Observations in the PK Analysis Data Set

Study / Treatment arm	Number of subjects	Number of PK observations Included
VLZ-MD-21		
15mg	156	933
30mg	165	999
All	321	1 932
VLZ-MD-22		
15-30mg	159	592
All		
All	480	2 524

Source: Table 1 on page 17 in vlz-ms-08.pdf

Table 6. Baseline Continuous Covariate Statistics for the PK Analysis Data Set, Stratified by Study

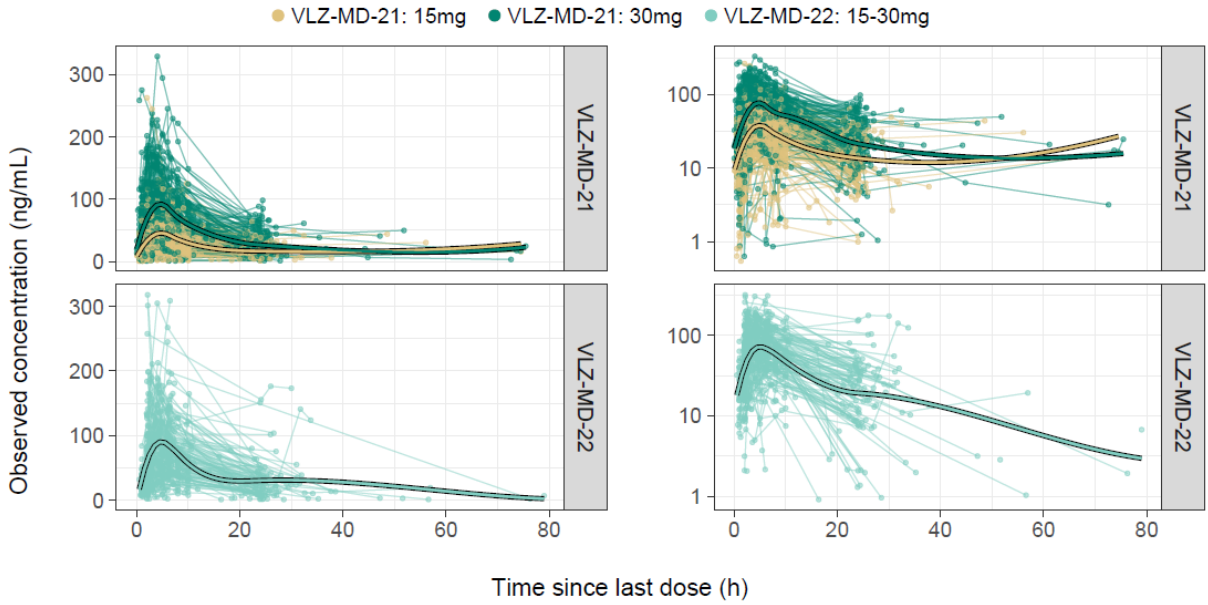
Covariate		VLZ-MD-21	VLZ-MD-22	All
Age (years)	min **median** max	12.0 **15.0** 17.0	7.00 **13.0** 17.0	7.00 **15.0** 17.0
	mean (SD)	14.8 (1.60)	13.1 (2.85)	14.2 (2.24)
	N	321	159	480
Body weight (kg)	min **median** max	31.5 **67.6** 140	21.4 **57.6** 172	21.4 **63.7** 172
	mean (SD)	70.7 (20.4)	62.2 (25.1)	67.9 (22.4)
	N	321	159	480
Height[a] (cm)	min **median** max	138 **165** 190	120 **159** 185	120 **164** 190
	mean (SD)	166 (9.30)	157 (13.2)	163 (11.5)
	N	321	159	480
CDRS-R	min **median** max	40.0 **57.0** 81.0	40.0 **57.0** 85.0	40.0 **57.0** 85.0
	mean (SD)	57.2 (8.62)	58.4 (9.38)	57.6 (8.89)
	N	321	159	480

[a] Height at screening. CDRS-R: Children's Depression Rating Scale - Revised; SD: standard deviation

Source: Table 2 on page 17 in vlz-ms-08.pdf

The observed plasma concentration data is show in Figure 1.

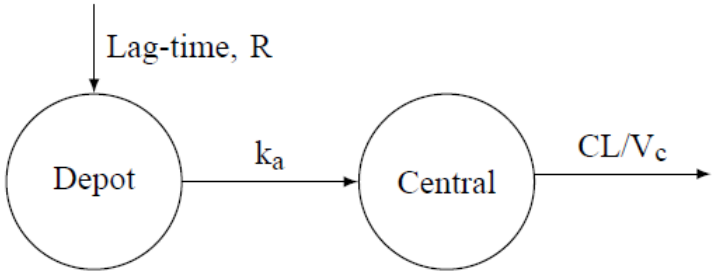
Figure 1. Observed Plasma Concentrations Versus Time Since Last Dose, Stratified by Study



Source: Figure 2 on page 22 in vlz-ms-08.pdf
Note: Each line represents the data for one subject and is colored by the treatment arm. The left panels represent the data on a linear scale and the right panels represent the data on a semi-logarithmic scale. Solid lines are smooths.

The structure of the rich and sparse PK model for vilazodone was a one compartment model with initial lag-time followed by sequential zero- and first-order absorption and a first-order elimination from the central compartment depicted in Figure 2.

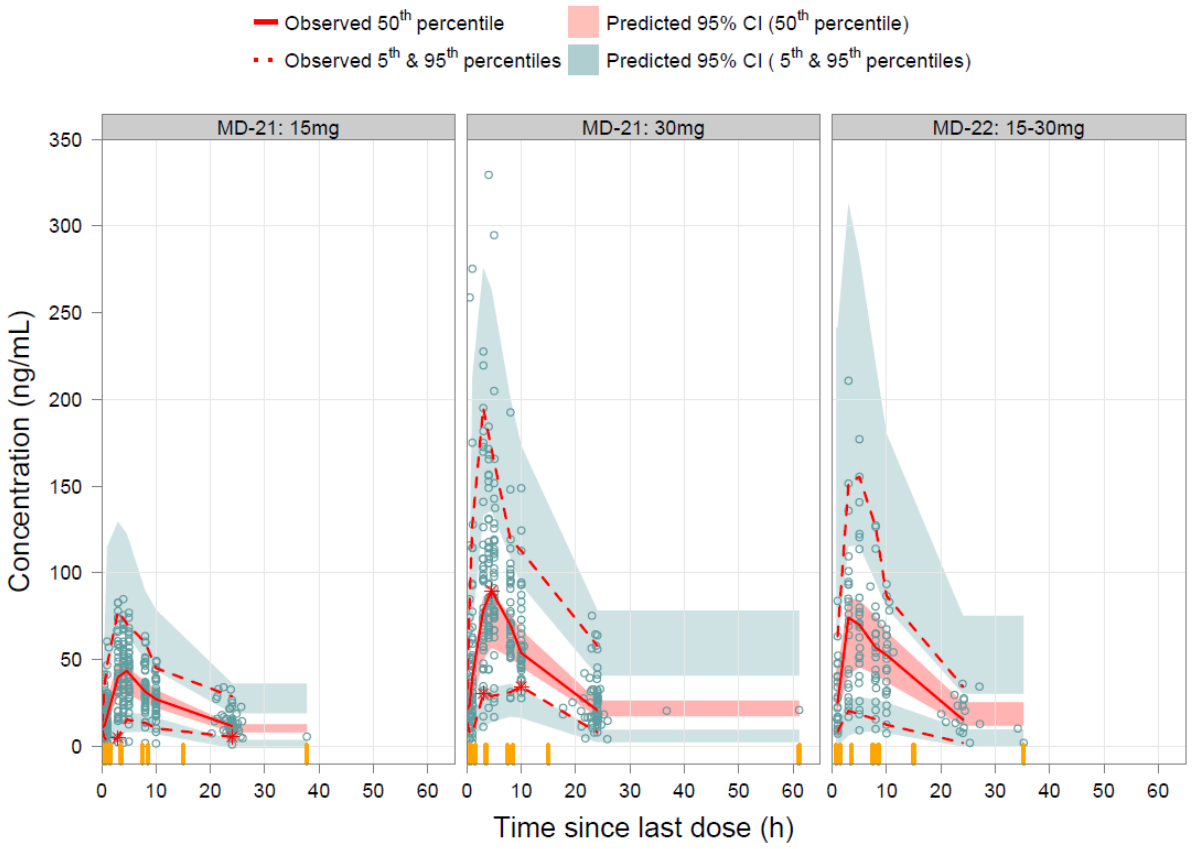
Figure 2. Schematic Representation of the Structure of the Rich and Sparse PK Model for Vilazodone



Source: Figure 19 on page 43 in vlz-ms-08.pdf
Note: The absorption of vilazodone is governed by an initial lag-time followed by zero-order absorption rate (R) into a depot-compartment. Vilazodone is absorbed from the depot compartment into the central distribution compartment with first-order absorption rate constant (ka). The one-compartment disposition model is parameterized with apparent clearance (CL/F) and apparent central volume of distribution (Vc/F).

The model fit along with visual predictive check is shown in Figure 3.

Figure 3. Visual Predictive Check of Vilazodone Concentrations, for the Rich PK Model, Stratified by Study and Treatment Arm



Source: Figure 20 on page 45 in vlz-ms-08.pdf
Note: Vilazodone concentrations are displayed versus time since last dose and stratified by the study and arm. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model. The red stars represent the observed percentiles outside the corresponding 95% confidence interval. The observed data are indicated by open circles. Orange vertical bars are the breaks for the bins.

The estimates of PK parameters are provided in Table 7.

Table 7. Parameter Estimates of the Rich PK Model With CL and V_c on a Linear and Log-Scale

		Rich PK model		Log-transformed CL/F and Vc/F	
	Unit	**Value**	**RSE (%)**	**Value**	**RSE (%)**
CL/F[a]	L/h	30.3	4.77		
V_c/F[a]	L	451	6.24		
k_a	h^{-1}	1.14	15.7	1.18	14.4
R	mg/h	13.7	16.3	13.9	14.0
Lag-time	h	0.237	18.4	0.256	14.6
Rel. IIV-R		1.73	22.7	1.76	37.5
log CL				3.26	1.47
log Vc				5.90	1.11
IIV-CL/F	(CV)	0.123	61.6	0.0920	108
IIV-V_c/F	(CV)	0.281	16.8	0.289	16.8
IIV-k_a	(CV)	0.455	10.8	0.470	20.2
IIV-F	(CV)	0.453	8.04	0.470	8.26
IIV-k_a:F	Corr.	0.702	8.95	0.701	12.9
Prop. RUV rich PK		0.159	3.48	0.161	3.52
Additive RUV	ng/mL	3.37	6.10	3.29	6.23

[a] Typical value for a subject of 82.2 kg weight in Run17 and 67 kg in Run25. CL/F and V_c/F are scaled allometrically with an exponent of 0.75 for CL/F and 1 for V_c/F.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.
CL/F: apparent clearance; Corr.: correlation; CV: coefficient of variation; F: bioavailability; IIV: interindividual variability; k_a: first-order absorption rate constant; OFV: objective function value; Prop.: proportional; R: zero-order absorption rate; RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR: shrinkage; V_c/F: apparent central volume of distribution

Source: Table 12 on page 52 in vlz-ms-08.pdf

The FDA precision requirements of a relative CIs within 0.6 and 1.4 are met. The summary statistics of secondary PK parameters are listed in Table 8.

Table 8. Summary Statistics for the Individual Estimates of the Secondary PK Parameters (AUC_{ss}, C_{max}, T_{max}, $T_{1/2}$, CL/F and V_c/F) by Sampling Design and Dose Group

			AUC_{ss} (mg h/L)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_c/F (L)
Sparse PK	VLZ-MD-21: 15mg	mean	0.630	44.385	3.80	12.30	25.9	440
		median	0.570	39.099	3.60	10.38	25.2	396
		min	0.215	14.153	1.70	1.92	13.9	109
		max	1.846	196.164	6.90	46.38	42.4	1334
		2.5^{th}%	0.246	18.180	2.30	4.97	15.6	171
		97.5^{th}%	1.217	86.418	6.31	30.50	39.0	1002
	VLZ-MD-21: 30mg	mean	1.202	85.075	5.14	10.97	27.0	412
		median	1.124	79.640	4.30	9.66	26.7	369
		min	0.199	12.289	2.00	3.56	15.5	181
		max	2.647	190.601	22.90	53.70	50.4	2154
		2.5^{th}%	0.499	30.695	2.41	5.45	16.6	189
		97.5^{th}%	2.316	153.020	13.27	24.34	41.9	723
	VLZ-MD-22: 15-30mg	mean	1.463	104.056	4.66	10.40	23.7	350
		median	1.246	94.999	4.10	9.40	23.1	320
		min	0.281	16.382	1.90	3.44	10.4	78
		max	5.009	357.907	11.40	25.37	51.7	816
		2.5^{th}%	0.592	41.150	2.80	4.33	12.0	137
		97.5^{th}%	3.566	212.514	8.96	19.57	38.9	682
Rich PK	VLZ-MD-21: 15mg	mean	0.615	43.079	4.21	10.57	26.5	400
		median	0.590	42.471	3.65	10.54	25.5	387
		min	0.116	6.726	1.80	6.54	16.9	177
		max	1.193	77.417	12.60	18.28	42.3	880
		2.5^{th}%	0.247	16.996	2.19	6.64	19.1	224
		97.5^{th}%	1.123	74.327	8.31	15.07	39.0	597
	VLZ-MD-21: 30mg	mean	1.413	108.433	3.87	9.49	27.2	363
		median	1.215	99.223	3.75	8.84	26.4	354
		min	0.436	31.671	1.20	4.69	16.5	151
		max	3.933	330.640	12.70	21.54	38.5	863
		2.5^{th}%	0.473	35.663	1.49	5.59	18.6	193
		97.5^{th}%	3.194	204.127	6.75	17.59	38.4	694
	VLZ-MD-22: 15-30mg	mean	1.260	99.678	4.22	8.89	26.2	345
		median	1.121	92.402	3.95	8.31	24.9	296
		min	0.406	29.508	2.50	5.20	13.9	138
		max	3.052	231.585	8.50	19.15	44.4	889
		2.5^{th}%	0.586	42.279	2.56	5.22	15.8	154
		97.5^{th}%	2.528	199.805	7.98	16.86	41.7	822
Rich and Sparse PK	VLZ-MD-21: 15mg	mean	0.626	44.050	3.91	11.86	26.0	430
		median	0.580	39.909	3.60	10.46	25.2	391
		min	0.116	6.726	1.70	1.92	13.9	109
		max	1.846	196.164	12.60	46.38	42.4	1334
		2.5^{th}%	0.246	17.223	2.29	5.06	15.9	173
		97.5^{th}%	1.195	83.105	6.64	28.10	39.0	914
	VLZ-MD-21: 30mg	mean	1.253	90.737	4.83	10.61	27.1	400
		median	1.171	83.011	4.10	9.27	26.7	368
		min	0.199	12.289	1.20	3.56	15.5	151
		max	3.933	330.640	22.90	53.70	50.4	2154
		2.5^{th}%	0.476	32.080	1.61	5.45	16.6	188
		97.5^{th}%	2.514	183.118	12.99	23.25	41.5	723
	VLZ-MD-22: 15-30mg	mean	1.432	103.395	4.60	10.17	24.1	349
		median	1.215	93.584	4.10	9.27	23.4	316
		min	0.281	16.382	1.90	3.44	10.4	78
		max	5.009	357.907	11.40	25.37	51.7	889
		2.5^{th}%	0.574	39.031	2.60	4.37	12.3	138
		97.5^{th}%	3.564	214.642	8.90	19.25	39.4	722

AUC_{ss} and C_{max} are calculated for a steady state dose of 30 mg/day in study VLZ-MD-22.

Source: Table 14 on page 53 in vlz-ms-08.pdf

Overall, the Applicant has met the clinical pharmacology requirements in the PWR.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9.Table of Clinical Studies for MDD in Pediatric Patients

Study Name	Trial Design/Duration	Primary Endpoint	No. of Patients (n) in Treatment Groups/Disposition	Study Population
Study VLZ-MD-21	Randomized, 8-week, placebo-controlled, fixed-dose, multicenter	CDRS-R total score	Total treated: N = 526 Placebo: n = 171 Viibryd 15 mg/day: n = 175 Viibryd 30 mg: n = 180 Completed: n= 452 (85.9%) Discontinued n=74 (14.1%)	12 to 17 years
Study VLZ-MD-22	Randomized, 8-week, placebo-controlled, fixed dose, multicenter	CDRS-R total score	Total treated: N = 470 Placebo: n = 186 Viibryd 15 to 30 mg/day: n = 187 Fluoxetine 20 mg n = 97 Completed n = 389 (82.8%) Discontinued n = 81 (17.2%)	7 to 17 years
Study VLZ-MD-23	Open-label, flexible-dose, 26-week	safety	Total treated: N = 330 Completed: n = 231 (70%) Discontinued: n = 99 (30%) Extension study for Study VLZ-MD-22 and de novo patients	7 to 17 years

Source: Study reports for VLM-MD-21, VLM-MD-22, and VLM-MD-23
Abbreviations: CDRS-R = Child Depression Rating Scale; CGI-S = Clinical Global Impression-Severity; CGI-I = Clinical Global Impression-Improvement

7.2. Review Strategy

This review focuses on the three studies (VLZ-MD-21, VLZ-MD-22 and VLZ-MD-23) submitted in response to a PMR and Pediatric Written Request to assess efficacy and safety of vilazodone in the pediatric population. The clinical and statistics reviewers completed the efficacy review for this application, with the statistics reviewer confirming the Applicant's efficacy analyses. The efficacy review discusses the two 8-week, placebo-controlled trials (LZ-MD-21 and VLZ-MD-22). The clinical reviewer conducted the safety review examining the two placebo-controlled studies in a single pooled data base to describe shorter-term effects, and the 26-week open-label safety study (VLZ-MD-23) for longer-term observations.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study VLZ-MD-21

Trial Design

Study VLZ-MD-21 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose 10-week (8-week double-blind treatment period) study evaluating the safety and efficacy of vilazodone for the treatment of MDD in male and female pediatric patients ages 12 to 17 years. The study was conducted at 56 sites in the United States. The study also incorporated sparse PK sampling.

To be eligible for inclusion in the study, patients were required to meet Diagnostic and Statistical Manual of Mental Disorders-4th Edition Text Revision (DSM-IV-TR) criteria for MDD, with the diagnosis confirmed via the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL), a semi-structured diagnostic interview. Patients were also required to have a Children's Depression Rating Scale-R (CDRS-R) >40, a Clinical Global Impression-Severity (CGI-S) score of ≥ 4, have a caregiver able to monitor safety, and have normal physical exam and laboratory finding. Female patients were additionally required to have a negative serum beta-hCG test. Subjects were excluded from the study based on a number of psychiatric, treatment-related, and other medical criteria. Notable exclusion criteria include:

- Any Axis I disorder other than MDD if that disorder required treatment within 3 months of the study. A number of disorders (most notably ADHD and anxiety disorders) could participate in the study provided that the comorbid disorder was not the focus of treatment in the 3 months prior to the study.

- Patients at risk of hurting themselves or others as judged by the investigator

- Patients at risk for suicide based on suicide attempt within the past year, investigator judgment, or Columbia Suicide Severity Rating Scale (C-SSRS) score.

Concomitant treatment with anxiolytics, monoamine oxidase inhibitors, antipsychotics and anticonvulsants/mood stabilizers was prohibited. Stimulants for treatment of ADHD were allowed provided the dose had been stable for 2 months prior to the study; however, clonidine and atomoxetine were not allowed . Prohibited medications were washed out within two week or five half-lives (whichever was longer, five weeks for Prozac).

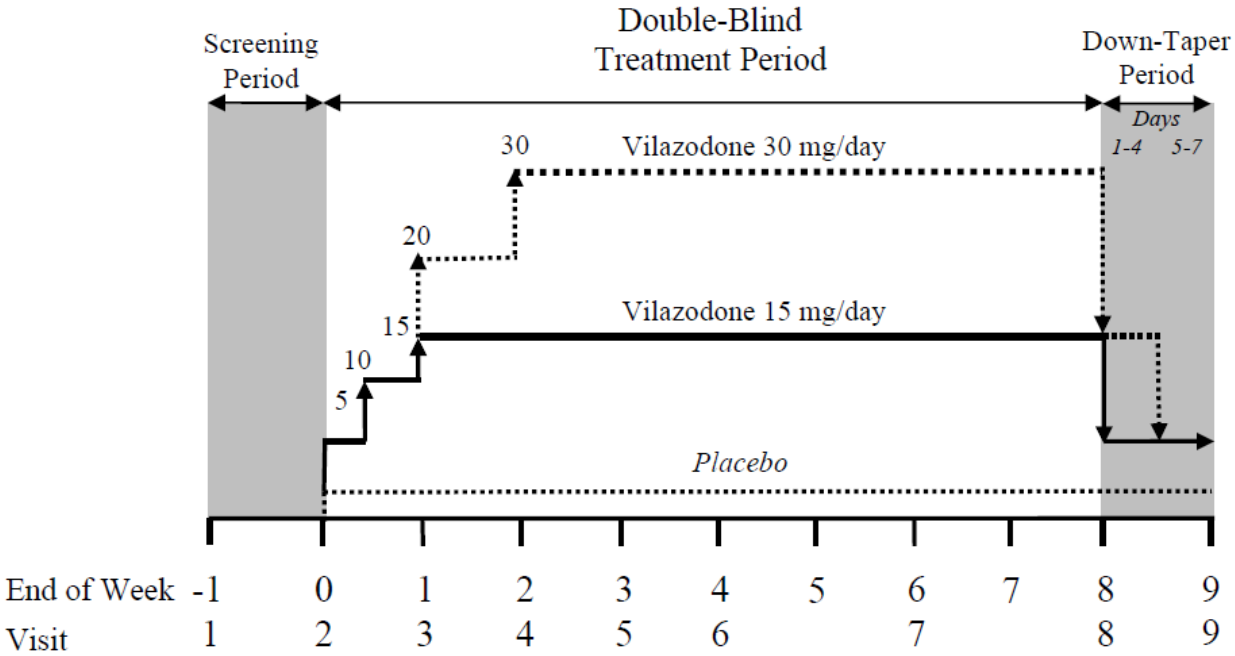
At the baseline visit, patients were randomly assigned to placebo, vilazodone 15 mg daily, or

vilazodone 30 mg daily. Treatment was initiated at 5 mg daily and titrated as follows:

- 15 mg/day group: Days 1 to 3, 5 mg; Days 4 to 7, 10 mg; Week 2 to Week 8, 15 mg
- 30 mg/day group: Days 1 to 3, 5 mg; Days 4 to 7, 10 mg; Week 2, 20 mg; Week 3 to Week 8, 30 mg

Subjects were instructed to take the study drug once daily with food. After completion of the 8-week placebo-controlled treatment period, the dose was tapered over one week before being discontinued. Patients who completed the double-blind treatment could be eligible to enter a 6-month open-label, extension study.

Figure 4. VLZ-MD-21 Study Design



Source: Clinical study report for VLZ-MD-21, Figure 9.1-1, page 34

Study Endpoints

The primary efficacy endpoint was the change from baseline to endpoint of the CDRS-R. The prespecified secondary endpoint was the change from baseline to endpoint on the Clinical Global Impressions-Severity (CGI-S).

Statistical Analysis Plan

The Applicant designed MD-21 to have 85% power to detect a 4-point difference on the Children's Depression Rating Scale - Revised (CDRS-R) between vilazodone and placebo at a 5% type I error controlled using match parallel gatekeeping. The Applicant conducted an interim analysis near the end of the study to ensure it would have the required power. The Applicant

originally planned a total sample size of 495 for MD-21 equally divided between vilazodone (15 mg, 30 mg) and placebo. The Applicant assumed a standard deviation of 11.1. The planned interim analyses were conducted at 75% of the originally planned sample size.

The Applicant estimated change from baseline in CDRS-R at Week 8 using a mixed effects model for repeated (MMRM) with fixed effects of treatment group, pooled study center, visit, and treatment-group-by-visit interaction and the baseline value and baseline-value-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Protocol Amendments

There were no protocol amendments.

8.1.1.1. Study Results

Compliance with Good Clinical Practices

The Applicant provided the following attestation:

> This clinical study complied with the ICH Guidances on General Considerations for Clinical Trials (ICH E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

Financial Disclosure

The Applicant has adequately disclosed financial interest/arrangements with clinical investigators. The Applicant included a Form 3455 for Dr. (b) (6), the principal investigator for Study VLZ-MD-21 (site (b) (6), along with a letter of explanation from Dr. (b) (6) stating that he received $278,987.67 to be a consultant and speaker for a variety of Forest products between the years 2004 and 2014. Site (b) (6) enrolled (b) (6) patients (of the total 526 patients in the entire study).

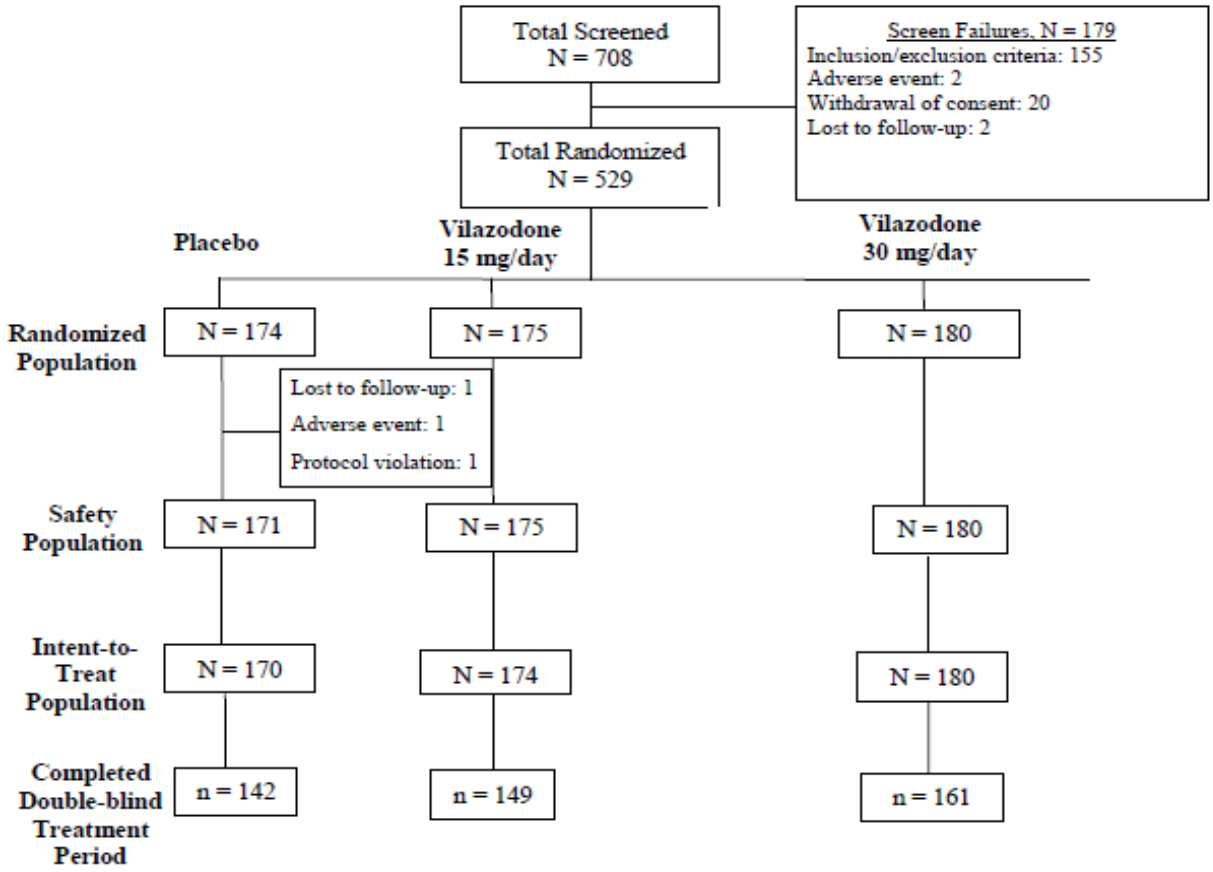
According to the Applicant's submission, there were no other investigators who had propriety interest in Viibryd or significant equity interest in Forest Research Institute as defined in 21 CFR54.2(b) and was not the recipient of significant payment as defined in 21 CFR 54.2(f).

> ***Reviewer's comment:*** *Because Site (b) (6) had a low enrollment, it is unlikely that Dr. (b) (6) could have influenced the findings of the study to any significant extent.*

Patient Disposition

Of the 708 patients screened, 529 patients were randomized (174 placebo, 175 vilazodone 15 mg/day, and 180 vilazodone 30 mg/day). There were 452 (86%) patients who completed the study, including 142 (83.0%) patients in the placebo group, 149 (85.1%) patients in the vilazodone 15 mg/day group, and 161 (89.4%) patients in the vilazodone 30 mg/day group. Figure 5, below, shows the Applicant's schematic of the disposition of subjects. Reasons for discontinuation in the treatment are summarized in Table 10 below.

Figure 5. Patient Disposition



Source: Study Report VLZ-MD-21, Figure 10.1-1p. 80

Table 10. Reason for Premature Discontinuation, n(%)

Reason	Placebo N=171	Vilazodone 15 mg/day N=175	Vilazodone 30 mg/day N=180	Total N=526
Adverse event	4(2.3)	9(5.1)	8(4.4)	21(4.0)
Insufficient therapeutic response	5(2.9)	3(1.7)	0	8(1.5)
Protocol violation	3(1.8)	4(2.3)	2(1.1)	9(1.7)
Withdrawal of consent	9(5.3)	7(4.0)	8(4.4)	24(4.6)
Lost to follow-up	6(3.5)	3(1.7)	1(0.6)	10(1.9)
Other	2(1.2)	0	0	2(0.4)

Source: VLZ-MD-21 Study Report Table 10.1-1, p. 81

Reviewer's note: *The 30 mg vilazodone group had the lowest withdrawal due to insufficient therapeutic response leaving open a consideration that a higher dose may have been more effective; however, the final efficacy results do not show a statistically significant response in either vilazodone group compared to placebo. Also, according to the label, adult studies demonstrated efficacy in adults at doses as low as 20 mg vilazodone daily for the treatment of MDD.*

Protocol Violations/Deviations

As shown in Table 11, below, there were 55 (10.4%) protocol violations in study VLZ-MD-21. Of the 55 (10.4%) protocol violations, 14 (8%) were in placebo, 22 (12.6%) in Vilazodone 15 mg/day , and 19 (10.6%)- in the vilazodone 30 mg/day group. The protocol violation with the highest incidence was taking a prohibited, non-psychotropic medication.

Table 11. Protocol Deviations of Randomized Patients

Deviation	*Placebo (N = 174) n (%)*	*Vilazodone 15 mg/day (N = 175) n (%)*	*Vilazodone 30 mg/day (N = 180) n (%)*	*Total (N = 529) n (%)*
Any protocol deviation	14 (8.0)	22 (12.6)	19 (10.6)	55 (10.4)
Discontinued because of a protocol violation	4 (2.3)	4 (2.3)	2 (1.1)	10 (1.9)
Failed to meet 1 or more inclusion or exclusion criteria	1 (0.6)	4 (2.3)	1 (0.6)	6 (1.1)
Less than 80% or greater than 120% treatment compliance	1 (0.6)	3 (1.7)	3 (1.7)	7 (1.3)
Took more than the prescribed dose in a day	4 (2.3)	2 (1.1)	1 (0.6)	7 (1.3)
Missed 5 or more consecutive doses of investigational product	0	2 (1.1)	6 (3.3)	8 (1.5)
Took a prohibited concomitant medication	7 (4.0)	11 (6.3)	10 (5.6)	28 (5.3)
Took psychotropic medication	0	1 (0.6)	0	1 (0.2)

Source: Study Report VLZ-MD-21 Table 10.2-1 p.82

Table of Demographic Characteristics

Table 12. Demographics for Study VLZ-MD-21

Characteristic	*Placebo (N = 171)*	*Vilazodone 15mg/day (N = 175)*	*Vilazodone 30mg/day (N = 180)*	*Total (N = 526)*
Age, years				
Mean	14.9	14.9	14.6	14.8
SD	1.7	1.6	1.6	1.6
Sex, n (%)				
Male	68 (39.8)	72 (41.1)	73 (40.6)	213 (40.5)
Female	103 (60.2)	103 (58.9)	107 (59.4)	313 (59.5)
Race, n (%)				
White	110 (64.3)	115 (65.7)	121 (67.2)	346 (65.8)
All Other Races	61 (35.7)	60 (34.3)	59 (32.8)	180 (34.2)
Black or African American	45 (26.3)	48 (27.4)	49 (27.2)	142 (27.0)
Asian	6 (3.5)	3 (1.7)	0	9 (1.7)
American Indian or Alaska Native	2 (1.2)	2 (1.1)	4 (2.2)	8 (1.5)
Native Hawaiian/Other Pacific Islander	0	0	0	0
Other	8 (4.7)	7 (4.0)	6 (3.3)	21 (4.0)
Ethnicity, n (%)				
Hispanic or Latino	21 (12.3)	22 (12.6)	19 (10.6)	62 (11.8)
Not Hispanic or Latino	150 (87.7)	153 (87.4)	161 (89.4)	464 (88.2)

Source: Study Report VLZ-MD-21 Table 11.2-1 p.84

Efficacy Results – Primary Endpoint

Study MD-21 did not show a treatment effect of either dose of vilazodone compared to placebo after 8 weeks of treatment (Table 13). At Week 8, the 30 mg dose arm had a -1.74 point difference from placebo (95% CI -4.20 to 0.71; p_{raw} = 0.1634, p_{adj} = 0.3267), the 15 mg dose arm had a -0.46 point difference from placebo (95% CI -2.95 to 2.03; p_{raw} = 0.7162, p_{adj} = 0.7162). An interim analysis was conducted after 372 patients had been randomized. Three patients did not have post-baseline CDRS-R measurements; therefore, the IA included 369 patients. The interim analysis recommended a new total sample size of 525 under the assumption of a 4-point treatment difference and an estimated standard deviation of 11.5 to maintain 85% power.

Table 13. Primary Efficacy Analysis: Change From Baseline to Week 8 in the Children's Depression Rating Scale-Revised Total Score-Intent-to-Treat Population

	Placebo (N=170)	*Vilazodone 15 mg/day (N=174)*	*Vilazodone 30 mg/day (N=180)*
Primary Analysis (MMRM)			
Baseline, mean ± SD	57.0 ± 8.29	57.6 ± 8.62	56.7 ± 8.52
Week 8, mean ± SD	34.0 ± 12.89	33.8 ± 12.00	32.5 ± 11.53
Change at Week 8, LS mean (SE)	-22.48 (0.921)	-22.94 (0.904)	-24.22 (0.872)
LSMD vs placebo (95% CI)		-0.46 (-2.95, 2.03)	-1.74 (-4.20, 0.71)
P-value[a]		0.7162	0.1634
Adjusted p-value[b]		0.7162	0.3267

a P-values are based on an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline-value-by-visit interaction as covariates.
b Adjusted p-values are based on the matched parallel gatekeeping procedure.
CI = confidence interval; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the Intent-to-Treat Population.
Source: Clinical study report for VLZ-MD-21, Table 11.4.1.1.1–1, page 90

8.1.2. Study VLZ-MD-22

Trial Design

Study VLZ-MD-21 was a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, flexible-dose 10-week (8-week double-blind treatment period) study evaluating the safety and efficacy of vilazodone for the treatment of MDD in male and female pediatric patients ages 7 to 17 years. The study was conducted at 55 sites in the United States (53) and Canada (2). The study also incorporated sparse PK sampling. With the exception of the expanded age range (7 to 17 years vs. 12 to 17 years), this study had the same inclusion criteria, exclusion criteria, and rules for concomitant medications as Study VLZ-MD-21 (see Section 8.1.1, above).

At the baseline visit, patients were randomized (2:2:1) to one of three treatment groups (placebo, vilazodone, or fluoxetine); randomization was stratified by study center and by country.

Patients randomized to the vilazodone dose group received the following dosage titration:

- 5 mg/day for Week 1 (Visit 3), Days 1 through 3 (3 days)
- 10 mg/day for Week 1 (Visit 3), Days 4 through 7 (4 days)
- 15 mg/day for Weeks 2 through 8 (Visits 4 through 8)
- 30 mg/day for Weeks 3 through 8 (Visits 5 through 8) (Investigator's discretion).

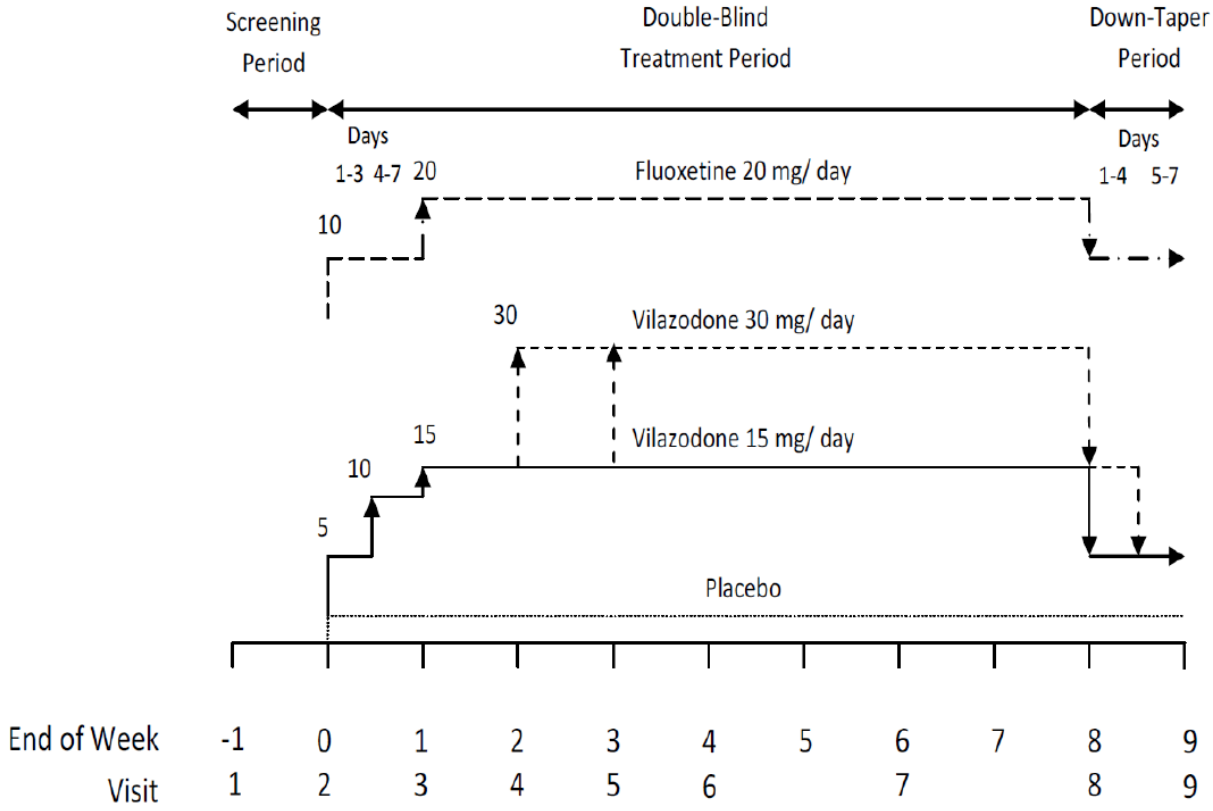
The dose was titrated to 15 mg/day by the end of Week 2 (Visit 4). Based on the patient's response and/or tolerability, and at the Investigator's discretion, the patient could remain on the 15 mg/day dosage for the remainder of the double-blind treatment period or the dosage increased to 30 mg/day.

Patients randomized to fluoxetine received 10 mg/day for Week 1 (Visit 3) (7 days) and 20 mg/day for Week 2 (Visit 4) through the end of Week 8 (Visit 8).

Dose increases were not allowed beyond Week 3 (Visit 5). A single dosage decrease to the next lower dose was allowed for tolerability.

Subjects were instructed to take the study drug once daily with food. After completion of the 8-week placebo-controlled treatment period, the dose was tapered over one week before being discontinued. Patients who completed the double-blind treatment could be eligible to enter a 6-month open-label, extension study.

Figure 6. VLZ-MD-22 Study Design



Source: Clinical study report for VLZ-MD-22, Figure 9.1-1, page 36

Study Endpoints

The primary efficacy endpoint was the change from baseline to endpoint of the CDRS-R. The prespecified secondary endpoint was the change from baseline to endpoint on the Clinical Global Impressions-Severity (CGI-S).

Statistical Analysis Plan

The Applicant designed MD-22 to have 85% power to detect a 4-point difference on the Children's Depression Rating Scale - Revised (CDRS-R) between vilazodone and placebo at a 5% type I error. The Applicant conducted an interim analysis near the end of the study to ensure that it would have the required power. The Applicant originally planned a total sample size of 400 for MD-22 with 160 in vilazodone, 160 in placebo, and 80 in fluoxetine arm. The Applicant assumed a standard deviation of 11.1. The originally planned interim analyses were conducted at 75% of the originally planned sample size. During a Type C meeting on 19 May 2017 held after the interim analysis in MD-22, the Applicant reported recruitment problems for MD-22 and raised a concern that they would not be able to recruit the revised sample size of 455. the Applicant requested an amendment in the PWR to reduce the required power to 81.5%. FDA did not agree, and the Applicant proposed a second blinded IA for SSR to provide assurance that MD-22 would have at least 85% power.

The Applicant estimated change from baseline in CDRS-R at Week 8 using MMRM with fixed effects of treatment group, pooled study center, visit, and treatment-group-by-visit interaction and the baseline value and baseline-value-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Protocol Amendments

No amendments were made to the protocols distributed to the study centers in the United States. One protocol amendment (Amendment #1, dated April 15, 2015) was made for study centers in Canada which expanded the exclusion criteria to include hypersensitive to the non-medicinal ingredients of the study drug such as lactose and gelatin.

Compliance with Good Clinical Practices

The Applicant provided the following attestation:

> This clinical study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
>
> This clinical study complied with the ICH Guidances on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, December 17, 1997) and GCP (ICH-E6; 62 FR 25692, May 9, 1997), as well as Part 312 of the CFR.

Financial Disclosure

The Applicant has adequately disclosed financial interest/arrangements with clinical investigators. The submission included a Form 3455 for Dr. (b) (6), a sub-investigator for Study VLZ-MD-22 (site (b) (6)) and a letter of explanation from Dr. (b) (6) stating that he received $278,987.67 to be a consultant and speaker for a variety of Forest products between the years 2004 and 2014. Site (b) (6) enrolled (b) (6) patients (of the total 473 patients in the entire study).

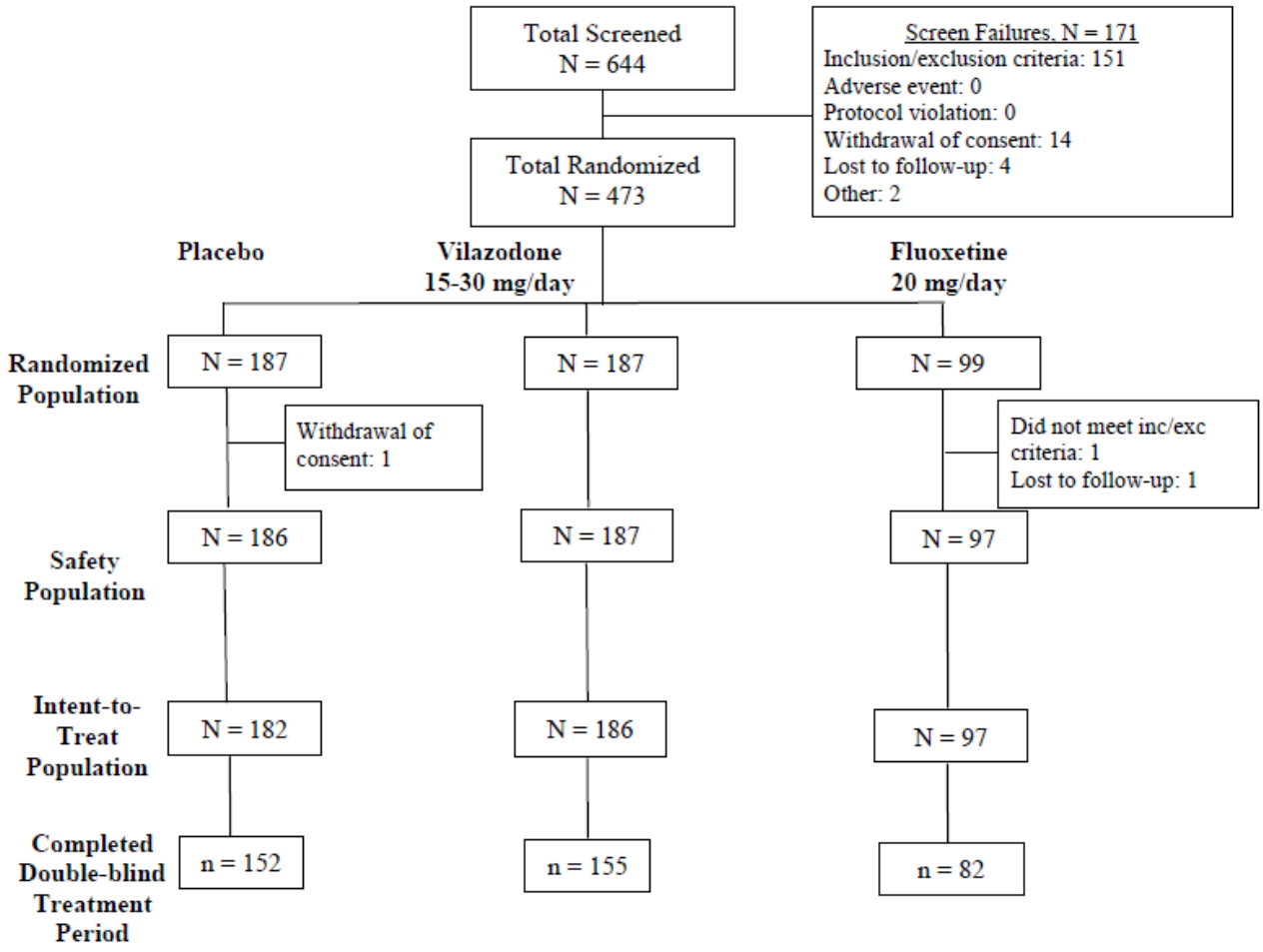
According to the Applicant's submission, there were no other investigators who had propriety interest in Viibryd or significant equity interest in Forest Research Institute as defined in 21 CFR54.2(b) and was not the recipient of significant payment as defined in 21 CFR 54.2(f).

> ***Reviewer's comment:*** *Because Site (b) (6) had a low enrollment, it is unlikely that Dr. (b) (6) could have influenced the findings of the study to any significant extent.*

Patient Disposition

Of the 644 patients screened, 473 patients were randomized (187 placebo, 187 vilazodone 15 to 30 mg/day, and 99 fluoxetine 20 mg/day). There were 389 (84.5%) patients who completed the study, including 152 (81.7%) patients in the placebo group, 155 (82.9%) patients in the vilazodone group, and 82 (84.5%) patients in the fluoxetine group. Figure 7, below, shows the Applicant's schematic of the disposition of patients. Reasons for discontinuation in the treatment are summarized in
Table 14, below.

Figure 7. Patient Disposition



Source: Study Report VLZ-MD-22, Figure 10.1-1p. 83

Table 14. Reason for Premature Discontinuation

Reason	Placebo N=186 n(%)	Vilazodone 15 to 30 mg/day N=187 n (%)	Fluoxetine 20 mg N=97 n(%)	Total N=470 n(%)
Adverse event	3(1.6)	10(5.3)	6(6.2)	19 (4.0)
Insufficient therapeutic response	2 (1.1)	2 (1.1)	0	4(0.9)
Protocol violation	3 (1.6)	0	0	3 (0.6)
Withdrawal of consent	10 (5.4)	10 (5.3)	2 (2.1)	22 (4.7)
Lost to follow-up	11 (5.9)	5 (2.7)	3 (3.1)	19 (4.0)
Non-compliance with study drug	4 (2.2)	4 (2.1)	4 (4.1)	12 (2.6)
Other	1 (0.5)	1 (0.5)	0	2 (0.4)

Source: Study Report VLZ-MD-22: Table 10.1-1

Reviewer's comment: *Reasons for withdrawal were comparable for all groups. Not unexpected, the incident of adverse events was higher for the drug treatment groups compared to the placebo group.*

Protocol Violations/Deviations

Table 15, below, shows that of the 14 (3%) protocol violations, 3.8% were in the placebo group, 2.1% in the vilazodone 15 to 30 mg/day group, and 3.1% in the fluoxetine group.

Table 15. Protocol Deviations

Patient Status	*Placebo (N = 186) n (%)*	*Vilazodone 15-30 mg/day (N = 187) n (%)*	*Fluoxetine 20 mg/day (N = 97) n (%)*	*Total (N = 470) n (%)*
Completed double-blind treatment period	152 (81.7)	155 (82.9)	82 (84.5)	389 (82.8)
Prematurely discontinued	34 (18.3)	32 (17.1)	15 (15.5)	81 (17.2)
Reason for premature discontinuation				
Adverse event	3 (1.6)	10 (5.3)	6 (6.2)	19 (4.0)
Insufficient therapeutic response	2 (1.1)	2 (1.1)	0	4 (0.9)
Withdrawal of consent	10 (5.4)	10 (5.3)	2 (2.1)	22 (4.7)
Lost to follow-up	11 (5.9)	5 (2.7)	3 (3.1)	19 (4.0)
Protocol violation	3 (1.6)	0	0	3 (0.6)
Non-compliance with study drug	4 (2.2)	4 (2.1)	4 (4.1)	12 (2.6)
Other	1 (0.5)	1 (0.5)	0	2 (0.4)
Entered double-blind down-taper period	152 (81.7)	159 (85.0)	82 (84.5)	393 (83.6)
Completed double-blind down-taper period	151 (81.2)	157 (84.0)	80 (82.5)	388 (82.6)

Source: Study report VLZ-MD-22-MDD: Table 10.1-1 p.84

Reviewer's note: *The frequency of protocol deviations was similar in all treatment groups.*

Table of Demographic Characteristics

Table 16, below, shows that the demographics were similar across all treatment groups. The mean age is 13.0 years. 60.2% were female, 63.6% white, 30.9% were black or African American, and 13.6% Hispanic or Latino.

Table 16. Demographics for Study VLZ-MD-22

Characteristic	*Placebo (N = 186)*	*Vilazodone 15-30 mg/day (N = 187)*	*Fluoxetine 20 mg/day (N = 97)*	*Total (N = 470)*
Age, years				
Mean	13.0	13.0	13.2	13.0
SD	2.9	2.9	2.8	2.9
Min, Max	7, 17	7, 17	7, 17	7, 17
Age, years, Group, n (%)				
7 - 11	61 (32.8)	55 (29.4)	30 (30.9)	146 (31.1)
12 - 17	125 (67.2)	132 (70.6)	67 (69.1)	324 (68.9)
Sex, n (%)				
Male	80 (43.0)	61 (32.6)	46 (47.4)	187 (39.8)
Female	106 (57.0)	126 (67.4)	51 (52.6)	283 (60.2)
Race, n (%)				
White	118 (63.4)	121 (64.7)	60 (61.9)	299 (63.6)
All other races	68 (36.6)	66 (35.3)	36 (37.1)	170 (36.2)
Black or African American	57 (30.6)	58 (31.0)	30 (30.9)	145 (30.9)
Asian	5 (2.7)	1 (0.5)	1 (1.0)	7 (1.5)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (0.5)	2 (1.1)	0	3 (0.6)
Other	5 (2.7)	5 (2.7)	5 (5.2)	15 (3.2)
Missing	0	0	1 (1.0)	1 (0.2)
Ethnicity, n (%)				
Hispanic or Latino	27 (14.5)	25 (13.4)	12 (12.4)	64 (13.6)
Not Hispanic or Latino	159 (85.5)	162 (86.6)	85 (87.6)	406 (86.4)

Source: Study Report VLZ-MD-22-MDD Table 11.2.1-1, p. 81

Efficacy Results – Primary Endpoint

Study MD-22 did not show a treatment effect of flexible dose (15 mg to 30 mg) vilazodone compared to placebo after 8 weeks of treatment (Table 17). At Week 8, the vilazodone arm had a -0.4 point difference from placebo (95% CI -3.08 to 2.27, p = 0.7662). In addition, the fluoxetine arm had a -2.39 point difference from placebo (95% CI -5.60 to 0.81, p = 0.1433). At the request of FDA, the Applicant conducted two blinded interim analyses: the first after 300 patients had been randomized (297 with a post-baseline observation), and the second after 427 patients had been randomized (421 with a post-baseline observation). The first interim analysis recommended a new total sample size of 455 (182 in vilazodone and placebo arms and 91 in the fluoxetine arm) under the assumption of a 4-point treatment difference and an estimated

standard deviation of 12.3 to maintain 85% power. The second recommended a new total sample size of 470 (188 in vilazodone and placebo arms and 94 in the fluoxetine arm) under the assumption of a 4 point treatment difference and an estimated standard deviation of 12.43.

Table 17. Primary Efficacy Analysis: Change from Baseline to Week 8 in the Children's Depression Rating Scale-Revised Total Score - Intent-to-Treat Population

	Placebo (N = 182)	*Vilazodone 15-30 mg/day (N = 186)*	*Fluoxetine 20 mg/day (N = 97)*
Primary Analysis (MMRM)			
Baseline, mean ± SD	57.7 ± 9.25	58.5 ± 9.42	58.1 ± 8.31
Week 8, mean ± SD	37.8 ± 13.75	37.2 ± 14.17	34.7 ± 12.85
Change at Week 8, LS mean (SE)	-20.32 (0.983)	-20.72 (0.977)	-22.71 (1.320)
LSMD vs placebo (95% CI) [a]	-	-0.40 (-3.08, 2.27)	-2.39 (-5.60, 0.81)
P-value[a]	-	0.7662	0.1433

[a] Estimates and p-values were obtained from an MMRM based on observed cases with treatment group, pooled study center, visit, and treatment group by visit interaction as fixed effects, and the baseline and baseline-by-visit interaction as covariates, using an unstructured covariance matrix.

N = number of patients in the Intent-to-Treat Population.

Source: Clinical study report for VLZ-MD-22, Table 11.4.1.1.1–1, page 93

8.1.1. Integrated Assessment of Effectiveness

These 8-week, placebo-controlled studies were designed to assess the efficacy of vilazodone in the treatment of MDD in the pediatric population. Study VLZ-MD-21 included adolescent patients 12 years to 17 years of age in a fix-dose trial assessing the doses of vilazodone 15 mg and vilazodone 30 mg daily compared to placebo. Study VLZ-MD-22 studied the wider range of pediatric patients 7 years to 17 years of age in a flexible dose study of vilazodone 15 mg to 30 mg with a placebo and an active comparator arm (fluoxetine).

The primary endpoint in both Studies VLZ-MD-21 and VLZ-MD-22 was the change from baseline to the end of Week 8 of the Children's Depression Rating Scale-Revised (CDRS-R) total score. There was numerical improvement in the CDRS-R in all treatment groups; however, neither vilazodone nor fluoxetine separated from placebo (See Table 18). Although these studies fulfill the PREA postmarketing requirements and the terms of the PWR, the results do not support the use of vilazodone in the pediatric patients 7 years to 17 years of age with a diagnosis of MDD.

Table 18. Change From Baseline to Week 8 in CDRS-R in Studies VLZ-MD-21 and VLZ-MD-22

CDRS-R	VLZ-MD-21			VLZ-MD-22		
	Placebo N = 170	Vilazodone 15 mg/day N = 174	Vilazodone 30 mg/day N = 180	Placebo N = 182	Vilazodone 15-30 mg/day N = 186	Fluoxetine 20 mg/day N = 97
CDRS-R						
Baseline Mean ± SD	57.0 ± 8.29	57.6 ± 8.62	56.7 ± 8.52	57.7 ± 9.25	58.5 ± 9.42	58.1 ± 8.31
Week 8 Mean ± SD	34.0 ± 12.89	33.8 ± 12.00	32.5 ± 11.53	37.8 ± 13.75	37.2 ± 14.17	34.7 ± 12.85
Change from Baseline at Week 8 (MMRM)						
LS Mean (LSMD) [p-value]	-22.48	-22.94 (-0.46) [0.7162]	-24.22 (-1.74) [0.3267]	-20.32	-20.72 (-0.40) [0.7662]	-22.71 (-2.39) [0.1433]
LSMD vs placebo (95% CI)		-0.46 (-2.95, 2.03)	-1.74 (-4.20, 0.71)		-0.40 (-3.08, 2.27)	-2.39 (-5.60, 0.81)

Source: Clinical Overview: Table 4-2, p. 11

8.1.2. Conclusions and Recommendations

Allergan submitted two studies MD-21 and -22 to fulfill a PWR to study vilazodone in patients 7 to 17 with MDD. Neither study showed any treatment effect of vilazodone relative to placebo on MDD symptoms as measured by the CDRS-R in these pediatric patients. The Applicant made reasonable efforts to comply with PWR including conducting interim analyses at 75% information time for MD-21 and MD-22. The Applicant's study designs, interim analyses, and statistical analyses were conducted in accordance with and fulfill the requirements of the PWR. Product labeling will reflect the completion of these studies, inability to demonstrate efficacy, and safety data (as outlined below), but the indication will not be expanded to include pediatric patients.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review is based on the Applicant's Summary of Clinical Safety in which they pool the safety data from Studies VLZ-MD-21, VLZ-MD-22 and VLZ-MD-23 into the following two Groups (see Table 9 for study descriptions) :

- Group 1: Pooled data from two short-term Phase 3 double-blind, placebo-controlled study of vilazodone: Study VLZ-MD-21 in adolescent patients (12 to 17) and Study VLZ-MD-22 (with a fluoxetine arm) in children and adolescent patients (7 to 17 years) .

- Group 2: Study VLZ-MD-23, a Phase 3 long-term safety study of vilazodone in pediatric patients with MDD, which enrolled rollover 318 patients from Study VLZ-MD-22 and 12 de novo patients.

The safety population for this data base includes enrolled patients who took at least one dose of study drug. This review included examination of all narratives to ensure that serious adverse events and discontinuations were appropriately categorized.

8.2.2. Review of the Safety Database

Overall Exposure

The Sponsor reports a total of 741 pediatric patients exposed to at least 1 dose of vilazodone in the Phase 3 pediatric MDD studies. Please refer to Table 9, above, for details describing the specific studies. The mean (standard deviation) of treatment exposure for Group 1 (the two short-term placebo-controlled studies, VLZ-MD-21 and VLZ-MD-22) is 51.8 (±12.3) days. Group 2 (Study VLZ-MD-23, the 26 week open-label study) enrolled 233 pediatric patients for at least 6 months with a mean (SD) treatment duration of 149.6 (±56.8) days.

The mean age of patients receiving vilazodone in Group 1 was 14.2 years with the majority aged 12 to 17 years (89.9%). In Group 2, the mean age of patients was 13.3 years with the majority aged 12 to 17 years (69.1%) with 5 (1.5%) patients aged 18 years. The majority of patients were female (59.7%) and white (66.2%).

Reviewer's comment: *All treatment groups had comparable demographics.*

Table 19. Demographics for Groups 1 and 2—Safety Population

	Group 1 (VLZ-MD-21 and VLZ-MD-22)						Group 2 (VLZ-MD-23)
		Vilazodone				Fluoxetine	
	Placebo (N = 357)	15 mg/day (N = 175)	30 mg/day (N = 180)	15-30 mg/day (N = 187)	Total (N = 542)	20 mg/day (N = 97)	Total vilazodone (N = 330)
Age (years)							
Mean (SD)	13.9 (2.6)	14.9 (1.6)	14.6 (1.6)	13.0 (2.9)	14.2 (2.3)	13.2 (2.8)	13.3 (2.9)
Min, Max	7, 17	12, 17	12, 17	7, 17	7, 17	7, 17	7, 18
Age (years) Group, n (%)							
7 – 11	61 (17.1)	0	0	55 (29.4)	55 (10.1)	30 (30.9)	95 (28.8)
12 - 17	296 (82.9)	175 (100.0)	180 (100.0)	132 (70.6)	487 (89.9)	67 (69.1)	230 (69.7)
18	-	-	-	-	-	-	5 (1.5)[a]
Sex, n (%)							
Female	209 (58.5)	103 (58.9)	107 (59.4)	126 (67.4)	336 (62.0)	51 (52.6)	197 (59.7)
Male	148 (41.5)	72 (41.1)	73 (40.6)	61 (32.6)	206 (38.0)	46 (47.4)	133 (40.3)
Race, n (%)							
White	228 (63.9)	115 (65.7)	121 (67.2)	121 (64.7)	357 (65.9)	60 (61.9)	219 (66.4)
All Other Races	129 (36.1)	60 (34.3)	59 (32.8)	66 (35.3)	185 (34.1)	36 (37.1)	111 (33.6)
Black or African American	102 (28.6)	48 (27.4)	49 (27.2)	58 (31.0)	155 (28.6)	30 (30.9)	93 (28.2)
Asian	11 (3.1)	3 (1.7)	0	1 (0.5)	4 (0.7)	1 (1.0)	7 (2.1)
American Indian or Alaska Native	2 (0.6)	2 (1.1)	4 (2.2)	0	6 (1.1)	0	0
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	0	2 (1.1)	2 (0.4)	0	2 (0.6)
Multiple	13 (3.6)	7 (4.0)	6 (3.3)	5 (2.7)	18 (3.3)	5 (5.2)	9 (2.7)
Missing	0	0	0	0	0	1 (1.0)	0
Ethnicity, n (%)							
Hispanic or Latino	48 (13.4)	22 (12.6)	19 (10.6)	25 (13.4)	66 (12.2)	12 (12.4)	42 (12.7)
Not Hispanic or Latino	309 (86.6)	153 (87.4)	161 (89.4)	162 (86.6)	476 (87.8)	85 (87.6)	288 (87.3)
Weight (kg)							

*Group 1=Pooled data from Study VLZ-MD-21 and Study VLZ-MD-21; Group 2=data from Study VLZ-MD-23).
Source: Sponsor's Summary of Clinical Safety Table 1-4.

Adequacy of the safety database:

The safety profile of vilazodone was previously characterized in the adult MDD development program. The original application included data from enough patients exposed to vilazodone for a long enough period of time to meet the ICH E1 guidelines for safety evaluation of drugs intended for chronic administration.

In addition to evaluating efficacy, the studies outlined in the PWR were intended to characterize the short-term and longer-term safety of vilazodone in the pediatric population. The studies met the requirements of the PWR in terms of age and sex distribution of the study populations, as well as duration of exposure.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There was no evidence of compromised data integrity. This NDA supplement was submitted by the PMRs for pediatric due dates in the most recent letter of Deferral Extension. The data presentation in this submission is well organized.

Categorization of Adverse Events

The Applicant used version 21.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to code adverse events (AEs) in all individual studies and the subsequent grouping categories. To ensure a consistent coding, any AE originally coded with a different coding system was re-coded with MedDRA. The Applicant included all serious adverse events (SAEs) occurring during the treatment period or within 30 days following the date of the last dose of study drug. Adverse event assessment included spontaneous reporting in response to open-ended questions such as, "How do you feel since your last visit?" as well as with specific outcome assessments such as the C-SSRS. Recorded AEs or SAEs included subjective reports by the patient or his/her representative, as well as investigator's observations.

> ***Reviewer's comment:*** *The Applicant describes an adequate system of coding and collecting adverse events. From the review, events were categorized appropriately.*

Routine Clinical Tests

Clinical laboratory tests included CBC, routine chemistry (including liver function studies, bilirubin and serum lipids), urinalysis, thyroid function, hepatitis screening, urine drug screening, blood alcohol level and serum beta-hCG. Other routine clinical tests include vital sign measurements (sitting position), ECG, physical exam and Columbia-Suicide Severity Rating Scale. Table 20, below, shows the schedule of events for the two data pools, Group 1 and Group 2.

> ***Reviewer's Comment:*** *The safety assessments in these studies are adequate to address relevant safety concerns and are typical for antidepressant clinical studies.*

Table 20. Schedule of Safety Evaluations (by Week) for Group 1 and Group 2 Studies

Safety Assessment	*VLZ-MD-21*	*VLZ-MD-22*	*VLZ-MD-23*
Concomitant medications	1, 2, 3, 4, 6, 8, 9	1, 2, 3, 4, 6, 8, 9	0, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 27
Adverse events	S; 0, 1, 2, 3, 4, 6, 8, 9	S; 0, 1, 2, 3, 4, 6, 8, 9	S[a]; 0, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 27
Clinical laboratory tests	S; 8	S; 8	S[a]; 4, 12, 20, 26
Vital signs	S; 0, 1, 2, 3, 4, 6, 8, 9	S; 0, 1, 2, 3, 4, 6, 8, 9	S[a]; 0, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 27
ECG	S;3, 8	S; 3, 8	S[a];4, 12, 20, 26
C-SSRS	S; 0, 1, 2, 3, 4, 6, 8, 9	S; 0, 1, 2, 3, 4, 6, 8, 9	S[a]; 0, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 27

S=Screening; a=Week 0 is the visit of the double-blind down-taper period of the lead-in study
*Source: ISS Table 5-2 p. 7

8.2.4. Safety Results

Deaths

No patients died in Study VLZ-MD-21 and VLZ-MD-22.

In study VLZ-MD-23, the open label study, a 13-year-old male died of an accidental gunshot wound to head while cleaning guns with his cousin after hunting. The patient was on Day 6 of vilazodone 30 mg/day.

> ***Reviewer's comment:*** *The one death in this safety data base appears to be an accident and not attributed to the study drug.*

Serious Adverse Events

Table 21 summarizes all of the serious adverse events (SAE) leading to hospitalization in this pediatric safety data base. The most prevalent SAEs are episodes related to suicidal ideation and behavior, and include the following cases in each treatment category:

- Group 1:
  - 3 cases in vilazodone arm (patients [redacted] (b) (6))
  - 1 case in placebo arm(patient [redacted] (b) (6))
  - 6 cases in fluoxetine arm (patients [redacted] (b) (6)).

- Group 2:
  - 3 cases in vilazodone arm (patients (b) (6)).

In Group 1, both the vilazodone (n=3) and fluoxetine (n=6) treatment groups have more incidents of suicidal ideation and behavior SAEs than the placebo group (n=1).

The incidences of SAEs for the Group 1 and Group 2 vilazodone treatment are comparable. However, the narratives reveal that the majority of SAEs recorded in Group 2 (i.e., Study VLZ-MD-23) occurred in patients who had previously been randomized to a placebo treatment arm in Study VLZ-MD-22.

Table 21. Serious Adverse Events (SAEs) in the Safety Data Base for Groups 1 and 2

ID #	Event	Treatment/ Duration	Summary Narrative
Group 1: Vilazodone treatment (all cases in Study VLZ-MD-21)			
(b) (6)	Increased alanine aminotransferase Depression* with suicidal thoughts.	15 mg/day 58 days	15 year old female -- Day 58: elevated aminotransferase of 64 U/L (NL: 5 to 20 U/L) and a diagnosis of infectious mononucleosis. Both resolved within 1 week. --Day 60: had suicidal thoughts, no plan. Withdrew from the study; took Viibryd off-label at 40 mg/day.
	Suicide attempt/overdose	30 mg/day 21 days	12 year old female Day 21: took 6 buspirone pills after argument with brother with intent to kill herself. Hospitalized to treat suicidal thoughts. Withdrew from study.
	Suicidal Ideation with plan and Insomnia	30 mg/day 11 days	16 year old female Day 0:Suicidal ideation without a plan Day 11: suicidal thoughts with a plan (reported cutting behavior). Study drug discontinued. Hospitalized 4 days; discharged on trazodone and Prozac.
	Altered mental status: unresponsive to stimuli	15 mg/day 20 days	15 year old female became unresponsive to verbal and physical stimulation on Day 20. Admitted to hospital for observation, responded to “ammonia” and mental status returned to normal. Patient discontinued the study.
	Pilonidal cyst	30 mg/day 2 days	15 year old female had pilonidal cyst with pain requiring hospitalization and IV ciprofloxacin, ondansetron, oxycodone, and metronidazole. Discharged next day, continued and completed study.
Group 1-Placebo			
(b) (6)	Suicidal gesture	14 days	15 year old male Day 14: slit wrist, suicidal ideations with plan to take pills. Hospitalized for 5 days: treated with Lexapro.
	Laryngo-tracheobronchitis	22 days	Day 22: Hospitalized for treatment. Lost to follow-up

ID #	Event	Treatment/ Duration	Summary Narrative
Group 1-Fluoxetine treatment			
(b) (6)	Suicide Attempt	20 mg/day 10 days	11 year old female Day 10: took 5 tablets of ranitidine in attempt to kill herself, taken to ER. No more information.
	Auditory hallucinations and suicidal ideation, no plan	20 mg/day 43 days	15 year old male Day 44: auditory hallucinations and suicidal ideation, no plan.
	Suicide attempt	20 mg/day 24 days	17 year old female Day 24: Hospitalized for suicidal ideation with intent, no plan. Withdrew from study.
	Suicidal ideation with intent	20 mg/day days	9 year old female 12 days after completion of study, hospitalized with suicidal intent. Taken to ER. No other information
	Suicidal ideation	20 mg/day 54 days	14 year old female Day 54: Hospitalized for suicidal ideation. No follow-up.
	Suicide attempt	20/mg/day 12 days	15 year old male Day 12: Drank ethyl alcohol and cut self with razor. Hospitalized for alcohol poisoning and upper GI hemorrhage and depression. Withdrew from study.
Group 2: Vilazodone treatment (open label)			
(b) (6)	Suicidal ideation with gesture	15-30 mg/day	15 year old male In Study -22: placebo** Day 20 of Study -23: admitted to hospital for suicidal ideation and cutting behavior. Withdrew from study.
	Appendicitis	15-30 mg/day	17 year old Day 28: hospitalized for appendicitis. Withdrawn from study.
	Suicidal ideation, with plan	30 mg/day 153 days	16 year old male In Study -22: placebo** Day 153: Hospitalized for Suicidal ideation with plan to overdose. Withdrawn from study
	Suicide attempt	15-30 mg/day 43 days	15 year old male In Study -22: placebo** Day 43: Hospitalized for attempt to kill self by cutting with a knife. Withdrawn from study.
	Abnormal behavior	15 mg/day 67 days	10 year old male In Study -22: placebo** Day 67: hospitalized for unusual behavior of swallowing coins, handcuffing self. Withdrawn from study; behavior returned to normal within 5 days.
	Dysphasia, paranoia	30 mg/day 23 days	15 year old female In Study -22: placebo** On Day 23: had dysphasia and paranoia. Withdrew from study Symptoms resolved 6 days later.
	Aggression	30 mg/day 160 days	13 year old male In Study -22: placebo** Day 160: hospitalized for aggressive behavior. Discontinued from study.

*Applicant did not code the event related to suicidality

**Patients in placebo group for lead-in Study LVM-MD-22
Source: Study Reports VLZ-MD-21, VLZ-MD-22, VLZ-MD-23: Appendices with Patient Narratives

Reviewer's Comment: *Events related to suicidal ideation and behavior are the most significant and prevalent SAEs in this data base, with a higher number of episodes in the vilazodone and fluoxetine treatment groups compared to the single case in the placebo-treatment group.*

Of note is the occurrence of suicidal ideation and behavior-related events and behavior changes occurring in vilazodone patients in Group 2 who had taken placebo in the preceding 8-week lead-in study. These cases provide support that vilazodone treatment may have the potential to increase the risk of suicidal ideatin and behavior AEs and behavior changes such as aggression or other abnormal behavior.

The higher number of episodes of suicidality-related SAEs in the drug treatment group is consistent with the current vilazodone label which contains a boxed warning for risk of suicidal thoughts and behaviors in pediatric patients and young adults.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 22 lists adverse events associated with early withdrawal from Groups 1 and 2. A review of the narratives showed that more than one event may have occurred in a single patient. This composite summary shows that suicidal ideation and behavior-related events occur with higher frequency in both the vilazodone and fluoxetine treatment groups compared to the placebo as a reason for dropping out in this safety data base.

Table 22. Composite Table of Dropouts and Discontinuation Due to Adverse Events

	Group 1			Group 2
Preferred Term of AE	**Placebo (N=357)**	**Vilazodone 15-30 mg/daily (N=547)**	**Fluoxetine 20 mg/daily (N=97)**	**Vilazodone 15-30 mg/day (N=318) n(%)**
Suicidal ideation/suicidal gesture	1(0.2)	6(1.0)	5(5.1)	6(1.8)
Dizziness	0	0	0	3(0.9)
Nausea	0	0	0	2(0.6)
Abnormal dreams/nightmare	1 (0.2)	2	1(1.0)	
Abdominal pain/discomfort	0	3(0.5)	0	1(0.3)
Abnormal behavior	0	0	0	1(0.3)
Aggression	0	0	0	1(0.3)
Anxiety	0	1(0.1)	0	
Amnesia	0	0	0	1(0.3)
Cholecystitis	0	0	0	1(1)
Diarrhea	0	3(0.5)	0	1(0.3)
Disinhibition	0	0	0	1(0.3)
Dysphagia	0	0	0	1(0.3)
Epistasis	0	1(0.1)	0	0
Fatigue	0	0	0	1(0.3)

	Group 1			Group 2
Preferred Term of AE	Placebo (N=357)	Vilazodone 15-30 mg/daily (N=547)	Fluoxetine 20 mg/daily (N=97)	Vilazodone 15-30 mg/day (N=318) n(%)
Gun shot wound	0	0	0	1(0.3)
Hallucinations, auditory	0	0	1(1.0)	0
Headache	2(0.5)	0	0	1(0.3)
Impulsive behavior	1(0.2)	0	0	0
Irritability	0	0	1(1.0)	1(0.3)
Insomnia	0	0	1(1.0)	0
Mental status change	0	0	1(1.0)	0
Muscle twitching	0	1(0.2)	0	1(0.3)
Panic attack	0	0	0	1(0.3)
Paranoia	0	0	0	1(0.3)
Paresthesia	0	1(0.2)	0	0
Restlessness	0	1(0.2)	0	0
Sedation	0	0	0	1(0.3)
Sleep disorder	0	1(0.2)	0	0
Syncope	0	0	0	1(0.3)
Upper GI hemorrhage	0	0	0	1(1.0)
Vomiting	0	0	2(2)	1(0.3)
Weight increase	0	0	0	1(0.3)

N=number of patients in the Safety Population; n=number of patients who discontinued because of an AE.
Source: Study Report VLZ-MD-21-MD: Table 12.3.1.3.1-1, p. 112; Study Report VLZ-MD-22: Table12.3.1.1-1, p. 127; Study Report VLZ-MD-23: Table 12.3.1.3.1-1p. 110 and Narratives in these three study reports.
Note: This table includes the SAEs listed in Table 21
AE = adverse event; GI = gastrointestinal

Significant Adverse Events

The C-SSRS was implemented at every study visit to screen for suicidal ideation and behavior. Table 23 summarizes these events by suicidal ideation, intentional self-injury, intentional overdose, suicide attempt, and self-injurious ideation; this category system splits out suicidal actions into separate categories rather than lumping all suicide attempts into a single category. Looking at the total of all suicidal ideation and behavior-related adverse events as measured by the C-SSR-S screening tool, it appears that patients in the vilazodone treatment [both Group 1 (2.2%) and Group 2 (3.9%)] and the fluoxetine treatment group (5.2%) had higher percentages of suicidal ideation and beahvior-related AEs compared to placebo (1.4%).

Table 23. Summary of Adverse Events Potentially Associated with Suicidal Ideation and Behavior During the Double-blind Treatment Period in Group 1 and the Open-label Treatment Period in Group 2 - Safety Population

	Group 1 (VLZ-MD-21 and VLZ-MD-22)							Group 2 (VLZ-MD-23)
		Vilazodone				Fluoxetine		
	Placebo (N = 357)	15 mg/day (N = 175)	30 mg/day (N = 180)	15-30 mg/day (N = 187)	Total (N = 542)	20 mg/day (N = 97)		Total Vilazodone (N = 330)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		n (%)
Patients with any Suicidality	5 (1.4)	4 (2.3)	6 (3.3)	2 (1.1)	12 (2.2)	5 (5.2)		13 (3.9)
Suicidal ideation	3 (0.8)	2 (1.1)	5 (2.8)	1 (0.5)	8 (1.5)	5 (5.2)		9 (2.7)
Intentional self-injury	1 (0.3)	2 (1.1)	0	1 (0.5)	3 (0.6)	1 (1.0)		4 (1.2)
Intentional overdose	0	0	1 (0.6)	0	1 (0.2)	0		0
Suicide attempt	0	0	1 (0.6)	0	1 (0.2)	0		2 (0.6)
Self-injurious ideation	1 (0.3)	0	0	0	0	0		0

Only terms with events are included in this table. A full list of terms included in the analysis can be found in the ISS SAP, Table 11-1.
Version 21.0 of MedDRA was used to code adverse events.

Source: Summary of Clinical Safety, Table 5-4, page

Reviewer's comment: *The results on the C-SSRS assessment are consistent with the spontaneous AE reports, with more suicidal ideation and behavior events in the vilazodone and fluoxetine groups than in the placebo groups.*

Treatment Emergent Adverse Events and Adverse Reactions

As Table 24 details, common adverse events occurring in at least 5% of the vilazodone group and twice the incidence of in the placebo group in Group 1 include the following: nausea, vomiting, diarrhea, dizziness and abdominal pain (combining terms: abdominal pain upper/abdominal discomfort/abdominal pain--review of AE datasets confirmed that there were no duplicates). The adverse events profile for vilazodone in Groups 1 and 2 are consistent.

Table 24. Summary of Common Adverse Events in Groups 1 and 2

Preferred Term	Group 1 (VLZ-MD-21 and VLZ-MD-22)						Group 2 (VLZ-MD-23)
		Vilazodone				Fluoxetine	
	Placebo (N=357)	15 mg/day (N=175)	30 mg/day (N=180)	15-30 mg/day (N=187)	Total (N=542)	20 mg/day (N = 97)	Total vilazodone (N = 330)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 Common TEAE	159 (44.5)	101 (57.7)	120 (66.7)	117 (62.6)	338 (62.4)	42 (43.3)	211 (63.9)
Nausea	27 (7.6)	51 (29.1)	49 (27.2)	40 (21.4)	140 (25.8)	6 (6.2)	52 (15.8)
Headache	58 (16.2)	22 (12.6)	29 (16.1)	24 (12.8)	75 (13.8)	10 (10.3)	58 (17.6)
Vomiting	13 (3.6)	11 (6.3)	21 (11.7)	24 (12.8)	56 (10.3)	4 (4.1)	26 (7.9)
Abdominal pain upper	17 (4.8)	7 (4.0)	28 (15.6)	13 (7.0)	48 (8.9)	4 (4.1)	21 (6.4)
Diarrhoea	14 (3.9)	15 (8.6)	16 (8.9)	16 (8.6)	47 (8.7)	2 (2.1)	15 (4.5)
Dizziness	10 (2.8)	8 (4.6)	13 (7.2)	10 (5.3)	31 (5.7)	2 (2.1)	14 (4.2)
Somnolence	5 (1.4)	8 (4.6)	4 (2.2)	12 (6.4)	24 (4.4)	2 (2.1)	10 (3.0)
Insomnia	8 (2.2)	5 (2.9)	7 (3.9)	10 (5.3)	22 (4.1)	6 (6.2)	25 (7.6)
Abdominal discomfort	3 (0.8)	7 (4.0)	8 (4.4)	7 (3.7)	22 (4.1)	1 (1.0)	8 (2.4)
Nasopharyngitis	11 (3.1)	6 (3.4)	11 (6.1)	3 (1.6)	20 (3.7)	4 (4.1)	17 (5.2)
Upper respiratory tract infection	9 (2.5)	7 (4.0)	7 (3.9)	6 (3.2)	20 (3.7)	5 (5.2)	31 (9.4)
Decreased appetite	4 (1.1)	7 (4.0)	6 (3.3)	7 (3.7)	20 (3.7)	3 (3.1)	5 (1.5)
Fatigue	10 (2.8)	4 (2.3)	7 (3.9)	8 (4.3)	19 (3.5)	1 (1.0)	8 (2.4)
Arthralgia	5 (1.4)	2 (1.1)	7 (3.9)	2 (1.1)	11 (2.0)	0	2 (0.6)
Weight increased	4 (1.1)	3 (1.7)	5 (2.8)	3 (1.6)	11 (2.0)	2 (2.1)	27 (8.2)
Abdominal pain	3 (0.8)	5 (2.9)	2 (1.1)	3 (1.6)	10 (1.8)	0	2 (0.6)

Source: Extracted from Table 2-2 in Summary of Clinical Safety p. 18.

Laboratory Findings

The protocols for the two pooled 8-week placebo controlled studies included laboratory tests at Weeks 4 and 8 and at Weeks 4, 12, 18 and 26 for the 26-week open label study in Group 2. Based on a review of the ISS descriptive statistics of all laboratory values for Groups 1 and 2, there were no significant mean change from baseline findings in either group. The Applicant identified outliers for each laboratory test based on pre-determined outlier criteria established in each protocol.

Table 25, below, summarizes the few laboratory values with a slightly higher incidence of outliers. For these select laboratory values, the incidence for Group 1 and the placebo group were similar. Group 2 had slightly higher incidence of outliers compared to Group 1 for the following laboratory values: bicarbonate, magnesium and urinary protein.

Table 25. Laboratory Values in Which the Treatment Group had Higher Outlier Incidence Compared to Placebo

	Group 1 (VLZ-MD-21 and VLZ-MD-22)						Group 2 (VLZ-MD-23)
		Vilazodone					
	Placebo (N=357) n/N (%)	15 mg/day (N=175) n/N (%)	30 mg/day (N=180) n/N (%)	15-30 mg/day (N=187) n/N (%)	Total (N=542) n/N (%)	Fluoxetine 20 mg/day (n=97) n/N (%)	Vilazodone (N=330) n/N (%)
Parameter							
Hemoglobin (g/L) <0.9	1/325(0.3)	0/155	2/168(1.2)	2/177(1.1)	4/500(08)	0/91	4/318(1.3)
ALT(U/L)≥3*ULN	0/326	1/158(0.6)	2/168(1.2)	0/179	3/505(0.6)	0/92	2/322(0.6)
Albumin(g/dL)>1.1*ULN	16/232(6.9)	9/102(8.8)	8/107(7.5)	11/138(8.0)	28/347(8.1)	7/77(9.10	27/248(10.9)
Bicarbonate(mmol/L)<0.9*LLN	29/268(10.8)	2/140(1.4)	6/142(4.2)	28/139(20.1)	36/421(8.6)	5/75(6.7)	59/253(23.3)
BUN (mmol/L)>1.2*ULN	7/323	2/158(1.3)	5/167(3.0)	7/176(4.0)	14/501(2.8)	0/92	7/316(2.2)
Cholesterol, total (mmol/L0>1.3*ULN	4/322(1.2)	0/158	0/168	8/173(4.6)	8/499(1.6)	4/91(4.4)	20/314(6.4)
Magnesium (mmol/L)>1.1*ULN	15/313(4.8)	3/155(1.9)	0/164	22/165(13.3)	25/484(5.2)	6/89(6.7)	66/302(21.9)
Phosphorus(mmol/L)>1.1*ULN	11/315(3.5)	4/152(2.6)	4/163(2.5)	6/176(3.4)	14/491(2.9)	3/91(3.3)	20/314(6.4)
Urine protein(g/L)≥2+	25/313(8.0)	3/155(1.9)2/166(1.2)	2/166(1.2)	33/170(19.4)	38/491(7.7)	12/87(7.7)	87/299(29.1)

Information extracted from Sponsor's Summary of Clinical Safety, Table 3-1, p. 31.

Table 26. Laboratory Values in Which the Treatment Group Had Higher Outlier Incidence Compared to Placebo

	Group 1 (VLZ-MD-21 and VLZ-MD-22)						Group 2 (VLZ-MD-23)
		Vilazodone, n/N (%)				Fluoxetine	
Parameter	Placebo (N=357)	15 mg/day (N=175)	30 mg/day (N=180)	15-30 mg/day (N=187)	Total (N=542)	20 mg/day (N=97)	Vilazodone (N=330)
Hemoglobin (g/L) <0.9	1/325(0.3)	0/155	2/168(1.2)	2/177(1.1)	4/500(08)	0/91	4/318(1.3)
ALT(U/L)≥3*ULN	0/326	1/158(0.6)	2/168(1.2)	0/179	3/505(0.6)	0/92	2/322(0.6)
Albumin(g/dL)>1.1*ULN	16/232(6.9)	9/102(8.8)	8/107(7.5)	11/138(8.0)	28/347(8.1)	7/77(9.10	27/248(10.9)
Bicarbonate(mmol/L)<0.9*LLN	29/268(10.8)	2/140(1.4)	6/142(4.2)	28/139(20.1)	36/421(8.6)	5/75(6.7)	59/253(23.3)
BUN (mmol/L)>1.2*ULN	7/323	2/158(1.3)	5/167(3.0)	7/176(4.0)	14/501(2.8)	0/92	7/316(2.2)
Cholesterol, total (mmol/L)0>1.3*ULN	4/322(1.2)	0/158	0/168	8/173(4.6)	8/499(1.6)	4/91(4.4)	20/314(6.4)
Magnesium (mmol/L)>1.1*ULN	15/313(4.8)	3/155(1.9)	0/164	22/165(13.3)	25/484(5.2)	6/89(6.7)	66/302(21.9)
Phosphorus(mmol/L)>1.1*ULN	11/315(3.5)	4/152(2.6)	4/163(2.5)	6/176(3.4)	14/491(2.9)	3/91(3.3)	20/314(6.4)
Urine protein(g/L)≥2+	25/313(8.0)	3/155(1.9) 2/166(1.2)	2/166(1.2)	33/170(19.4)	38/491(7.7)	12/87(7.7)	87/299(29.1)

Information extracted from Sponsor's Summary of Clinical Safety, Table 3-1, p. 31.

Vital Signs

Each clinical visit included measurements of sitting blood pressure, sitting pulse and weight. The incidence of post-baseline outliers for heart rate and blood pressure was small with similar incidence in all treatment groups in Groups 1 and 2.

Weight and height were adjusted using standardized z-scores for gender and age. After accounting for growth by age and gender, no patient experienced a change of > 2 standard deviations from the expected normal growth.

Electrocardiograms (ECGs)

The protocols for the two studies in Group 1 included ECGs monitoring at baseline, Weeks 3 and 8. In Group 2, ECGs collection was at Weeks 4, 12, 20 and 26. There were no post-baseline ECG abnormalities in the submitted data.

Human Reproduction and Pregnancy

There were three reports of pregnancies in this safety data base. Two patients in Study VLZ-MD-21 had positive pregnancies test; both were in the placebo group and discontinued the study (it appears that the Applicant did not include these case in the discontinuation patient list). Subject (b) (6), in Study VLZ-MD-23, was confirmed to be pregnant at an unscheduled follow-up visit during Week 27 and had an elective abortion.

8.2.5. Integrated Assessment of Safety

The safety profile for this pediatric data base is similar to the adult safety data presented in the current vilazodone label. This pediatric data base included adverse events related to suicidal ideation and behavior, which is consistent with the boxed warning in current labeling. The most common AEs occurring in at least 5% of the vilazodone group and twice the incidence in the placebo group in the two placebo-controlled studying include: nausea, vomiting, diarrhea, dizziness, and abdominal pain. These will be noted in labeling.

8.3. Conclusions and Recommendations

Although the indication statement will not be expanded to include pediatric patients, safety findings will be reflected in Section 8.4, and the Boxed Warning will be retained. Based on the data presented with this supplement, the pediatric and adult safety profiles for vilazodone are largely similar.

9 Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U. S. C. 335), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. This NDA 022567 for Viibryd (vilazodone hydrochloride) 10 mg, 20 mg, and 40 mg tablets, efficacy supplement 21 is submitted to fulfill requirements of the Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) established on January 21, 2011and the Pediatric Written Request (PWR) issued by FDA on November 20, 2012 (and amended on July 18, 2018) to obtain information on vilazodone in pediatric patients 7 years to 17 years of age with major depressive disorder (MDD).

Under this NDA 022567, efficacy supplement 021, the Applicant submitted three clinical study reports to fulfill requirements of the PREA PMRs and the PWR for pediatric patients 7 years to 17 years of age with MDD. The PREA PMR study reports are summarized in this Unireview by Roberta Glass, MD, Clinical Reviewer, DPP. Both studies, PREA PMR 1723-2/PWR Study #1 VLZ-MD-21 and PREA PMR 1723-3/PWR Study #2 VLZ-MD-22, failed to achieve statistically significant decreases in the primary efficacy endpoint, CDRS-R total score compared with PBO at Week 8 for either vilazodone 15 mg/day or 30 mg/day.

The Applicant is appropriately not pursuing an indication for Viibryd in pediatric patients with MDD and not planning to market the 5 mg dose evaluated in the pediatric studies. Labeling information on the two failed studies is restricted to Section 8.4 Pediatric Use. Safety information, based on the pediatric studies including the OL, LT safety study, include adverse events reported in at least 5% of pediatric patients treated with Viibryd and occurring at a rate of at least twice that for pediatric patients receiving PBO, specifically, nausea, vomiting, diarrhea and abdominal pain/discomfort, and dizziness. A separate Division of Pediatric and Maternal Health (DPMH) Labeling Review for NDA 022567/S-021 for Viibryd (vilazodone hydrochloride) 10 mg, 20 mg and 40 mg will be entered in the Document, Archiving, Reporting and Regulatory Tracking System (DAARTS).

10 Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant is not pursing an expanded indication based on these negative studies. Section 8.4 of labeling will address the findings of the pediatric clinical studies as follows:

> The safety and effectiveness of VIIBRYD have not been established in pediatric patients for the treatment of MDD.
>
> Efficacy was not demonstrated in two adequate and well controlled, 8-week studies including a total of 1002 pediatric patients ages 7 years to 17 years of age with MDD. The following adverse reactions were reported in at least 5% of pediatric patients treated with VIIBRYD and occurred at a rate at least twice that for pediatric patients receiving placebo: nausea, vomiting, diarrhea, abdominal pain/discomfort, and dizziness.
>
> Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Section 8.4 will also include a description of findings from the JAS study:

> In a juvenile animal study, male and female rats were treated with vilazadone (10, 50, and 200 mg/kg/day) starting on postnatal day (PND) 21 through 90. A delay in the age of attainment of vaginal patency (i.e. sexual maturation) was observed in females starting at 50 mg/kg/day with a No Observed Adverse Effect Level (NOAEL) of 10 mg/kg/day. This NOAEL was associated with AUC levels similar to those measured at a maximum dose tested in pediatrics (30 mg). Adverse behavioral effects (lack of habituation in an acoustic startle test) were observed in males at 200 mg/kg and females starting at 50 mg/kg both during drug treatment and the recovery periods. The NOAEL for this finding was 50 mg/kg for males and 10 mg/kg for females, which was associated with AUC levels greater than (males) or similar (females), to those observed with the maximum dose tested in pediatric patients. An 8% decrease in femur mineral density was observed in female rats at 200 mg/kg, compared to the control group. The NOAEL for this finding was 50 mg/kg, which was associated with an AUC level greater than those measured at the maximum dose tested in pediatrics.

11 Postmarketing Requirements and Commitment

No new postmarketing requirements will be issued. The studies submitted fulfill the PREA PMRs issued with the original product approval (and subsequently amended).

12 Division Director (Clinical) Comments

I have personally reviewed the above information and made substantive edits to the content of the review. I agree with the conclusions and the labeling recommendations.

13 Appendices

13.1. Financial Disclosure

Covered Clinical Study VLZ-MD-21

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 74		
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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study VLZ-MD-22

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 68		
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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study VLZ-MD-23

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 65		
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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2. Nonclinical Pharmacology/Toxicology

Table 27. Mean Pharmacokinetic Data of the Parent Drug in Juvenile Rats Following Oral Administration of Vilazodone

Parameter (Unit)	*10 mg/kg/day*		*50 mg/kg/day*		*200 mg/kg/day*	
	PND 21	*PND 90*	*PND 21*	*PND 90*	*PND 21*	*PND 90*
	Males					
AUC_{last} (ng•h/mL)	1330	1300	11600	16600	28200	30200
C_{max} (ng/mL)	264	263	975	1660	2200	2450
T_{max} (h)	5	3	5	5	5	3
$T_{1/2}$ (h)	NR	NR	2.8	2.1	2.9	3.2
Accumulation Ratio	NA	0.98	NA	1.4	NA	1.1
	Females					
AUC_{last} (ng•h/mL)	1440	2570	4410	24400	29300	46700
C_{max} (ng/mL)	241	485	678	2370	2090	4110
T_{max} (h)	3	3	8	5	5	5
$T_{1/2}$ (h)	NR	NR	NR	2.8	5.7	3.5
Accumulation Ratio	NA	1.8	NA	5.5	NA	1.6

NA = Not applicable; NR = Not reportable

The table is excerpted from the Applicant's Study No. 69563, P.50.

Table 28. Mean Pharmacokinetic Data of Metabolite M17 in Juvenile Rats Following Oral Administration of Vilazodone

Parameter (Unit)	*10 mg/kg/day*		*50 mg/kg/day*		*200 mg/kg/day*	
	PND 21	*PND 90*	*PND 21*	*PND 90*	*PND 21*	*PND 90*
	Males					
AUC_{last} (ng•h/mL)	51.8	49.0	520	182	1100	692
C_{max} (ng/mL)	9.23	10.7	41.4	29.1	78.7	69.7
T_{max} (h)	5	3	5	5	8	3
$T_{1/2}$ (h)	NR	1.8	2.8	NR	NR	4.0
Accumulation Ratio	NA	0.95	NA	0.35	NA	0.63
Metabolite/Parent Ratio	0.075	0.073	0.087	0.021	0.075	0.044
	Females					
AUC_{last} (ng•h/mL)	56.6	55.1	164	182	1130	570
C_{max} (ng/mL)	9.37	9.52	32.1	28.5	83.8	42.4
T_{max} (h)	3	3	8	5	8	3
$T_{1/2}$ (h)	NR	NR	NR	NR	NR	4.3
Accumulation Ratio	NA	0.97	NA	1.1	NA	0.50
Metabolite/Parent Ratio	0.076	0.041	0.072	0.014	0.075	0.024

NA = Not applicable; NR = Not reportable

The table is excerpted from the Applicant's Study No. 69563, P.51.

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