NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	211964/S-03
Priority or Standard	Standard
Submit Date(s)	June 29, 2021
Received Date(s)	June 29, 2021
PDUFA Goal Date	April 29, 2022
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	April 29, 2022
Established/Proper Name	Viloxazine hydrochloride
(Proposed) Trade Name	Qelbree
Pharmacologic Class	Norepinephrine Reuptake Inhibitor
Code name	SPN-812
Applicant	Supernus Pharmaceuticals, Inc.
Dosage form	Extended-Release Capsules
Applicant proposed Dosing Regimen	200 mg to 600 mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 to 17 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Attention deficit hyperactivity disorder (ADHD)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Attention deficit hyperactivity disorder in adults and pediatric patients 6 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	406506008 Treatment of attention deficit hyperactivity disorder in patients 6 years of age and older
Recommended Dosing Regimen	200 mg to 600 mg once daily

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See archived signatory memos for each discipline.

Glossary

ADHD	Attention deficit hyperactivity disorder
AE	adverse event
AESI	adverse event of special interest
AISRS	Adult ADHD Investigator Symptom Rating Scale
AV	atrioventricular
BRIEF-A	Behavior Rating Inventory of Executive Function-Adult Version
BMI	body mass index
bpm	beats per minute
C-SSRS	Columbia Suicide Severity Rating Scale
CDTL	Cross-Discipline Team Leader
CFB	change from baseline
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression- Improvement
CGI-S	Clinical Global Impression- Severity of Illness
CI	confidence interval
CL/F	apparent clearance
ClinRO	clinician reported outcome
COA	clinical outcome assessment
CP	Child Pugh
CR	complete response
CSR	clinical study report
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
ECG	electrocardiogram
EOS	end of study
ER	extended-release
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
HAM-A	Hamilton Anxiety Rating Scale
ICH	International Conference on Harmonisation
IR	immediate-release
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LFT	liver function tests
LS	least squares
MAR	missing at random
MDD	major depressive disorder

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
NDA	new drug application
ObsRO	observer reported outcome
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PerfO	performance outcome
PGx	pharmacogenomics
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PP	per protocol
PRO	patient reported outcome
PT	preferred term (MedDRA)
QT (interval)	time from the start of the Q wave to the end of the T wave
QTc	corrected QT (interval)
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SD	standard deviation
SDQ	Symptoms of Depression Questionnaire
SE	standard error
SM	study medication
sNDA	supplemental new drug application
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Viloxazine extended-release (viloxazine ER, marketed as trade name Qelbree) is a norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age. Viloxazine ER is available as 100-mg, 150-mg, and 200-mg extended-release capsules. Dosing and administration instructions in currently approved labeling indicate that capsules may be swallowed whole or opened and the entire contents sprinkled over a teaspoonful of applesauce.

In this supplement, the Applicant seeks to extend the indicated population to include adults with ADHD, with a proposed dosing regimen in adults of 200 mg to 600 mg once daily. The Applicant has also proposed updating the dosage and administration instructions in the prescribing information (PI) to include additional soft food vehicles ((b) (4) pudding) and to permit use of a larger volume of soft food (up to 1 tablespoon). In addition, the Applicant has submitted data from a pharmacokinetic study in subjects with hepatic impairment; this study is intended to fulfill an outstanding postmarketing requirement.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness for viloxazine ER as a treatment for ADHD in pediatric patients in three adequate and well-controlled studies (Studies 812P301, 812P302, and 812P303). A fourth study in pediatric patients (812P304) did not have statistically significant results on its primary endpoint, which assessed the efficacy of viloxazine 600 mg compared with placebo. Viloxazine ER was approved with a dosing regimen of 100 mg to 400 mg once daily in pediatric patients 6 years of age and older. Please refer to the original new drug application (NDA) review for full details regarding the data that supported the original approval (NDA 211964 Integrated Review, archived November 6, 2020).

To support inclusion of adult patients with ADHD in the indicated population, the Applicant submitted Study 812P306, a randomized, double-blind, placebo-controlled, flexible-dose (200 mg to 600 mg) study in adults with ADHD. The primary efficacy endpoint was the mean change from Baseline to Week 6 (end-of-study) on the Adult ADHD Investigator Symptom Rating Scale (AISRS), a clinical outcome assessment that captures symptoms of inattention, hyperactivity, and impulsivity and uses prompts relevant to the adult population. Viloxazine ER demonstrated a statistically-significant effect compared to placebo on the primary efficacy endpoint. The analysis of the key secondary efficacy endpoint, the Clinical Global Impression–Severity, was also statistically significant and provided evidence of the clinical meaningfulness of the primary endpoint result.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Viloxazine extended-release (viloxazine ER) is a norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age, with recommended dosages ranging from 100 mg to 400 mg once daily. In this supplemental new drug application, the Applicant has provided substantial evidence of effectiveness for viloxazine ER as a treatment for adult patients with ADHD. The review team recommends broadening of the indicated population to include adults. The review team has also determined that the Applicant has fulfilled the postmarketing requirement to provide data regarding the pharmacokinetics of viloxazine ER in patients with hepatic impairment.

Three randomized, double-blind, placebo-controlled studies in patients 6 to 17 years of age provided substantial evidence to support use of viloxazine ER as a treatment for ADHD in the pediatric population. The efficacy and safety study in adult subjects with ADHD submitted in this efficacy supplement builds upon that body of data and provides substantial evidence that adults with ADHD can similarly benefit from treatment with viloxazine ER. The adult study allowed dosing from 200 mg to 600 mg and demonstrated statistical significance on the primary efficacy endpoint. The study was not designed to evaluate dose-response and no definitive conclusions about the relative efficacy of the included doses can be drawn. However, given the positive results of this study, it is reasonable to include the 600-mg strength as a treatment option for adult patients who may benefit from a dose higher than that approved for pediatric patients.

In adults, risks associated with the use of viloxazine ER include effects on heart rate and blood pressure, suicidal ideation and behavior, insomnia, headache, fatigue, nausea, decreased appetite, and somnolence; the safety profile in adults largely mirrored the safety profile in pediatric patients.

Of note, pregnancy occurs more commonly in adults than in pediatric patients; therefore, risks related to use of viloxazine ER during pregnancy or lactation may be of particular interest to adults with ADHD. However, data about the effects of viloxazine ER on pregnant and lactating individuals and on fetuses are limited. No additional human pregnancy or lactation data were available from clinical studies or postmarketing databases at the time of this review. Nonclinical studies suggest that viloxazine may cause maternal harm if used during pregnancy; patients should discontinue viloxazine ER when pregnancy is recognized unless the benefits outweigh the potential risk. Postmarketing requirements for a single-arm pregnancy study and for a lactation study are outstanding.

The review team recommends approval of viloxazine ER 200 mg to 600 mg once daily for the treatment of ADHD in adults. The prescribing information will be updated to include the most common adverse reactions observed in adults and to revise the warning and precautions so that they apply to the adult population. The prescribing information will also include data on the pharmacokinetics of viloxazine ER in patients with hepatic impairment, but no dose adjustments are recommended in this population. The required postmarketing pregnancy and lactation studies should collect data from adult patients taking viloxazine ER to gather additional safety data.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Attention deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental condition marked by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. According to the diagnostic criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders Fifth Edition (DSM-5), symptoms must have first appeared before the age of 12 and must have been present for at least 6 months (American Psychiatric Association 2013). • ADHD is typically diagnosed in childhood, but symptoms can persist into adulthood. The prevalence of ADHD in adults is estimated to be approximately 2.5% worldwide. DSM-5 criteria for diagnosis require at least six symptoms (from either or both the inattentive or hyperactivity/impulsivity domains) in pediatric patients < 17 years of age. Fewer (but at least five) symptoms are required in patients ≥ 17 years of age. Symptoms of inattention often continue over the lifespan; hyperactive and impulsive symptoms appear to diminish with time. Hyperactivity in adulthood may also manifest as a feeling of internal restlessness (Posner et a 2020; Faraone et al 2015). • ADHD has been associated with a higher risk of accidents, substance use, suicidal ideation and behavior, mood disorders, and anxiety disorders as well as with difficulties in social interactions, employment, educational functioning (Posner et al. 2020; Faraone et al. 2015; Anker et al. 2018).	• ADHD is a commonly occurring and impairing condition. Although ADHD is usually first recognized in childhood and symptom presentation may evolve over time, adults with ADHD can experience significant functional impairments, psychiatric comorbidities, and safety risks related to accidents, substance use, and suicidal ideation and behavior.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Stimulant medications are the first-line treatments for ADHD in adults and pediatric patients. Stimulant medications carry risks of abuse and dependence and are also associated with adverse reactions (such as increased heart rate and blood pressure, diminished appetite, insomnia, psychosis, and mania) that may limit use in some patients. • Non-stimulant medications that are currently approved for treatment of ADHD include clonidine extended-release, guanfacine extended-release, and atomoxetine. No clinical studies have evaluated the efficacy and safety of clonidine extended-release and guanfacine extended-release in adults with ADHD, but approved labeling does not include an age limit for the indicated population. Atomoxetine is a norepinephrine reuptake inhibitor that is approved for use for treatment of ADHD in pediatric and adult patients. Clinical studies for atomoxetine included two randomized, double-blind, placebo-controlled studies in adult patients with ADHD.	• Adults with ADHD may benefit from having a range of effective and safe pharmacologic options available. Viloxazine ER provides another non-stimulant medication option for adult patients who prefer non-stimulants, who are unable to tolerate stimulants, or who seek to avoid risks of abuse and dependence that would be associated with controlled substances.
Benefit	• Three pediatric studies previously provided substantial evidence of effectiveness to support use of viloxazine ER 100 mg, 200 mg, and 400 mg for the treatment of ADHD in a related clinical population, pediatric patients with ADHD. In a fourth pediatric study, viloxazine ER 600 mg failed to separate from placebo. • The Applicant has now submitted Study 812P306, a randomized, double-blind, placebo-controlled, flexible dose (viloxazine ER 200 mg to 600 mg) efficacy and safety study in adult subjects with ADHD. Subjects were randomized 1:1 to either viloxazine ER or placebo. The primary efficacy analysis demonstrated a statistically-significant treatment effect in subjects treated with viloxazine ER compared with placebo, with a placebo-subtracted treatment difference of -3.7 points on the Adult ADHD Investigator Rating Scale (AISRS) total score (95% CI: -6.2, -1.2). The mean change in the key secondary endpoint, the Clinical Global Impression Scale–Severity, was greater in the viloxazine ER group	• The Applicant has conducted an adequate and well-controlled study (812P306) in which flexibly-dosed viloxazine ER 200 mg to 600 mg demonstrated a statistically-significant and clinically-meaningful effect on ADHD symptoms in adults, which supports expansion of the indicated population to include adults with ADHD. • Although Study 812P306 did not formally assess dose response and no definitive conclusions could be drawn about the relative benefit of the 600 mg dose compared with the other dose groups, the review team concluded that labeling should reflect the viloxazine ER 600 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to placebo, with a placebo-subtracted difference in the least mean squares change from baseline of -0.4 (95% CI: -0.7, -0.2). • A limitation of Study 812P306 was the lack of a fixed-dose design; no formal evaluation of the relationship between the treatment response and dose was conducted in this study. Of the 129 viloxazine ER-treated subjects who completed the study, 79 were receiving viloxazine ER 600 mg at the Week 6 visit. An exploratory analysis in subjects who completed the study found numerical improvements in subjects who received the 600 mg dose, although the magnitude of the effect appeared to be smaller than the effect observed in subjects on the 400 mg dose.	dose to provide an additional treatment option for adults who may experience benefit with a higher dose.
Risk and Risk Management	• Viloxazine ER is in the same pharmacologic class as atomoxetine. Sudden death, stroke, and myocardial infarction have been reported in adults taking atomoxetine. However, serious cardiovascular events were not observed in the viloxazine ER development program. A review of available postmarketing data for viloxazine ER did not uncover data to suggest an association between viloxazine ER and serious cardiovascular adverse reactions. • Postmarketing reports have identified a risk of liver injury in patients taking atomoxetine. Of note, cases of fatal hepatitis were reported when immediate-release viloxazine was previously marketed outside of the United States for the treatment of depression. However, no signal for drug-induced hepatotoxicity emerged in the viloxazine ER development program or in the available postmarketing data. • Priapism and effects on urinary outflow are listed as risks of atomoxetine but have not been reported commonly in patients exposed to viloxazine ER in clinical studies. The prescribing information for atomoxetine includes a warning about a risk of aggression, but aggression was not among the most frequent adverse reactions in clinical studies of viloxazine ER. • Data from the single controlled adult study are insufficient to conclude	• The review of safety data from the adult development program did not reveal any unanticipated safety signals. • The most common adverse reactions and the observed effects on heart rate and blood pressure in adults generally overlapped with those reported in pediatric subjects and are already described in labeling. Inclusion of the adult safety data in the prescribing information is sufficient to inform healthcare practitioners about the potential risks associated with viloxazine ER treatment in this population; the review team did not recommend any additional safety related labeling changes. • Reports of suicidal ideation in subjects taking viloxazine were uncommon in Study 812P306. However, the review team

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that the risk of suicidal ideation and behavior identified in the four pediatric controlled studies does not apply to adults • The most commonly reported adverse reactions in adults, adverse reactions reported in ≥ 5% of subjects treated with viloxazine and at ≥ 2X the frequency reported in subjects on placebo, included: insomnia (23%), headache (17%), fatigue (12%), nausea (12%), decreased appetite (10%), and somnolence (6%). Dry mouth (10%) and constipation (6%) were not among the most common adverse reactions in pediatric subjects but did occur commonly in adults. Irritability was a common adverse reaction in pediatric subjects but not in adults. • In the pediatric program, somnolence, fatigue, nausea, and increases in heart rate occurred more commonly in subjects exposed to the 600-mg dose, although overall the safety profile of the 600-mg dose did not differ meaningfully from the 400-mg dose. The flexible design of the adult study did not permit formal assessment of whether adverse events were dose-related, but an exploratory analysis did not find notable differences in adverse events in subjects who reached the 600-mg dose. • Study 812P311, an open-label, long-term safety extension in adults with ADHD, is ongoing. The Applicant submitted interim results with this efficacy supplement. Relatively few adult subjects with ADHD have received viloxazine ER treatment for 6 months (43 subjects) and 1 year (22 subjects), but the available data did not reveal unanticipated safety signals with long-term use in adults. • The Applicant also submitted Study 812P112.2, an assessment of the effect of mild, moderate, and severe hepatic impairment on the pharmacokinetics of viloxazine ER. This study was intended to fulfill a postmarketing requirement (PMR 3942-5). The clinical pharmacology review concluded that the study was conducted adequately and fulfills the PMR, that the observed differences in	concluded that the low frequency of suicidal ideation in the single controlled adult study was not sufficient to determine that this risk is not relevant to adults. The warning about this risk in Section 5 of the prescribing information will apply to both the pediatric and adult populations. • In an adequately conducted study in subjects with hepatic impairment, the Applicant found that no dose adjustment is needed when treating this population with viloxazine ER. The prescribing information will incorporate the data from this study in Section 12.3 (Pharmacokinetics). This study fulfills a postmarketing requirement. • With the expansion of the indicated population to adults, more patients with ADHD who are contemplating pregnancy or who become pregnant may consider use of viloxazine ER. This efficacy supplement did not include any new data that would justify changes to the pregnancy and lactation information in labeling. Based on the available nonclinical data, the prescribing information describes a potential risk of maternal harm in pregnant individuals exposed to viloxazine and advises that patients discontinue viloxazine in the case of pregnancy unless the benefits of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exposure are not expected to be clinically meaningful, and that no dose adjustment is recommended for patients with hepatic impairment. • Nonclinical studies suggest that viloxazine may cause maternal harm if used during pregnancy. Patients should discontinue viloxazine ER when pregnancy is recognized unless the benefits outweigh the potential risk. No additional human data regarding the risks of viloxazine ER in individuals who are pregnant or lactating were included with this supplement. No pregnancies have been reported in the literature or postmarketing pharmacovigilance databases. Postmarketing requirements for a single-arm pregnancy study and a lactation study are outstanding.	continuing treatment outweigh risks. The Applicant will conduct postmarketing pregnancy and lactation studies to obtain additional safety data. • No older adults enrolled in the adult efficacy and safety study. Section 8.5 of the prescribing information indicates that studies of viloxazine ER in the treatment of ADHD did not include sufficient numbers of subjects ages 65 years and older to determine whether they respond differently from younger subjects.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☐	**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		Section 8, (8.1.1, 8.1.2, 8.2.3, 8.2.5.1, 8.2.6)
		☒	Patient reported outcome (PRO)	Section 8 (8.1.1, 8.1.2, 8.2.3)
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 8 (8.2.5.1, 8.2.6)
		☐	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

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that can persist into adulthood in 10% to 60% of cases. ADHD is thought to be present in approximately 2.5% of adults (Posner et al. 2020). ADHD is characterized by hyperactivity, impulsivity, or inattention severe enough to cause functional impairment. ADHD has been associated with depression, suicidal behavior, substance use disorders, and poor educational and occupational outcomes. Many symptoms of ADHD in adults resemble the symptoms of ADHD that present in childhood, but attentional dysfunction is usually the most prominent feature (Balint et al. 2009).

Although stimulant medications are considered first-line pharmacologic treatment options for ADHD, these agents carry potential risks of heart rate increases, psychiatric adverse reactions (e.g., psychosis and mania), lowered seizure threshold, insomnia, decreased appetite and weight, as well as abuse, misuse, and diversion. Therefore, non-stimulant medication options may be preferable for certain patients. Non-stimulant options currently available for the treatment of ADHD include the selective noradrenergic reuptake inhibitor atomoxetine and the alpha 2 agonists (guanfacine extended-release and clonidine extended-release). These non-stimulant medications are not controlled under the Controlled Substances Act. Table 1 summarizes available non-stimulant medications for the treatment of ADHD.

Viloxazine ER is a non-stimulant medication that is available for the treatment of ADHD in the pediatric population; however, adults are not currently included in the indicated population.

Table 1. Summary of Non-stimulant Treatment Armamentarium for Adult ADHD[a]

Product (s) Name	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Atomoxetine	2002	40 to 100 mg daily	Two clinical studies in adults and four studies in pediatric subjects	Suicidal ideation, liver injury, cardiovascular symptoms, effects on blood pressure/heart rate, psychiatric symptoms, priapism, urinary hesitancy, concomitant use of potent cytochrome P450 2D6 (CYP2D6) inhibitors or poor metabolizers
Guanfacine (extended-release)	2009	1 to 4 mg daily	Based on results of studies in pediatric subjects only	Hypotension, bradycardia, syncope, sedation, somnolence Taper slowly to avoid transient elevations in blood pressure.
Clonidine (extended-release)	2010	0.1 to 0.4 mg total daily dose (morning/ bedtime)	Based on results of studies in pediatric subjects	Hypotension, bradycardia, syncope, somnolence, sedation, may worsen sinus node dysfunction and atrioventricular (AV) block Must discontinue slowly to avoid potential of rebound hypertension.

[a]The approved indication for these drugs is for treatment of ADHD without reference to age.
Source: Prescribing Information for atomoxetine, clonidine extended-release, guanfacine extended-release.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On November 8, 2019, the Applicant submitted a 505(b)(1) new drug application (NDA) for viloxazine extended-release (ER) capsules (referred to in this review as viloxazine ER; also known as SPN-812) for the treatment of ADHD in pediatric patients 6 through 17 years of age. A complete response (CR) letter was issued on November 6, 2020, because of manufacturing facility deficiencies. The Applicant addressed the CR with a resubmission on February 3, 2021—resolving the deficiencies that precluded approval during the initial cycle. The Agency and Applicant did not reach full agreement on labeling prior to the CR action and labeling negotiations resumed after the resubmission. The most notable unresolved issues included the description of viloxazine ER's mechanism of action and effects on weight and suicidal ideation and behavior.

Viloxazine ER, proprietary name Qelbree, was approved for treatment of ADHD in pediatric patients 6 through 17 years of age on April 2, 2021. Substantial evidence of effectiveness was established in three randomized, double-blind, placebo-controlled studies evaluating viloxazine ER 100 mg, 200 mg, and 400 mg.

Five postmarketing requirements (PMRs) were defined upon the initial approval of viloxazine ER:

1. An adequately powered, double-blind, placebo-controlled efficacy and safety study of viloxazine ER in male and female subjects ages 4 to <6 years with ADHD

2. A long-term (6-month), open-label safety extension study to evaluate the safety and tolerability of viloxazine ER as monotherapy for ADHD in subjects ages 4 to <6 years

3. A descriptive study to collect prospective and retrospective data in individuals exposed to viloxazine ER during pregnancy

4. A lactation study in lactating people who have received therapeutic doses of viloxazine ER

5. A pharmacokinetic (PK) study of viloxazine ER in subjects with hepatic impairment

With this supplement, the Applicant has proposed expanding the indicated population to adults. This submission includes data from a new controlled study evaluating the efficacy and safety of viloxazine ER in adults with ADHD and interim data from an ongoing open-label safety study in adults with ADHD. The Applicant has also included data from Study 812P112.2, the hepatic impairment study intended to fulfill PMR 3942-5. In addition, the Applicant included the clinical study report (CSR) for Study 812P113.4, a PK study evaluating the effects of

paroxetine on the PK of viloxazine.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory activity relating to the current submission includes the following interactions and communications between the Applicant and the Division of Psychiatry (the Division):

- In a November 8, 2019 Type C Written Responses Only meeting, the Division gave the Applicant feedback about the clinical development plan for an efficacy supplement to add the treatment of adult patients with ADHD to the indicated population for viloxazine ER. The Applicant had planned Study 812P306, a phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group, flexible-dose study evaluating the efficacy and safety of viloxazine ER in adults with ADHD. The Applicant sought input on the adult program, including the acceptability of the flexible-dose design, the selected doses, and the primary and key secondary endpoints for Study 812P306 as well as the adequacy of the long-term safety database. The Applicant also asked if additional studies would be needed to assess PK in adults or safety and efficacy in the population of older adults.

  The Division advised that a fixed-dose study would be preferred for the adult development program as it would allow for a systematic determination of dose response. A flexible-dose design would potentially be considered acceptable depending on the safety and efficacy profile in the pediatric studies. The Division indicated that, as the Applicant was planning only one study for adults, it would be unlikely that any secondary endpoint would be appropriate for labeling. The Division also indicated that a separate study in older adults would not be required, but that the Applicant should open enrollment to subjects aged 55 years and older who otherwise would meet inclusion criteria. The Applicant ultimately opened enrollment to subjects up to age 65 but maintained the flexible-dose design of the study.

- Upon protocol modification for Study 812P306, submitted March 16, 2020, the Division responded with a request for the Applicant to pre-specify an estimand for primary analysis (July 31, 2020). The Applicant replied on August 12, 2020, and the Division offered feedback on October 15, 2020.

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

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were conducted for this sNDA.

4.2. Product Quality

No product quality issues that would preclude approval were identified. See the full Office of Pharmaceutical Quality (OPQ) review for details.

4.3. Clinical Microbiology

No clinical microbiology information was submitted with this application.

4.4. Devices and Companion Diagnostic Issues

The use of this drug product does not require medical devices or companion diagnostics.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no nonclinical studies or nonclinical information submitted with this efficacy supplement. All nonclinical studies have been reviewed under the original NDA 211964. The nonclinical assessment and recommendation remain unchanged. The current label is updated with new safety margins to reflect the maximum daily recommended dosage of 600 mg in adults.

5.2. Referenced NDAs, BLAs, DMFs

NDA 211964 original submission

6 Clinical Pharmacology

6.1. Executive Summary

This submission included two new clinical pharmacology studies: a hepatic impairment study to fulfill PMR 3942-5 and a drug interaction study evaluating the effect of paroxetine on viloxazine. Based on the submitted information, the review team concluded that:

1. The hepatic impairment study was adequately conducted and fulfills PMR-3942-5. The Applicant has therefore satisfied this PMR.

2. Dose adjustment is not recommended for patients with hepatic impairment when administered viloxazine ER.

3. Dose adjustment is not recommended when viloxazine ER is co-administered with paroxetine.

6.2. Summary of Clinical Pharmacology Assessment

See the NDA 211964 Integrated Review, archived November 6, 2020.

6.2.1. Pharmacology and Clinical Pharmacokinetics

See the NDA 211964 Integrated Review, archived November 6, 2020.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

See the NDA 211964 Integrated Review, archived November 6, 2020.

Therapeutic Individualization

Hepatic Impairment
Viloxazine C_{max} (geometric means) were approximately 24% higher for subjects with mild hepatic impairment (Child Pugh (CP) 5 or 6) compared to matched healthy subjects; AUC_{0-t} and AUC_{inf} were approximately 21% higher for subjects with mild hepatic impairment compared to their respective matched healthy subjects. Viloxazine C_{max}, AUC_{0-t}, and AUC_{inf} were approximately 5%, 6%, and 3% lower, respectively, for subjects with moderate hepatic impairment (CP 7 to 9) compared to matched healthy subjects. Viloxazine C_{max} was approximately 15% lower for subjects with severe hepatic impairment (CP 10 to 15) compared to matched healthy subjects and viloxazine AUC_{0-t} and AUC_{inf} were approximately 23% and 25% higher, respectively, for subjects with severe hepatic impairment compared to healthy subjects. Dose adjustment is not recommended for patients with hepatic impairment when administered viloxazine ER.

CYP2D6 Inhibitors
Co-administration of a single dose of viloxazine ER 700 mg with 20 mg paroxetine daily for 10 days increased viloxazine C_{max}, AUC_{0-t}, and AUC_{inf} by approximately 16%, 35%, and 35%, respectively, compared to viloxazine ER alone. Dose adjustment is not recommended when viloxazine ER is co-administered with paroxetine.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

See the NDA 211964 Integrated Review, archived November 6, 2020.

6.3.2. Clinical Pharmacology Questions

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Dose adjustment is not recommended for patients with hepatic impairment when administered viloxazine ER.

Study 812P112.2 2 assessed the effect of mild (CP 5 or 6), moderate (CP 7 to 9) and severe hepatic (CP 10 to 15) impairment on the pharmacokinetics (PK) profile of viloxazine. The statistical comparison of the pharmacokinetics of viloxazine in hepatic impaired patients versus their matched controls is summarized in Table 2. The changes in exposure (C_{max}, AUC_{0-t}, and AUC_{inf}) were less than 30% between subjects with mild, moderate, or severe hepatic impairment compared to subjects with normal hepatic function—which is not considered clinically significant. Therefore, dose adjustment is not recommended for patients with hepatic impairment when administered viloxazine ER.

Table 2. Relative Bioavailability of Viloxazine ER Comparing Subjects with Mild, Moderate, and Severe Hepatic Impairment to Normal Healthy Volunteer Matches after Single Dose Administration of Viloxazine ER 200 mg or 400 mg

Mild HI (Group 1) vs. Normal Healthy Matches (Group 4a), (400 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 1	Group 4a	(Group 1/Group 4a)	Lower	Upper	CV%
C_{max} (µg/mL)	2.94	2.38	123.69	98.94	154.64	25.77
AUC_{0-t} (h*µg/mL)	66.9	55.3	121.02	99.47	147.23	22.54
AUC_{inf} (h*µg/mL)	68.3	56.3	121.39	100.38	146.79	21.83
Moderate HI (Group 2) vs. Normal Healthy Matches (Group 4b), (400 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 2	Group 4b	(Group 2/Group 4b)	Lower	Upper	CV%
C_{max} (µg/mL)	2.33	2.46	94.54	72.06	124.03	31.58
AUC_{0-t} (h*µg/mL)	53.7	57.1	94.13	64.12	138.20	45.76
AUC_{inf} (h*µg/mL)	56.2	57.9	97.00	65.85	142.88	46.19
Severe HI (Group 3) vs. Normal Healthy Matches (Group 4c), (200 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 3	Group 4c	(Group 3/Group 4c)	Lower	Upper	CV%
C_{max} (µg/mL)	1.25	1.46	85.42	68.81	106.03	23.92
AUC_{0-t} (h*µg/mL)	37.4	30.3	123.39	90.65	167.97	34.63
AUC_{inf} (h*µg/mL)	39.4	31.7	124.54	89.45	173.39	37.32

[a] Geometric Mean based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test, Groups 1, 2, and 3)/Geometric Mean (Reference, Groups 4a, 4b, 4c)
[c] Confidence Interval
Group 1: SPN-812 400 mg (Mild Hepatic Impairment) (n=8); Group 2: SPN-812 400 mg (Moderate Hepatic Impairment) (n=8); Group 3: SPN-812 200 mg (Severe Hepatic Impairment) (n=8); Group 4a: SPN-812 400 mg (Healthy Matches to Mild Hepatic Impairment) (n=8); Group 4b: SPN-812 400 mg (Healthy Matches to Moderate Hepatic Impairment) (n=8); Group 4c: SPN-812 200 mg (Healthy Matches to Severe Hepatic Impairment) (n=7)

Source: Study 812P112.2 CSR, p. 100.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No. Dose adjustment is not recommended when viloxazine ER is co-administered with paroxetine.

Study 812P113.4 evaluated the effect of multiple-dose paroxetine on the pharmacokinetics of viloxazine after administration of viloxazine ER with and without paroxetine under fasted conditions. Table 3 summarizes the exposure (C_{max}, AUC_{0-t}, and AUC_{inf}) change following administration of viloxazine ER alone and coadministration with paroxetine. The exposure change was up to 35%, which is not considered clinically significant. Therefore, dose adjustment is not recommended when viloxazine ER is co-administered with paroxetine.

Table 3. Statistical Analysis of Viloxazine Pharmacokinetic Parameters following Administration Alone and Coadministration with Paroxetine after Multiple Doses

Dependent Variable (n=22)	GeoMean[a]		Ratio (%)[b] (Period 3/Period 1)	90% CI [c] Lower	90% CI [c] Upper
	Period 3	Period 1			
C_{max}	4.79	4.13	116.04	109.49	122.99
AUC_{0-t}	109	81.1	134.65	127.65	142.03
AUC_{inf}	111	82.0	134.80	127.94	142.03

[a] Geometric Mean for (Period 3; Test); (Period 1; Reference) based on Least Squares Mean of log-transformed parameter values
[b] Ratio (%) = Geometric Mean (Period 3)/Geometric Mean (Period 1)
[c] Confidence Interval
Source: Study 812P113.4 CSR, p. 66.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 4. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-up	No. Patients Enrolled	Study Population	No. Centers and Countries
Controlled Studies to Support Efficacy and Safety								
812P306	NCT04016779	Double-blind, placebo-controlled, flexible-dose study	Viloxazine ER 200-600 mg oral capsules or placebo daily	Primary endpoint: Adult ADHD Investigator Symptom Rating Scale (AISRS) total score Key secondary endpoint: Clinical Global Impression–Severity of Illness (CGI-S) scale	5 weeks screening, 6 weeks double-blind treatment	N= 374 randomized (n=190 viloxazine ER and n=184 placebo)	Ages 18-65 years with ADHD	38 U.S. sites
Studies to Support Safety								
812P311	NCT04143217	Open-label extension study of viloxazine ER mono-therapy	Flexible dose of viloxazine ER 200-600 mg oral capsule daily	Safety assessments	52 weeks or until medication available for adults	N=157 (as of 5/31/21), ongoing, no final results available	Ages 18-65 with ADHD who completed Study 812P306	38 U.S. sites

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow-up	No. Patients Enrolled	Study Population	No. Centers and Countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
812P112.2	N/A	Open-label	Single-dose study to assess effect of hepatic impairment on PK of viloxazine ER	PK parameters	32 days	N=45	Adults with and without hepatic impairment	4 U.S. sites
812P113.4	N/A	Open-label three-treatment, three-period, crossover drug-drug interaction study	Effect of multiple-dose paroxetine on the PK of viloxazine ER after administration of viloxazine ER with and without paroxetine under fasted condition in healthy adults	Primary: PK of viloxazine ER after administration with and without paroxetine under fasted conditions Secondary: Describe the single-dose PK of viloxazine ER and 5-hydroxyviloxazine glucuronide, multiple-dose PK of paroxetine, and assess the safety and tolerability of viloxazine ER and paroxetine in healthy adults.	Up to 7 weeks (including screening)	N=22	Healthy adults with cytochrome P450 2D6 (CYP2D6) extensive metabolizer phenotype	1 U.S. site

Source: Adapted from the Applicant's Tabular Listing of All Clinical Studies, Table 5.2, pp. 1-5.

7.2. Review Strategy

The adequate and well-controlled studies (812P301, 812P302, and 812P303) that supported approval of viloxazine ER for the treatment of ADHD in the pediatric population were reviewed with the original NDA application (see the NDA 211964 Integrated Review for full details of the pediatric efficacy and safety data, archived November 6, 2020). One controlled study in adults, 812P306, and interim data from an ongoing open-label extension study, 812P311, were reviewed for this efficacy supplement. The review focused on the dataset from the completed controlled Study 812P306. Interim data from the open-label study, 812P311, were considered in the safety review.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 812P306

Trial Design

Study 812P306 was a phase 3, randomized, double-blind placebo-controlled, multicenter, parallel-group, flexible-dose study in adults with ADHD. Adult subjects diagnosed with ADHD were randomized in a 1:1 ratio to viloxazine ER (200 to 600 mg) or placebo once daily as oral capsules. Subjects underwent up to 5 weeks of screening, followed by 6 weeks of treatment with study medication.

Subjects 18 to 65 years of age were eligible to enroll after meeting DSM-5 criteria for ADHD, with a diagnosis made at least 6 months prior to screening and confirmed using the Structured Clinical Interview for DSM-5 Clinical Trials (SCID-5-CT). Subjects must have had a score of ≥ 26 on the Adult ADHD Investigator Symptom Rating Scale (AISRS) and ≥ 4 (moderately ill or worse) on the Clinical Global Impression–Severity (CGI–S) scale at Screening and Baseline.

Exclusion criteria were:

- Pregnancy or lactation
- Hypersensitivity to the investigational drug product or excipients
- Moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, was likely to affect central nervous system functioning (e.g., seizures, encephalopathy)
- Any history of schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, autism, post-traumatic stress disorder, or obsessive/compulsive disorder
- Any current psychiatric disorder (per DSM-5 criteria) other than ADHD with the following exceptions: ADHD was primary diagnosis with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias. Subject could not receive pharmacological treatment for the comorbidity/secondary diagnoses at time of screening nor for the duration of study
- Symptoms of Depression Questionnaire (SDQ) mean score of >3 at screening
- Hamilton Anxiety Rating Scale (HAM-A) score of >21 at screening

- Attempted suicide within 6 months prior to screening, or significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia Suicide Severity Rating Scale (C-SSRS) for the 6 months prior to screening

- A current diagnosis or history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) per DSM-5 criteria within the 12 months prior to screening or positive toxicology screen

- Treatment-resistant ADHD based on a history of receipt of greater than two approved ADHD medications that failed to adequately improve the subject's symptoms

- History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations, or near drowning with hospital admission

- Abnormal and clinically significant findings on vital signs, electrocardiogram, or laboratory assessments, including bradycardia, tachycardia, prolonged QTc interval, dysrhythmia, elevations of transaminases, bilirubin, or creatinine > 1.5 the upper limit of normal

- Clinically significant systemic illness, including cardiovascular or hepatic disease

Concomitant medications were prohibited during the study, except for over-the-counter medications for minor ailments (e.g., acetaminophen, ibuprofen) and nutritional supplements (e.g., multivitamins, fish oil). Herbal supplements were also prohibited.

Study Endpoints

The primary endpoint was the change-from-baseline (CFB) at end-of-study (EOS; Week 6) in the AISRS Total score, an 18-item clinical outcome assessment that measures symptoms of inattention, hyperactivity, and impulsivity. Higher scores indicate greater severity of ADHD symptoms. The AISRS contains prompts that refer to adult activities (e.g., ability to remain in seat during meetings, ability to remember appointments and obligations, losing items at work). The key secondary endpoint was CFB at EOS in the CGI-S score. The CGI-S is a clinician-rated assessment of severity of ADHD symptoms on a Likert-type scale that ranges from no symptoms (1) to extremely ill (7).

Statistical Analysis Plan

Analysis Populations:

- Randomized Population: All subjects who completed Baseline assessments, met inclusion/exclusion criteria, and were randomized.

- Full Analysis Set (FAS): The subset of subjects in the Randomized Population who took at

least one dose of study medication (SM) and had a baseline and at least one post-baseline assessment of AISRS. Subjects in the FAS were analyzed according to the treatment to which they were randomized. The efficacy analyses was conducted using the FAS.

- Per Protocol (PP) Population: The PP Population is a subset of subjects in the FAS who completed all seven visits through EOS with no missing AISRS assessments and no major protocol violations. Subjects in the PP Population were analyzed according to the treatment received.

- Safety Population: The Safety Population includes all subjects randomized into the study who received at least one dose of study medication. Subjects in the Safety Population were analyzed according to the treatment received. The safety analyses were conducted using the Safety Population.

The primary analysis for the primary efficacy endpoint was analyzed using MMRM (mixed model for repeated measures) with CFB in AISRS score as the dependent variable; baseline AISRS total score as a covariate; and treatment, study visit, and treatment-by-study visit interaction as independent fixed-effect variables. The model parameters were estimated using the restricted maximum likelihood (REML) method with unstructured variance covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. If the unstructured covariance model failed to converge, the first (co)variance structure that did not have a convergence problem would be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound Symmetry. All observed values were included in the analysis regardless of occurrence of an intercurrent event. Missing data for subjects discontinued prematurely due to adverse event (AE) or lack of efficacy were explicitly imputed using multiple imputation derived from the placebo arm. Missing data for other reasons was not imputed.

Sensitivity Analysis was performed by assuming that missing outcomes were missing not at random (MNAR), meaning that the probability that an observation is missing may depend on its underlying unobserved value. Placebo-based multiple imputation was used to fill-in all missing values. This approach was considered a “worst-case” sensitivity analysis as it assumed that after discontinuation, subjects from the viloxazine ER treatment group would adopt the outcome model estimated from the placebo arm.

The key secondary endpoint was analyzed using MMRM. The model included the CFB in CGI-S score as the dependent variable; baseline CGI-S score as a covariate; and treatment, study visit, and treatment-by-study visit interaction as fixed-effect variables. Missing data was not imputed regardless of the discontinuation reason.

Sample Size Calculation: Assuming an effect size of 0.407, 128 subjects per treatment group (256 total subjects for two arms) in the Full Analysis Set (FAS) was to yield 90% power at a significance level of 0.05 (two-sided) to reject the equality of treatment means between the placebo and the viloxazine ER treatment group. Assuming approximately 30% subject drop-out before the completion of the study, an adjusted sample size of 366 subjects (183 per arm) was

to be randomized to obtain 128 subjects per arm in the FAS at the completion of the study.

Protocol Amendments

The protocol was amended three times. The initial protocol was dated May 17, 2019, and was submitted as a draft version.

Protocol version 2.0 was dated August 8, 2019, and was submitted to the IND on November 18, 2019. In this revision, the Applicant removed the ASRSv1.1 assessment as the key secondary objective/endpoint, replaced the Brown Executive Function/Attention (EF/A) Scales with the Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A) as a secondary endpoint and added the categorical CGI-S as a secondary endpoint. The inclusion/exclusion criteria were modified to allow inclusion of subjects with a history of major depressive disorder except for severe symptoms as measured by the additional screening instrument, the SDQ. Consequences of positive urine drug screen at Baseline and post-baseline visits were updated as follows: if a subject had a positive result at Baseline (Visit 2), the subject was to be excluded; if the subject had a positive result at any post-baseline visit (Visits 3 through 7), efficacy measurements would not be performed at that study visit. Drug screening information was updated to specify the type of urine drug screen and to add serum drug screen for ethanol. The interactive medical adherence platform for assessing study medication dosing compliance was removed.

Protocol version 3.0 was dated November 22, 2019. In this revision, the Applicant made minor updates and clarifications to the timing and definitions of various study-related activities, but the major modification was revising the inclusion/exclusion criteria to increase the maximum age of inclusion from 55 years to 65 years of age and to clarify that subjects with allowed concurrent psychiatric disorders could not be receiving any pharmacological treatment for those disorders at screening or for the duration of the study.

Protocol version 4.0 was dated March 6, 2020, and submitted to the Division on March 16, 2020. In this revision, the Applicant agreed to lower the inclusion criteria cutoff mean score for the SDQ from >3.5 to >3.0, added language to provide further guidance to Investigators regarding flexible dosing, and agreed to modify response option 1 in the CGI-S scale to include a version that did not include the word “normal” as a response option.

8.1.2. Study Results

Compliance with Good Clinical Practices

Study 812P306 was conducted in compliance to the applicable International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP).

Financial Disclosure

The Applicant submitted Form 3454. The submitted information is noted. All required staff completed disclosures for Study 812P306.

Data Quality and Integrity

The reviewer identified no concerns regarding data quality or integrity. All datasets and documentation were adequate to complete review of the study.

Patient Disposition

Table 5. Study 812P306 Analysis Sets

Category	Overall numbers	Viloxazine group	Placebo group
Assessed for Eligibility	601	-	-
Randomized	374	190	184
Received allocated medication	372	189	183
Discontinued	105	62	43
Safety Population	372	189	183
FAS analyzed	354	175	179
PP Population analyzed	247	118	129

Source: Adapted from CSR, p. 44 ; confirmed by FDA statistical reviewer (ADSL dataset).

Twenty subjects (15 in the viloxazine ER group; 5 in the placebo group) were excluded from the FAS population because they did not have post-baseline efficacy assessments. A total of 75% of the subjects (27% and 22% in the viloxazine ER group and the placebo group, respectively) in the FAS completed the study.

Table 6. Study 812P306 Subject Disposition of Full Analysis Set

Category	Viloxazine ER (N=175) n (%)	Placebo (N=179) n (%)	Total (N=354) n (%)
Completed study	127 (73)	140 (78)	127 (75)
Discontinued from study	48 (27)	39 (22)	48 (25)
Adverse event	17 (10)	7 (4)	24 (7)
Lack of efficacy	1 (1)	4 (2)	5 (1)
Lost to follow-up	8 (5)	5 (3)	13 (4)
Noncompliance with study med.	3 (2)	2 (1)	5 (1)
Physician decision	3 (2)	0	3 (1)
Withdrew consent	5 (3)	5 (3)	10 (3)
Other	11 (6)	16 (9)	27 (8)

Source: Statistical Reviewer (ADSL dataset)

Protocol Violations/Deviations

Thirty-four subjects (9.6%) had major protocol deviations: 17 subjects in each group (9.7% in the viloxazine ER group and 9.5% in the placebo group). The most common protocol deviations were related to efficacy assessments (n=9, 2.5%), inclusion criteria (n=5, 1.4%), exclusion criteria (n=4, 1.1%), and prohibited co-medication (n=4, 1.1%). No single site accounted for a significant number of major deviations or violations. A number of deviations or violations resulted from study visit changes necessitated by the emerging COVID-19 pandemic. The protocol deviations or violations did not appear to impact results.

Table of Demographic Characteristics

Table 7 depicts the baseline demographic characteristics of subjects. In general, the study population appears to mirror the clinical population. Although smaller numbers of certain race and ethnic groups were included, there are no data available to suggest the study population was not representative of adult patients with ADHD in the clinical population.

Table 7. Study 812P306 Demographic Characteristics of the Primary Efficacy Analysis (Full Analysis Set)

Demographic Parameters	Viloxazine ER (N=175)	Placebo (N=179)	Total (N=354)
Sex, n (%)			
Male	98 (56)	96 (53.6)	194 (54.8)
Female	77 (44)	83 (46.4)	160 (45.2)
Age			
Mean years (SD)	34.2 (10.2)	35.4 (10)	35.4 (10.1)
Median (years)	33	34	34
Min, max (years)	18, 58	18, 60	18, 60
Age Group, n (%)			
< 65 years	175	179	354
≥ 65 years	0	0	0
Race, n (%)			
White	142 (81.1)	136 (76)	278 (78.5)
Black or African American	21 (12)	28 (15.6)	49 (13.8)
Asian	6 (3.4)	8 (4.5)	14 (4)
American Indian or Alaska Native	0	1 (0.6)	1 (0.3)
Multiple	2 (1.1)	3 (1.7)	5 (1.4)
Other	4 (2.3)	3 (1.7)	7 (2)
Ethnicity, n (%)			
Hispanic or Latino	47 (26.9)	32 (17.9)	79 (22.3)
Not Hispanic or Latino	128 (73.1)	147 (82.1)	275 (77.7)
Region, n (%)			
United States	175 (100)	179 (100)	354 (100)

Source: Clinical reviewer analysis from Applicant ADSL dataset, JMP Clinical; confirmed by FDA statistical reviewer.

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

All subjects in the safety population from both groups had a history of ADHD. Baseline AISRS total scores, AISRS Inattention subscale scores, AISRS Hyperactivity/Impulsivity subscale scores, CGI-S scores, and SDQ scores were similar between the viloxazine ER and placebo groups. The overall mean (SD) AISRS score was 38.1 (6.6). AISRS Inattention and AISRS Hyperactivity/ Impulsivity subscale scores were 21.3 (3.49) and 16.8 (5.03), respectively. The mean CGI-S score at Baseline was 4.6 (0.62) and mean SDQ average score and total score were 2.4 (0.41) and 106.5 (18.0), respectively.

Over half of subjects had taken at least one prior medication (n=214, 57.5%); the proportion of subjects was similar between treatment groups. Likewise, over half of subjects (n=198, 53.2%)

took at least one concomitant medication during the study. The frequency of concomitant medication use was slightly higher in the placebo group, with 50.8% in the viloxazine ER group and 55.7% in the placebo group. For both groups, propionic acid derivatives (e.g., ibuprofen, naproxen) were the most common Anatomic Therapeutic Chemical (ATC) class Level 4 concomitant medications (viloxazine ER, n=35, 18.5%; placebo n=25, 13.7%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most subjects were between 80% and 120% compliant (n=321, 94.4%), with the proportion of subjects with this compliance rate similar between the viloxazine ER and placebo groups. Mean compliance rates were similar between the viloxazine ER and placebo groups (98.5% and 98.4%).

Subjects were not coadministered other medications to treat the symptoms of ADHD for this study, and rescue medication use was not included in the protocol.

Efficacy Results—Primary Endpoint

The primary efficacy endpoint was the CFB at EOS (Week 6) in the AISRS total score. A total of 273 subjects (77%) had observed AISRS total scores at Week 6 (Table 8). In the primary analysis, subjects who had missing outcomes due to AE or lack of efficacy had their missing outcomes imputed using multiple imputation derived from the placebo arm; missing data for other reasons were not imputed (that is, remaining as missing). Table 9 summarizes the numbers of subjects whose missing outcomes were imputed versus not imputed at each visit in the primary analysis.

Table 8. Number of Subjects with Observed AISRS Total Score vs. Missing at Each Visit (Full Analysis Set)

	Number of Subjects with Observed AISRS Total Scores			Number of Subjects with Missing AISRS Total Scores		
	Viloxazine ER	Placebo	Total	Viloxazine ER	Placebo	Total
Baseline	175	179	354	0	0	0
Week 1	175	179	354	0	0	0
Week 2	157	170	327	18	9	27
Week 3	147	163	310	28	16	44
Week 4	142	153	295	33	26	59
Week 6 (EOS)	130	143	273	45	36	81

Source: FDA statistical reviewer from ADEFF1 dataset.

Table 9. Number of Subjects Whose Missing AISRS Total Score was Imputed vs. Not Imputed in the Primary Analysis

	Number of Subjects Whose Missing Data were Imputed in Primary Analysis			Number of Subjects Whose Missing Data were Not Imputed in Primary Analysis		
	Viloxazine ER	Placebo	Total	Viloxazine ER	Placebo	Total
Baseline	0	0	0	0	0	0
Week 1	0	0	0	0	0	0
Week 2	7	4	11	11	5	16
Week 3	12	5	17	16	11	27
Week 4	15	9	24	18	17	35
Week 6 (EOS)	18	11	29	27	25	52

Source: FDA statistical reviewer from ADEFF1 dataset.

The primary analysis for the primary efficacy endpoint was analyzed using MMRM (mixed model for repeated measures), with CFB at EOS (Week 6) in AISRS score as the dependent variable, baseline AISRS total score as a covariate, and treatment, study visit, and treatment-by-study visit interaction as independent fixed effect variables. The model parameters were estimated using the restricted maximum likelihood (REML) method with unstructured variance covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. The planned model met convergence criteria, so alternative methods proposed in the

protocol were not needed. The biometrics reviewer confirmed the Applicant's results, which were statistically significant in favor of viloxazine ER (see Table 10 and Table 11).

The biometrics reviewer also conducted a sensitivity analysis using only the observed AISRS values, without the imputed values described earlier. The imputation method, using the placebo group as the reference, is a conservative estimation. As expected, the sensitivity analyses confirmed the results and conclusions from the primary analysis.

Table 10. Primary Analysis of Change from Baseline to Week 6 in AISRS Total Score (Study 812P306)

Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-Subtracted Difference (95% CI)[a]	p-value
Viloxazine ER	175	38.5 (6.56)	-15.5 (0.91)	-3.7 (-6.2, -1.2)	0.004
Placebo	179	37.6 (6.62)	-11.7 (0.9)	-	-

Abbreviations: AISRS = Attention-Deficit Hyperactivity Disorder Investigator Symptom Rating Scale; CI = confidence interval; LS = least squares; N: number of subjects included; SD = standard deviation; SE = standard error.
LS mean differences (viloxazine ER - placebo), 95% CIs, and p-values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in AISRS total score as the repeated dependent variable and fixed effect term for baseline AISRS total score, treatment, study visit, and treatment-by-study visit interaction as independent variables. Missing values were imputed and replaced by values derived from the placebo arm for subjects discontinued due to AE or lack of efficacy.
[a] Difference (drug minus placebo) in least-squares mean change from Baseline.
Source: Extracted from CSR, Table 6 (p. 53); confirmed by FDA statistical reviewer (ADDEFF1 dataset).

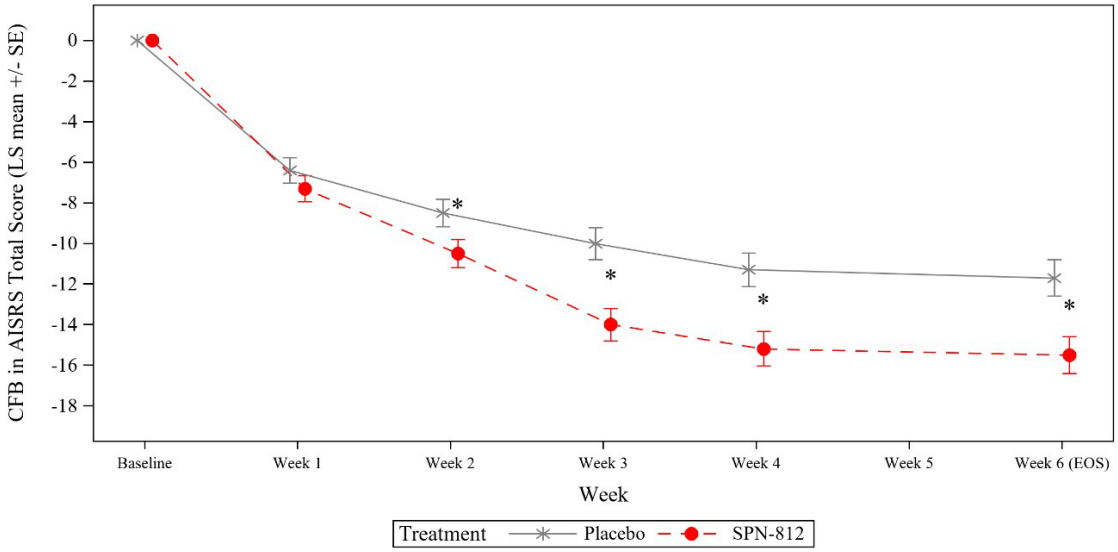
The changes from Baseline in AISRS total score by treatment group and by visit in the FAS are summarized in Table 11 and displayed in Figure 1. The least squares (LS) mean for treatment difference slightly diminished starting at the Week 3 visit; however, the amount of decrease did not appear large.

Table 11. Analysis of Change from Baseline by Visit in AISRS Total Score (Study 812P306)

Visit	Treatment Arm	LS Mean Change from Baseline	LS Mean Difference (95% CI)	p-value
Week 1	Viloxazine ER	-7.3 (0.63)	-0.9 (-2.7, 0.8)	0.2941
	Placebo	-6.4 (0.62)	-	-
Week 2	Viloxazine ER	-10.5 (0.7)	-2.0 (-3.9, -0.1)	0.0397
	Placebo	-8.5 (0.68)	-	-
Week 3	Viloxazine ER	-14 (0.81)	-4.0 (-6.2, -1.8)	0.0005
	Placebo	-10 (0.79)	-	-
Week 4	Viloxazine ER	-15.2 (0.85)	-3.9 (-6.2, -1.5)	0.0014
	Placebo	-11.3 (0.83)	-	-
Week 6	Viloxazine ER	-15.5 (0.91)	-3.7 (-6.2, -1.2)	0.004
	Placebo	-11.7 (0.9)	-	-

Abbreviations: AISRS = ADHD Investigator Symptom Rating Scale; CI = confidence interval; LS = least-squares; SD = standard deviation; SE = standard error.
LS mean differences (SPN-812 - placebo), 95% CIs, and p-values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in AISRS total score as the repeated dependent variable and fixed effect term for baseline AISRS total score, treatment, study visit, and treatment-by-study visit interaction as independent variables. Missing values were imputed and replaced by values derived from the placebo arm for subjects discontinued due to AE or lack of efficacy.
Source: Extracted from CSR, Table 14.2.1.1 (812p306tables-and-figures.pdf; pp. 97- 101), confirmed by the FDA statistical reviewer (ADDEFF1 dataset).

Figure 1. Profiles of Change from Baseline in AISRS Total Score by Treatment Group and Week (Full Analysis Set), Study 812P306



Abbreviations: AISRS = ADHD Investigator Symptom Rating Scale; CFB = change from baseline; EOS = End of Study; LS = least squares; SE = standard error
Note: No study visit was scheduled/performed at Week 5. LS mean CFB, LS mean differences (SPN-812 - placebo), 95% CIs, and p-values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in AISRS total score as the repeated dependent variable and fixed effect term for baseline AISRS total score, treatment, study visit, and treatment-by-study visit interaction as independent variables. Error bars depict the SE. Lower LS mean values = improvement.
* Indicates significant p-value ($p<0.05$) at a specific week. Baseline change of 0 is plotted for reference.
Source: CSR, Figure 3 (812p306-report-body.pdf; p. 54).

Efficacy Results – Secondary and other relevant endpoints

The key secondary efficacy endpoint was the CFB at EOS (Week 6) in the CGI-S score. Based on the primary analysis, the result was statistically significant in favor of viloxazine ER (Table 12).

Table 12. Analysis of Change from Baseline in Clinical Global Impression – Severity of Illness Score (Study 812P306)

Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)[a]	p-value
Viloxazine ER	4.6 (0.65)	-1.4 (0.1)	-0.4 (-0.7, -0.2)	0.0023
Placebo	4.6 (0.60)	-1 (0.1)	-	-

Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error.
LS mean CFB, LS mean differences (SPN-812 - placebo), 95% CIs, and p-values were obtained from an MMRM with CFB in CGI-S score as the repeated dependent variable, fixed effect term for baseline CGI-S score, and treatment, study visit, and treatment-by-study visit interaction as independent variables.
[a] Difference (drug minus placebo) in least-squares mean change from Baseline.
Source: CSR, Table 7 (812p306-report-body.pdf; p. 57); confirmed by FDA statistical reviewer (ADQS dataset).

Dose/Dose Response

Study 812P306 was not designed to systematically evaluate dose response; the flexible dose design limited the study's ability to provide conclusive data about the efficacy of specific doses. Enrolled subjects could receive doses of viloxazine ER ranging from 200 mg to 600 mg; subjects could increase or decrease their dosage as needed for effect or tolerability. The review team conducted an exploratory analysis of the treatment effect in subjects receiving viloxazine ER 200 mg, 400 mg, or 600 mg at different study timepoints. Of the 129 viloxazine ER-treated subjects in the FAS who completed the study, 79 were receiving viloxazine ER 600 mg at the Week 6 visit. Subjects receiving viloxazine ER 600 mg reported numerical improvement on the AISRS. Of note, the magnitude of the treatment effect in subjects receiving the 600-mg dose appeared smaller than that observed in the subjects receiving the 400-mg dose (Table 13). The numerical treatment effect appeared to increase over time in subjects taking viloxazine ER 400 mg, but it remained relatively flat in subjects taking viloxazine ER 600 mg. It is possible that the subset of subjects who opted to continue titration up to 600 mg were experiencing less benefit than subjects who opted to remain on the 400-mg dose. However, the numerical increase in the treatment effect and the flat trajectory were also observed in the 400-mg placebo and 600-mg placebo groups, respectively. Overall, the study data were insufficient to characterize the efficacy of the 600-mg dose compared with the 400-mg dose.

Table 13. Exploratory Dose-Response Analysis on AISRS (Observed Case on FAS)

Treatment	Dose Level	Visit Number	n	Change from Baseline in AISRS Total Score			
				Mean[a]	SD	Minimum	Maximum
Placebo	200 mg	5	3	-1.3	8.1	-10	6
		6	2	-10.5	7.8	-16	-5
		7	2	-7.5	12	-16	1
	400 mg	3	179	-6.3	7.6	-30	7
		4	172	-8.6	8.6	-35	7
		5	57	-12.6	10.2	-36	3
		6	28	-19.7	10.9	-39	4
		7 (Week 6)	25	-21.2	8.7	-36	-2
	600 mg	5	103	-9.4	10	-38	11
		6	122	-10.3	10	-39	8
		7 (Week 6)	116	-10.5	11.2	-46	7
Viloxazine ER	200 mg	5	12	-16.8	11.4	-41	2
		6	12	-18.1	8.6	-28	-2
		7	10	-20	9.7	-34	-5
	400 mg	3	175	-7.3	9	-39	8
		4	158	-10.9	9.7	-40	11
		5	63	-15.8	10.5	-42	11
		6	43	-19.5	11.5	-42	1
		7 (Week 6)	40	-20.8	12.2	-42	0
	600 mg	5	71	-13.5	11.4	-41	2
		6	87	-13.6	11.4	-44	6
		7 (Week 6)	79	-13.4	12.1	-45	5

[a]Mean=raw mean without modeling.
Source: FDA statistical reviewer using EC and ADEFF1 datasets.

Durability of Response

Study 812P306 was not designed to evaluate durability of response.

Persistence of Effect

Study 812P306 was not designed to evaluate persistence of effect.

Additional Analyses Conducted on the Individual Trial

Exploratory subgroup analyses on the primary efficacy endpoint, CFB to Week 6 in AISRS Total score, and for the key secondary endpoint, CFB in CGI-S, were conducted for sex and race. The

majority of the subjects (79%) were White. The results appeared consistent between male and female subjects (Table 14 and Table 15). All subjects were under 65 years old, so subgroup analysis by age was not explored.

Table 14. Exploratory Subgroup Analysis of Change from Baseline in AISRS Total Score to Week 6 (Study 812P306)

		Treatment Arm	Baseline N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference (95% CI)
Sex	Male	Viloxazine ER	98	37.7 (6.77)	-15.2 (1.2)	-3.9 (-7.3, -0.5)
		Placebo	96	37.7 (6.59)	-11.3 (1.22)	-
	Female	Viloxazine ER	77	39.6 (6.16)	-15.8 (1.42)	-3.6 (-7.4, 0.3)
		Placebo	83	37.5 (6.7)	-12.3 (1.32)	-
Race	White	Viloxazine ER	142	38.2 (6.51)	-15 (1)	-3.3 (-6.1, -0.5)
		Placebo	136	38.2 (6.56)	-11.7 (1.01)	-
	Other Races	Viloxazine ER	33	39.8 (6.71)	-17.8 (2.32)	-6 (-12.2, 0.2)
		Placebo	43	35.8 (6.58)	-11.7 (2.01)	-

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; AISRS = ADHD Investigator Symptom Rating Scale; N = number of subjects included; CI = confidence interval; LS = least-squares; SD = standard deviation; SE = standard error.
LS mean differences (SPN-812 - placebo), 95% CIs were obtained from a mixed model for repeated measures (MMRM) with change from baseline in AISRS total score as the repeated dependent variable and fixed effect term for baseline AISRS total score, treatment, study visit, and treatment-by-study visit interaction as independent variables.
Source: CSR, Tables 14.2.3.3.1 and 14.2.3.3.2 (812p306 tables-and-figures.pdf, pp. 164-183); confirmed by FDA statistical reviewer (ADEFF1 dataset).

Table 15. Exploratory Subgroup Analysis of Change from Baseline in CGI-S Score to Week 6 (Study 812P306)

		Treatment Arm	Baseline (N)	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference (95% CI)
Sex	Male	Viloxazine ER	98	4.5 (0.63)	-1.4 (0.13)	-0.3 (-0.7, 0)
		Placebo	96	4.6 (0.59)	-1.0 (0.13)	-
	Female	Viloxazine ER	77	4.7 (0.67)	-1.5 (0.15)	-0.5 (-0.9, -0.1)
		Placebo	83	4.6 (0.61)	-1.0 (0.14)	-
Race	White	Viloxazine ER	142	4.6 (0.63)	-1.4 (0.11)	-0.4 (-0.7, -0.1)
		Placebo	136	4.6 (0.61)	-1.0 (0.11)	-
	Non-White	Viloxazine ER	33	4.8 (0.7)	-1.7 (0.26)	-0.7 (-1.4, 0)
		Placebo	43	4.5 (0.55)	-1.0 (0.22)	-

Abbreviations: CGI-S = Clinical Global Impression - Severity of Illness; N = number of subjected included; CI = confidence interval; LS = least-squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.
LS mean differences (SPN-812 - placebo), 95% CIs were obtained from a mixed model for repeated measures (MMRM) with change from baseline in CGI-S score as the repeated dependent variable and fixed effect term for baseline CGI-S score, treatment, study visit, and treatment-by-study visit interaction as independent variables.
Source: CSR, Tables 14.2.3.4.1 and 14.2.3.4.2 (812p306_tables-and-figures.pdf, pp. 184-203); Confirmed by FDA statistical reviewer (ADQS dataset)

8.1.3. Assessment of Efficacy Across Trials

Only one controlled trial in adults was performed.

8.1.4. Integrated Assessment of Effectiveness

The results of Study 812P306 demonstrated the efficacy of viloxazine ER, flexible dose (200 mg to 600 mg) for adult subjects with ADHD. Because the study's design included flexible dosing, a formal analysis of efficacy in dose subgroups was not prespecified. The primary endpoint, CFB on the AISRS, reached statistical significance with the potential for clinical benefit for adult patients with ADHD. These results support the Applicant's proposed indication for the use of viloxazine ER to treat ADHD in adults; broadening the indication to adults and pediatric patients 6 years of age and older.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary source of safety data for this review was Study 812P306, the short-term, placebo-controlled trial in adult subjects with ADHD. Interim data from an ongoing open-label extension study, 812P311, were also reviewed, although the small sample size made it difficult to draw conclusions about safety signals. The existing safety database for the currently marketed indication, ADHD in pediatric patients 6 to 17 years of age, was reviewed with the original marketing application. No new pediatric safety data were introduced with this supplemental application.

The clinical review focused on treatment-emergent adverse events (TEAEs), laboratory parameters, vital signs, electrocardiograms (ECGs), and also on adverse events of special interest for this patient population and drug class, including suicidal ideation and behavior, other psychiatric TEAEs, and cardiovascular changes.

8.2.2. Review of the Safety Database

Overall Exposure

For drugs intended for chronic administration, the International Conference on Harmonisation (ICH) E1 guideline recommends a safety database of 300 to 600 subjects exposed for at least 6 months and 100 subjects exposed for 1 year. Overall exposure for viloxazine ER includes subjects in the pediatric and adult development programs. Chronic exposure numbers in the pediatric development program exceeded the recommended ICH numbers; at the time of initial approval, 682 pediatric subjects had received viloxazine ER for at least 6 months and 347 pediatric subjects had received viloxazine ER for at least 1 year. As of this review, 277 adult subjects with ADHD have received at least one dose of viloxazine ER. In the ongoing open-label study in adults, 43 subjects have been treated with viloxazine ER for at least 6 months and 22 subjects have been treated for at least 1 year. For additional information about the safety database, please refer to the original NDA 21194 review (archived November 6, 2020).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The majority of existing safety data for viloxazine ER were compiled from the pediatric registration studies. The most common adverse events (AEs) in pediatric subjects 6 to 17 years of age were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability. The currently approved Prescribing Information (PI) includes a boxed warning describing higher rates of suicidal thoughts and behavior that were reported in pediatric subjects treated with viloxazine ER. Warnings and precautions from the current PI include blood pressure and heart rate increases, activation of mania or hypomania, and somnolence and fatigue. Safety assessments in the adult study, therefore, included monitoring for these potential AEs.

The overall safety database for viloxazine ER was considered adequate at the time of the review of the initial NDA. The adult data adds to this database. Safety assessments in the adult study were adequate to assess the known risks of viloxazine ER. No findings in this review led the clinical reviewer to believe any new safety signals were identified.

Issues Regarding Data Integrity and Submission Quality

Data were organized in a way that facilitated review and there were no concerns about data integrity.

Categorization of Adverse Events

The Applicant coded reported AE terms (under the variable AETERM) to Medical Dictionary for Regulatory Activities (MedDRA) v22.1. AEs were categorized by dictionary-derived term (AEDECOD) and body system or organ class (AEBODSYS). The Applicant used AE categorization typical for psychiatric drug studies. A spot-check of submitted data showed proper coding, categorization, and recording of AEs.

Routine Clinical Tests

Routine clinical tests included physical examinations, vital signs, weight, ECGs, clinical laboratory testing, and monitoring for suicidal ideation and behavior (SI/B) as assessed by the C-SSRS.

Clinical laboratory tests included serology, hematology (including red blood cell count, hemoglobin, hematocrit, platelet count, and white blood count with differential), electrolytes (chloride, phosphate, potassium, sodium), liver function tests (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin), renal function parameters (blood urea nitrogen, creatinine), other blood chemistry (glucose, calcium, albumin, total protein, bicarbonate, follicle stimulating hormone in post-menopausal females), urinalysis (macroscopic examination, pH, specific gravity, protein, glucose, ketone, occult blood, white blood cells, nitrites, bilirubin, urobilinogen), screens for drugs of abuse (serum ethanol, urine drug screens), and blood (at screening) and urine (other time points) pregnancy testing for subjects of childbearing potential. For a breakdown of clinical test scheduling, see Table 16.

Table 16. Schedule of Clinical Safety Assessments, Study 812P306

	Screening	Baseline	Treatment				End of Study
Visit	1	2	3	4	5	6	7
Physical examination	X						X
Height	X						
FSH	X						
Serum pregnancy	X						
Serology	X						
Hematology/serum chemistry	X	X					X
Urinalysis	X	X					X
ECG	X	X					X
Serum drug screen	X						
Urine drug screen	X	X	X	X	X	X	X
Urine pregnancy		X	X	X	X	X	X
Orthostatic BP/HR	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X

Source: Adapted by clinical reviewer from Applicant's protocol for 812P306, Table 2, p. 40.

Open-label Study 812P311 was designed to monitor and collect long-term safety data on the use of viloxazine ER as monotherapy for the treatment of ADHD in the adult population. The study is ongoing. Primary safety endpoints include TEAEs, clinical safety laboratory test results, vital signs, weight, ECGs, physical examination, and the C-SSRS. Following the first dose, subjects attend a study visit every 2 weeks for the first 4 weeks, and then study visits occur every 8 weeks up through 156 weeks. The assessment schedule for each on-site visit is similar to that of Study 812P306 (see Table 16). Sites also perform follow-up phone calls to each subject every 4 weeks after Study Visits 3 through 21 to assess AEs, changes in concurrent medications, and obtain results of pregnancy tests.

8.2.4. Safety Results

Deaths

No subjects died during the controlled study, 812P306, and no deaths have been reported in the interim data submitted for the open-label study, 812P311.

Serious Adverse Events

Two serious adverse events (SAEs) were reported in Study 812P306, both in the placebo group. One subject experienced moderate cardiac failure, congestive. The other subject experienced

severe pancreatitis. Study medication (placebo) was withdrawn in both cases.

Five SAEs involving two subjects have been reported for Study 812P311, including one each of syncope, spinal column injury, pulmonary embolism, fall, and deep vein thrombosis.

- Three SAEs occurred in a 56-year-old female subject (USUBJID (b) (6); syncope, spinal column injury, fall). On Day 341 of study enrollment and 1 day after receiving a COVID vaccination, this subject experienced fatigue, poor appetite, and dizziness and subsequently fell and hit her head against a bedframe. She sustained facial lacerations and a cervical spine injury. Electrocardiogram revealed tachycardia but no other findings. The Investigator assessed the SAE as not related to viloxazine ER treatment. No action was taken with the study medication.

- The other two SAEs occurred in a 31-year-old male subject (USUBJID (b) (6); pulmonary embolism, deep vein thrombosis) with medical history of ADHD and a jaw fracture. This subject had received viloxazine ER in Study 812P306 and reported adverse events of lethargy and emotional disorder that were described as mild and possibly related to study drug. On Day 97 of enrollment in Study 812P311, the subject reported SAEs of left lower extremity deep vein thrombosis and bilateral pulmonary embolism. The subject was discontinued from the study and is recovering. The Investigator assessed these events as not related to the study drug.

Overall, SAEs were uncommon in subjects exposed to viloxazine ER in the adult development program and no clear pattern of SAEs suggestive of a drug-related effect was apparent. In one subject, an adverse reaction to vaccination appeared to be a plausible triggering event. In the other subject, the available information is insufficient to determine whether the event was related to viloxazine ER exposure.

Dropouts and/or Discontinuations Due to Adverse Effects

During Study 812P306, 26 subjects discontinued the study medication due to treatment-emergent adverse events (TEAEs). This includes 17 subjects (9%) receiving viloxazine ER and 9 subjects (4.9%) receiving placebo.

Table 17. Overall Discontinuations Due to TEAE and Most Common System Organ Classes, Study 812P306

	Placebo N=183	Viloxazine N=189
Discontinuations	9 (4.9%)	17 (9.0%)
Psychiatric disorders	4 (2.2%)	6 (3.2%)
Gastrointestinal disorders	2(1.1%)	7 (3.7%)
Nervous system disorders	1 (0.5%)	5 (2.6%)

Source: Clinical reviewer, adapted from Applicant's ADAE dataset.

The most common system organ classes (SOC) containing TEAEs leading to discontinuation at a higher rate for viloxazine ER compared with placebo in the controlled Study 812P306 were psychiatric disorders, gastrointestinal disorders, and nervous system disorders.

As expected, insomnia occurred more frequently in viloxazine ER compared with placebo. Other psychiatric AEs leading to discontinuation included panic attack, anxiety, confusional state, and emotional poverty.

Within gastrointestinal disorders, TEAEs more frequently leading to discontinuation in the viloxazine ER group included constipation, abdominal discomfort, diarrhea, dry mouth, and nausea. These are expected with this drug and class.

Within nervous system disorders, TEAEs leading to discontinuation more frequently in the viloxazine ER group included headache, dizziness, lethargy, and migraine.

Other SOC classes in which TEAEs led to discontinuation included general disorders/ administration site conditions (fatigue, chills), investigations (one subject in each group discontinued due to hepatic enzymes increased and transaminases increased), skin and subcutaneous tissue disorders, cardiac disorders, ear and labyrinth disorders, infections, musculoskeletal and connective tissue disorders, reproductive system and breast disorders, and vascular disorders.

The clinical reviewer summarized discontinuation data from interim results of the open-label Study 812P311. In this sample of 157 adult subjects with ADHD treated with open-label viloxazine ER, a total of 26 individual subjects (16.6%) discontinued treatment due to TEAEs. Similar to the controlled study, the most common SOC classes leading to discontinuation were psychiatric disorders, including 12 occurrences in 11 subjects (7%); gastrointestinal disorders, including 12 occurrences in seven subjects (4%); and nervous system disorders, including nine occurrences in eight unique subjects (5%). As expected, the most frequent reasons for discontinuation included insomnia, nausea, and fatigue.

Of note, there were three occurrences of increased liver function tests leading to discontinuation in two subjects (1%) in Study 812P311. One subject (USUBJID (b) (6)) experienced what was described as "elevated liver enzymes." The second subject (USUBJID

(b) (6)) experienced elevated alanine aminotransferase and aspartate aminotransferase levels.

Significant Adverse Events

The nonclinical development program identified a potential risk of convulsions. Adverse events of special interest (AESI) were defined as seizure or AEs that were likely to represent a seizure in both the pediatric and adult development programs. Viloxazine ER was not associated with seizures in the pediatric studies. No subjects experienced events that were categorized as AESIs in adult Studies 812P306 or 812P311.

Treatment Emergent Adverse Events (TEAEs)

Insomnia, nausea, dry mouth, constipation, headache, fatigue, and decreased appetite were the most frequently reported treatment-emergent adverse events (TEAEs) in Study 812P306. The most commonly experienced TEAEs occurring at least twice the rate in the viloxazine ER group as compared with the placebo group are summarized in Table 18 below.

Table 18. Treatment-Emergent Adverse Events Reported in ≥ 2% of Subjects Treated with Viloxazine and at Twice the Frequency Reported in Subjects Treated with Placebo

Treatment-Emergent Adverse Events	Placebo N=183 (%)	Viloxazine N=189 (%)
Insomnia[a]	7	23
Headache (including migraine)	7	17
Fatigue	3	12
Nausea	3	12
Decreased appetite, anorexia	3	10
Dry mouth	2	10
Somnolence	2	6
Constipation	1	6
Dizziness	2	4
Vomiting	0.5	4
Tachycardia	0.5	4
GERD	0.5	2

[a]Grouped term: includes insomnia, initial insomnia, and middle insomnia
Source: Clinical reviewer, adae.xpt.

In pediatric subjects, somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability were the most commonly described adverse events—occurring at a rate twice that of placebo. The TEAEs from the controlled study in adults were therefore generally similar to those observed in the pediatric controlled trials.

Of note, Study 812P306, a flexible-dose study, allowed adult subjects to titrate up to 600 mg daily. In the pediatric studies, some adverse events were reported more frequently in subjects taking viloxazine ER 600 mg, in particular somnolence, fatigue, and nausea. In addition, a larger percent of subjects who experienced an increase in heart rate from Baseline to EOS of at least 25 beats per minute (bpm; 10% in the 600 mg group, at least 5% in all dose groups) without additional benefits (see original NDA 21194 review). Although a flexible-dose design is not optimal to explore differences in safety between doses of viloxazine ER, the clinical reviewer summarized the TEAE profile of events occurring at each terminal dose level. The most commonly reported TEAEs did not differ significantly between dose groups, with 22%, 14.5%, and 14% of subjects in the 200 mg, 400 mg, and 600 mg viloxazine ER groups reporting insomnia and 14.6%, 11.3%, and 11.6% of participants reporting headache.

Interim data for Study 812P311 showed a similar pattern of TEAEs, albeit without a comparison group. Of the 157 subjects enrolled thus far, 109 (69.4%) of subjects reported any TEAE. The most frequent TEAEs reported for viloxazine ER-treated subjects in the ongoing open-label study are summarized in the Table 19 below.

Table 19. Treatment-Emergent Adverse Events in ≥ 2% Subjects, Study 812P311, Interim Data

Treatment-Emergent Adverse Event	Viloxazine N=157 (%)
Insomnia*	15
Nausea	15
Fatigue	10
Headache	10
Anxiety	5
Vomiting	5
Dry mouth	5
Dizziness	5
Decreased appetite	5
Erectile dysfunction	4
Diarrhea	3
Coronavirus infection	3
Constipation	3
Restlessness	3
Irritability	3
Tachycardia	3
Palpitations	3
Dyspepsia	3
Apathy	3
Sinusitis	2
Upper respiratory infection	2
Migraine	2

Treatment-Emergent Adverse Event	Viloxazine N=157 (%)
Somnolence	2
Back pain	2

Source: Clinical reviewer, adapted from Applicant adae.xpt dataset, JMP Clinical.

Laboratory Findings

No abnormal median values (occurring outside of the reference ranges) of laboratory values were observed at Baseline or EOS for the controlled trial, 812P306. No significant changes in laboratory findings were noted.

Assessments of liver function were of particular interest because of reports of hepatobiliary adverse reactions, including of fatal cases, associated with the postmarketing use of the immediate-release form of viloxazine from the European Database of Suspected Adverse Drug Reactions (Eudra Vigilance). No Hy's Law cases were reported in Study 812P306. The TEAE of increased transaminases occurred at approximately equal frequency in the drug and placebo groups, with five subjects reporting increased transaminases in each treatment group (2.6% and 2.7%, respectively). Shifts from within normal ranges at Baseline to high at EOS were observed at similar frequencies for high alanine aminotransferase in the viloxazine ER and placebo groups (9.5% versus 8.2%), high alkaline phosphatase (2.1% versus 0.5%), high bilirubin (0.5% versus 3.8%), and low bilirubin (3.7% versus 2.7%).

In the interim study data for 812P311, in addition to the subjects who discontinued due to liver function test (LFT) abnormalities as previously discussed in Section 8.2.4, there were also two subjects with shifts to high LFT levels during the study. Both resolved with no change in study treatment, and neither was coded as an AE.

- Subject (b) (6) experienced an isolated increase in aspartate aminotransferase (AST) from 30 U/L ((b) (6)) to 340 U/L ((b) (6)). The subsequent AST level reverted to within reference range at 32 U/L ((b) (6)). No overlapping AEs occurred.

- Subject (b) (6) experienced increases in alanine aminotransferase (ALT) levels starting on (b) (6), at 54 U/L (previous level was 40 U/L on (b) (6)). The subsequent ALT level then increased to 117 U/L on (b) (6), before reverting to within reference range on (b) (6) at 37 U/L. The subject also experienced a corresponding increase in AST on (b) (6), at 117 U/L. Previous and subsequent levels were within reference range. This subject experienced AEs of tachycardia and hypertension during this time, which both resolved as of (b) (6).

Due to the incomplete dataset, it is difficult to draw any conclusions about these occurrences. No information about concomitant medications were available, and, because the study is

ongoing, further information may be forthcoming.

In addition, there were eight subjects (5%) who experienced ALT elevations to at least twice the upper limit of normal during the study and three subjects (2%) who experienced an AST elevation to at least twice the upper limit of normal in the study. No other hepatic findings were noted. The clinical reviewer recommends continued monitoring for reports of hepatic enzyme changes and hepatobiliary adverse reactions in the postmarketing period.

High bicarbonate was experienced more frequently in the placebo group in Study 812P306, with five subjects (2.6%) in the viloxazine ER group and 12 subjects (6.6%) in the placebo group experiencing a shift from within normal ranges at Baseline to high at EOS.

No significant differences were observed between groups for any hematological parameters for controlled Study 812P306. Likewise, observed shifts in urinalysis patterns were comparable between the treatment groups.

For open-label Study 812P311, interim data revealed no potentially clinically-meaningful trends for laboratory findings.

In general, the laboratory findings did not identify additional safety signals beyond those described in the original NDA review for the pediatric population.

Vital Signs

In general, no important mean differences were observed between the treatment groups for heart rate, diastolic and systolic blood pressure, respiratory rate, and temperature in the controlled study, 812P306.

Heart rate increase of at least 20 bpm from Baseline at any point in the study was more frequently seen in the viloxazine ER group (n=52, 29%) compared with the placebo group (n=23, 13%). Tachycardia reported as a TEAE, as seen above, was also reported more frequently in the viloxazine ER group than the placebo group (4% versus 0.5%). This is an expected effect of the class of noradrenergic reuptake inhibitors to which viloxazine ER belongs. Heart rate increase of at least 20 bpm from baseline was seen in 38 (24%) of the subjects with exposures from the interim dataset of the open-label 812P311 study.

Diastolic blood pressure increases of at least 15 mmHg were also reported more frequently for viloxazine ER (n=23, 13%) as compared with placebo (n=16, 9%) in controlled Study 812P306. This is an expected effect of the class of noradrenergic reuptake inhibitors to which viloxazine ER belongs. However, a review of the terms “blood pressure increased, blood pressure diastolic increased, blood pressure systolic increase, and hypertension” revealed a similar number of subjects in each group, with frequency below 2% in Study 812P306. Analysis of interim data for open-label Study 812P311 found that 22 subjects (14%) had diastolic blood pressure increases of at least 15 mmHg.

Systolic blood pressure changes were not significantly different in the viloxazine ER group compared with the placebo group (n=43, 23% for viloxazine ER and n=43, 23% for placebo), per the clinical reviewer's independent analysis of the Applicant datasets. Systolic blood pressure increases of at least 15 mmHg were reported for 42 subjects (27%) in the open-label study.

The cardiovascular-related vital sign changes reported in the study are consistent with those described in the product label and do not reflect a new safety signal.

Body weight decrease was reported as an adverse event for two subjects (1.1%) in the viloxazine ER group as compared with none in the placebo group in Study 812P306. Weight increase was reported for no subjects in the viloxazine group ER and one subject in the placebo group. Overall, reported maximum mean (standard deviation) change in weight across the study was 0.8 kg (1.6 kg) for the viloxazine ER group and 1.5 kg (1.6 kg) for the placebo group. The mean (SD) change in weight between baseline and the last measurement was -0.8 kg (1.7 kg) for the viloxazine ER group and 0.2 kg (4.0 kg) for the placebo group.

Interim data from the ongoing 812P311 study showed that of the 66 subjects with weights reported after 6 months of viloxazine ER, there was a mean (SD) weight change of -1.5 kg (4.4 kg). Weight changes ranged from -11.8 kg to 6.5 kg.

Overall, the vital sign results are consistent with what would be expected of this drug, and no new safety concerns were discovered. Interim data from the ongoing 812P311 open-label study did not show any concerning or unexpected trends for changes in vital signs.

Electrocardiograms (ECGs)

No clinically meaningful differences in changes in ECG parameters were noted between the groups in the controlled study, 812P306.

QT

No concerning differences in QT interval changes were observed between the groups in controlled Study 812P306. The mean change from Baseline was less than or equal to 30 msec for the majority of subjects in both treatment groups (96.1% of subjects in the viloxazine ER group and 94.4% in the placebo group). Likewise, the change from Baseline for the QTcF interval was reported as less than or equal to 30 msec for the majority of both groups (98.7% of subjects in the viloxazine ER group and 98.8% in the placebo group). Three subjects in the placebo group had a trial maximum QTcF of ≥450 msec; one of those also had a QTcF of ≥450 msec at baseline. Likewise, two subjects (1%) in the viloxazine ER group had a QTcF of ≥450 msec during the study; one of those subjects also had a QTcF of ≥450 at baseline. A review of the datasets by this reviewer found no subjects with a change in QTcF of ≥60 msec in controlled Study 812P306.

In open-label Study 812P311, interim data showed six subjects (4%) with maximum QTcF of ≥450 msec during post-baseline measurements, and two subjects (1%) with ≥60 msec change.

Overall, no concerning trends towards changes in QTcF interval changes were observed for viloxazine-ER exposed subjects in the controlled trial or in the interim dataset from the ongoing open-label trial.

Immunogenicity

No concerns about viloxazine ER-induced immune responses were identified in the development program.

8.2.5. Analysis of Submission-Specific Safety Issues

As previously summarized, one AESI was identified due to nonclinical concerns of seizure. No AESI were identified in the study. In addition, because of the class to which this drug belongs, suicidal ideation and behaviors (SI/B) were prospectively monitored at each study visit as assessed by the C-SSRS.

8.2.5.1. Suicidal Ideation and Behaviors (SI/B)

During the controlled Study 812P306, one subject (0.5%) in the viloxazine ER group reported suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline prior to randomization. One subject in the viloxazine ER group (0.5%) engaged in non-suicidal self-injurious behavior. No subject in the placebo group answered any C-SSRS question with 'yes' at baseline or End of Study (Week 6, EOS).

Three subjects in the viloxazine ER group (1.6%) reported suicidal ideation (wish to be dead) on the C-SSRS.

- Subject (b) (6), reported a prior history of suicidal ideation (lifetime/within last 6 months) and suicide attempt (lifetime) on the screening C-SSRS. The subject was discontinued for noncompliance at Week 6 (took prohibited medication lorazepam). The subject reported suicidal ideation at Week 3 (Visit 5), Week 4 (Visit 6), and at early discontinuation visit (Visit 7). Suicidal ideation was reported as an AE but did not result in a change in dose or discontinuation of study medication.

- Subject (b) (6) reported no prior history of suicidal ideation or behavior on the screening C-SSRS. The subject took two doses of viloxazine ER and discontinued the study medication due to the adverse event of insomnia. The subject reported suicidal ideation during the early discontinuation visit. Suicidal ideation was reported as an AE that started 1 day after last dose of study drug and resolved 4 days later. The Investigator considered this occurrence to be possibly related to study medication; the timing of the AE and the resolution after discontinuation could be consistent with a drug-related effect.

- Subject (b) (6) reported no prior history of suicidal ideation or behavior on the screening C-SSRS and subsequently reported a wish to be dead on the Week 6 C-SSRS. The subject reported an adverse event of insomnia during the study, leading to a reduction in dose. The subject completed the study.

No TEAEs of SI/B have been reported for the ongoing open-label study 812P311.

Overall, few subjects reported SI/B in the adult controlled study, though the reports that did occur were limited to the group treated with viloxazine ER. There are not enough data to conclude that the risk identified in the pediatric population does not apply to adults, particularly as this risk is seen in other norepinephrine reuptake inhibitors.

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

See Section 8.2.5.1 for a discussion of the C-SSRS results.

8.2.7. Safety Analyses by Demographic Subgroups

In Study 811P306, 56.7% of White subjects, 40.4% of Black subjects, 57% of Asian subjects, and 50% of subjects identifying as multiple race reported TEAEs. TEAEs were reported more commonly in female subjects (60.5%) compared with male subjects (50.7%). However, because of the small sample sizes for the demographic subgroups, no formal conclusions can be drawn regarding any potential differences in safety in these populations. No potential differences would be expected for this drug or class of medications.

8.2.8. Specific Safety Studies/Clinical Trials

Study 812P112.2, a study of single-dose viloxazine in healthy subjects and subjects with hepatic impairment, was submitted as a part of this efficacy supplement submission and is intended to fulfill the postmarketing requirement. For more details, see Section 6.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The available safety data did not raise concern about carcinogenicity associated with viloxazine ER.

Human Reproduction and Pregnancy

No new cases of pregnancy exposure have been found in the published literature or in the Applicant's pharmacovigilance database since the time of original approval. No cases related to lactation or infertility have been reported. There is an outstanding postmarketing requirement for a single-arm pregnancy safety study that was issued at the time of the original approval. Current labeling is in the Pregnancy and Lactation Labeling Rule (PLLR) formatting; no changes

to Subsections 8.1 or 8.2 of labeling are recommended. Please see the DPMH Maternal Health Review for full details regarding the information related to human reproduction, pregnancy, and lactation (review in DARRTS).

Pediatrics and Assessment of Effects on Growth

The Applicant did not submit any pediatric data with this supplement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Controlled Substances Staff (CSS) completed a consultative review evaluating data related to the abuse liability of viloxazine ER for the review of the initial NDA 211964. The CSS staff concluded that viloxazine ER does not have clinically relevant abuse liability. Viloxazine ER is not scheduled under the Controlled Substances Act. Refer to the review for the original NDA 211964 for a summary of overdose, drug abuse potential, withdrawal, and rebound with viloxazine ER.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Available postmarketing data are limited, as viloxazine ER was only recently approved (April 2, 2021). As previously mentioned, viloxazine immediate-release had been authorized for the treatment of depression outside the United States. The Applicant has not identified any safety signals in the postmarketing period thus far.

The Division requested consultation from the Division of Pharmacovigilance (DPV) to assist in the evaluation of the available postmarketing data, particularly reports of suicidal ideation or behavior, cardiovascular adverse reactions, seizures (which had been identified as an adverse event of special interest in the development program because of nonclinical study findings), and hepatic injury (as there had been two reported cases of fatal hepatitis when viloxazine immediate-release was authorized in Europe).

DPV reviewed all expedited (15-day) reports, reviewed the FDA Adverse Event Reporting System (FAERS) reports, screened periodic adverse drug experience reports, and performed a literature review to assess adverse events identified between April 2, 2021, and February 8, 2022. DPV retrieved 127 FAERS reports and identified 31 reports that were either expedited (15-day) or coded with the preferred terms related to the adverse events of interest (completed suicide; delusion; generalized tonic-clonic seizure; hallucination; hallucination, auditory; hallucinations, mixed; hallucination, visual; intentional self-injury; loss of consciousness; mania, paranoia; physical assault; schizoaffective disorder; seizure; self-injurious ideation; suicidal behavior; and suicidal ideation).

The DPV review did not identify any hepatic adverse events. Twenty-two unique reports were identified for viloxazine ER and cardiovascular, seizure, or serious psychiatric adverse events.

The majority of these provided only limited information regarding past medical history, concomitant medications, and patient follow-up. Twelve of these reported discontinuation of viloxazine ER, with six reporting a positive dechallenge.

- Suicidal ideation and behavior (SI/B): 13 reports of SI/B were identified, including eight reports of suicidal ideation, two reports of completed suicide, two reports of self-injurious ideation, and one report of suicidal behavior.

- Other serious psychiatric adverse events: four reports of hallucinations (including auditory, mixed, and visual), one report of homicidal ideation, and one report of mania have been identified.

- Cardiovascular adverse events: one report of loss of consciousness and one report of tachycardia have been identified.

- Seizure: Two adverse events of seizures were reported. One of these events occurred in a patient with a previous history of seizure disorder.

The postmarketing surveillance thus far has identified adverse reactions that are captured in labeling for viloxazine ER. Given the small number of reports and limited information reported (i.e., with regard to previous medical history, concomitant medications, and information related to patient follow-up), no new safety signals were identified from this postmarket evaluation of viloxazine ER.

Expectations on Safety in the Postmarket Setting

FDA will continue to monitor for new safety signals in the postmarketing period.

8.2.11. Integrated Assessment of Safety

Overall, the data reviewed with this efficacy supplement appears to support the safety of viloxazine in adults with ADHD. The results of the studies reviewed in this supplement complement the results seen in the pediatric studies. The most commonly observed AEs in adult subjects with ADHD included insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation. We recommend continuing to monitor for SI/B, insomnia, other psychiatric AEs, blood pressure/heart rate changes, and hepatic impairment.

8.3. Conclusions and Recommendations

The safety results of Study 812P306 reflect no unusual findings in adult subjects with ADHD compared with what is expected for this drug and class. Overall, the safety profile of viloxazine ER in adults appears similar to that seen in pediatric subjects during the initial NDA 211964

review. The clinical reviewer concluded that the study results did not reveal any new safety concerns for the use of viloxazine ER in relation to the previously reviewed pediatric data. The efficacy data provided by Study 812P306 provides evidence of effectiveness for viloxazine ER's use in adult patients with ADHD. Submitted data analyzed in this review supports the Applicant's proposed indication of viloxazine ER for the treatment of ADHD in adults and pediatric patients 6 years and older. The clinical reviewer recommends ongoing monitoring for SI/B, insomnia, other psychiatric AEs, blood pressure/heart rate changes, and hepatic impairment.

9 Advisory Committee Meeting and Other External Consultations

The review team did not seek input from an Advisory Committee or other external stakeholders because this sNDA included efficacy and safety data for an already-approved product and for an established indication, no novel clinical study design issues or concerns with interpretation of the efficacy data were identified, and the review did not find any serious safety risks that have not been described previously in the PI.

10 Pediatrics

Viloxazine ER is indicated for the treatment of ADHD in pediatric patients ages 6 to 17 years. No additional pediatric data were submitted with this efficacy supplement.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Existing prescription drug labeling for viloxazine ER (marketed under trade name Qelbree) was modified to reflect the broadening of the indicated population to include adults with ADHD and to reflect the safety and efficacy results of Study 812P306. In addition, labeling was updated to include relevant data from the hepatic impairment study, Study 812P112.2, and a multiple-dose paroxetine pharmacokinetic study, Study 812P113.4.

The boxed warning for suicidal ideation and behavior was slightly modified to delete pediatric-specific language. Although few subjects in the adult studies reported suicidal ideation or behavior, the data are insufficient to conclude that the risk identified in the pediatric studies is not applicable to adult patients.

Section 1 (Indications and Usage) was updated with the addition of the indication for adult patients with ADHD.

Section 2 (Dosage and Administration) was updated to include the recommended adult dosage (200 mg to 600 mg once daily) and to revise the instructions for administration. Current labeling indicates that the contents of the capsule may be mixed into a teaspoon of applesauce. The Applicant conducted studies to evaluate the acceptability of yogurt and chocolate pudding as soft food vehicles and also evaluated the volume of food substance into which the capsule contents may be mixed. The biopharmaceutics review concluded that the in vitro release study results for yogurt were inconclusive; the results for chocolate pudding were acceptable. The review also found that mixing the contents of the capsule into volumes ranging from a 1 teaspoon to 1 tablespoon is acceptable. The administration instructions were modified to specify that the contents of the capsule may be sprinkled into a teaspoon or tablespoon of pudding or applesauce (within 15 minutes for pudding or within 2 hours for applesauce).

Section 5 (Warnings and Precautions) was updated to reflect the results of the adult study. The language describing the warnings regarding the risks of suicidal ideation and behavior, effects on heart rate and blood pressure, and somnolence and fatigue now includes adult data.

Section 6 (Adverse Reactions) was updated to incorporate the adverse reactions reported in the adult controlled study, to provide percentages of adverse reactions leading to discontinuations in the pediatric studies, and to add the current adult exposure numbers.

Section 7 (Drug Interactions) was updated to remove some specific examples from Table 3 as they may become outdated or be misinterpreted as a comprehensive list.

Section 8 (Use in Specific Populations) was updated to revise the risk summary sections and to revise the safety margins to the maximum daily recommended dosage of 600 mg. The Division

recommended deletion of the Applicant's proposed Section 8.7 (b) (4) because there are no specific concerns with this population.

Section 11 (Description) was modified to state that Qelbree contains viloxazine in the form of viloxazine hydrochloride.

Section 12 (Clinical Pharmacology) was updated to reflect the updated maximum dose of viloxazine as 600 mg, to reflect the estimated steady-state C_{max} and AUC_{0-t} of viloxazine and its major metabolites, and to report the findings of the hepatic impairment and the multiple-dose paroxetine studies.

Section 13 (Non-Clinical Toxicology) was updated to reflect the maximum dose of 600 mg.

Section 14 (Clinical Studies) was updated to add the results of the adult controlled study. As noted above in regulatory background (Section 3), the Division previously advised the Applicant that the secondary endpoint in the adult study, the CGI-S, was unlikely to appear in labeling because only one study would be conducted in adults and the results on the secondary endpoint would therefore not be replicated. However, the Division reconsidered this advice during the review. The Division noted that the pediatric program provided substantial evidence of effectiveness for the ADHD indication and that the adult study pertains to a related clinical population; that pediatric labeling includes a related secondary endpoints (i.e., CGI-I as the key secondary endpoint); that the CGI-S is a validated endpoint that is commonly described in labeling for psychiatric conditions; that the CGI-S provides additional information for healthcare practitioners about the clinical meaningfulness of the study results; and that the CGI-S analysis was prespecified and statistically significant. Therefore, the description of Study 812P306 results in labeling will include both the results on the primary and key secondary endpoints.

Section 17 (Patient Counseling Information) was updated to reflect the administration instructions for sprinkling the contents of capsules on applesauce or pudding if needed.

12 Risk Evaluation and Mitigation Strategies (REMS)

The PI and medication guide adequately describe the safe use of viloxazine ER. No specific serious risks were identified in this review that would necessitate a risk evaluation and mitigation strategy (REMS).

13 Postmarketing Requirements and Commitment

One post-marketing requirement study was completed and submitted with this efficacy supplement. The results of Study 812P112.2, a study to evaluate the pharmacokinetics of viloxazine ER capsules in subjects with hepatic impairment, were reviewed. Please refer to Section 6 for more details regarding the study. The study was adequately conducted and fulfills the outstanding postmarketing requirement.

The remaining postmarketing requirements include a single-arm pregnancy study, a lactation study, an efficacy and safety study in patients 4 to ≤ 6 years of age, and a long-term safety study in patients 4 to ≤ 6 years of age.

14 Deputy Division Director (Signatory) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

1. American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders (5th ed.), https://doi.org/10.1176/appi.books.9780890425596.

2. Posner J, GV Polanczyk, E Sonuga-Barke E, 2020, Attention-Deficit Hyperactivity Disorder, Lancet, 395(10222):450–62.

3. Faraone SV, P Asherson, T Banaschewski, J Biederman, JK Buitelaar, JA Ramos-Quiroga, LA Rohde, EJS Sonuga-Barke, R Tannock, B Franke, 2015, Attention-Deficit/Hyperactivity Disorder, Nat Rev Dis Primers, 1(15020):1–23.

4. Anker E, B Bothild, T Heir, 2018, Comorbid Psychiatric Disorders in a Clinical Sample of Adults with ADHD and Associations with Education, Work, and Social Characteristics: A Cross-Sectional Study, BMJ Open, doi:10.1136/bmjopen-2017-019700.

5. Balint S, P Czobor, S Komlosi, A Meszaros, V Simon, I Bitter, 2009, Attention Deficit Hyperactivity Disorder (ADHD): Gender- and Age-related Differences in Neurocognition, Psychol Med, 39(8):1337–45.

15.2. Financial Disclosure

The submitted information, including Form 3454 on Financial Disclosure, is noted.

Covered Clinical Study (Name and/or Number): 812P306

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 218		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): not provided		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3454 was provided		
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: 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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

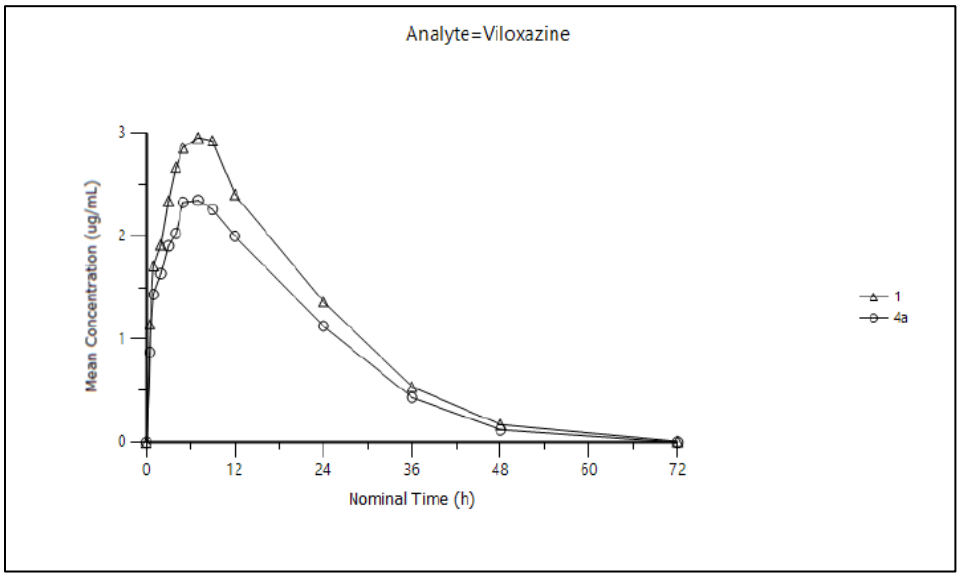
15.3. OCP Appendices

15.3.1. Hepatic impairment study (812P112.2)

Study 812P112.2 assessed the effect of mild (CP 5 or 6), moderate (CP 7 to 9) and severe hepatic (CP 10 to 15) impairment on the pharmacokinetics (PK) profile of viloxazine. The study was an open-label, multi-center, parallel, single dose, one treatment study. Mild and moderate hepatic impaired and their matched normal healthy subjects were administered a single dose of 400 mg (2 x 200 mg) viloxazine ER. Severe hepatic impaired and their matched healthy subjects were administered a single dose of 200 mg viloxazine ER. Blood samples for pharmacokinetic analysis were collected at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 36, 48, and 72 hours post-dose. The concentrations of viloxazine and its inactive major metabolite, 5-hydroxyviloxazine glucuronide (5-HVLX-gluc) in plasma were determined using validated achiral chromatographic tandem mass spectrometry (LC/MS/MS) methods.

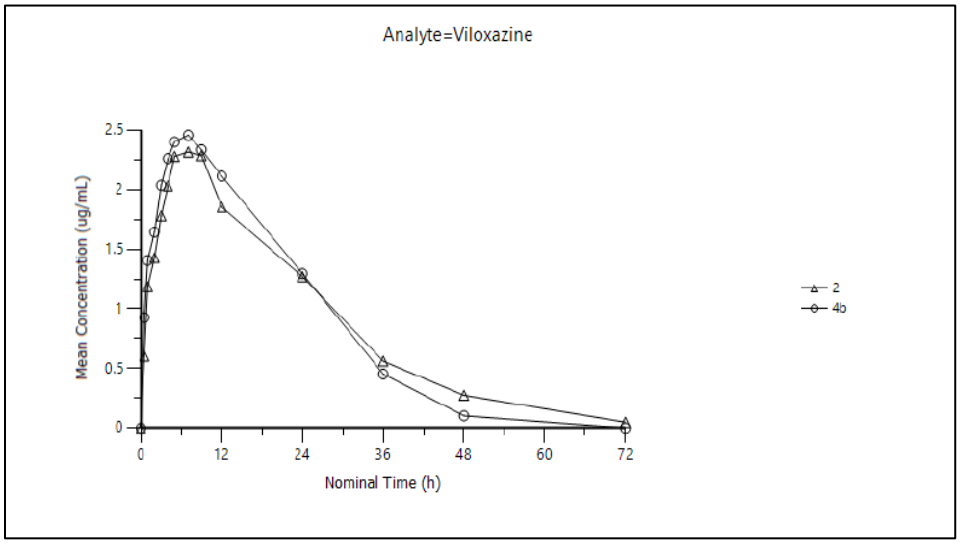
The mean viloxazine plasma concentration time profile in hepatic impaired subjects are provided in the following figures.

Figure 2. Mean Viloxazine Plasma Concentration-Time Profiles Comparing Subjects with Mild Hepatic Impairment (Group 1) to Normal Healthy Volunteer Matches (Group 4a) after Viloxazine 400 mg



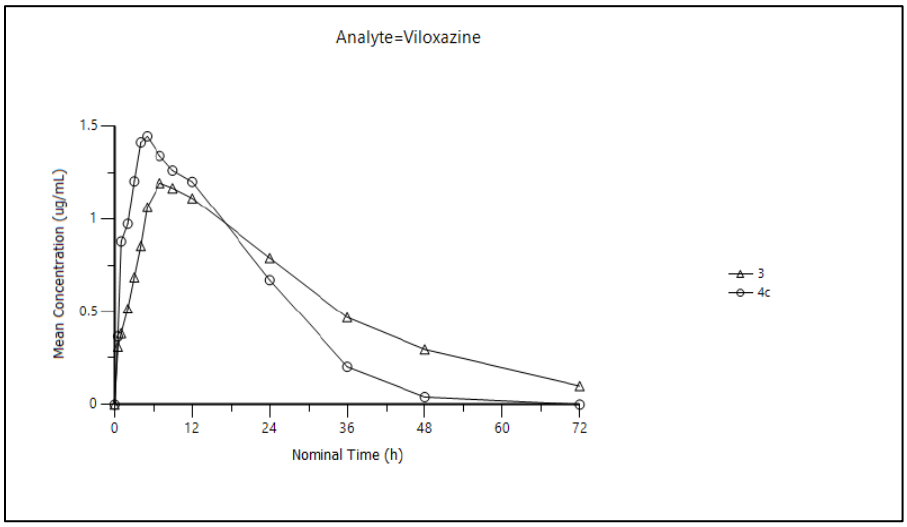
[1]Mild hepatic impairment, [4a]Matched healthy subjects
Source: Study 812P112.2 CSR, p. 80.

Figure 3. Mean Viloxazine Plasma Concentration-Time Profiles Comparing Subjects with Moderate Hepatic Impairment (Group 2) to Normal Healthy Volunteer Matches (Group 4b) after Viloxazine 400 mg



[2]Moderate hepatic impairment, [4b]Matched healthy subjects
Source: Study 812P112.2 CSR, p. 81.

Figure 4. Mean Viloxazine Plasma Concentration-Time Profiles Comparing Subjects with Severe Hepatic Impairment (Group 3) to Normal Healthy Volunteer Matches (Group 4c) after Viloxazine 200 mg



[3]Severe hepatic impairment, [4c]Matched healthy subjects
Source: Study 812P112.2 CSR, p. 82.

Table 20 summarizes the statistical comparison of the pharmacokinetics of viloxazine in hepatic impaired patients versus their matched controls.

Table 20. Relative Bioavailability of Viloxazine Comparing Subjects with Mild, Moderate, and Severe Hepatic Impairment to Normal Healthy Volunteer Matches after Single Dose Administration of Viloxazine 200 mg or 400 mg

Mild HI (Group 1) vs. Normal Healthy Matches (Group 4a), (400 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 1	Group 4a	(Group 1/Group 4a)	Lower	Upper	CV%
C_{max} (µg/mL)	2.94	2.38	123.69	98.94	154.64	25.77
AUC_{0-t} (h*µg/mL)	66.9	55.3	121.02	99.47	147.23	22.54
AUC_{inf} (h*µg/mL)	68.3	56.3	121.39	100.38	146.79	21.83
Moderate HI (Group 2) vs. Normal Healthy Matches (Group 4b), (400 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 2	Group 4b	(Group 2/Group 4b)	Lower	Upper	CV%
C_{max} (µg/mL)	2.33	2.46	94.54	72.06	124.03	31.58
AUC_{0-t} (h*µg/mL)	53.7	57.1	94.13	64.12	138.20	45.76
AUC_{inf} (h*µg/mL)	56.2	57.9	97.00	65.85	142.88	46.19
Severe HI (Group 3) vs. Normal Healthy Matches (Group 4c), (200 mg)						
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]	
	Group 3	Group 4c	(Group 3/Group 4c)	Lower	Upper	CV%
C_{max} (µg/mL)	1.25	1.46	85.42	68.81	106.03	23.92
AUC_{0-t} (h*µg/mL)	37.4	30.3	123.39	90.65	167.97	34.63
AUC_{inf} (h*µg/mL)	39.4	31.7	124.54	89.45	173.39	37.32

[a] Geometric Mean based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test, Groups 1, 2, and 3)/Geometric Mean (Reference, Groups 4a, 4b, 4c)
[c] Confidence Interval
Group 1: SPN-812 400 mg (Mild Hepatic Impairment) (n=8); Group 2: SPN-812 400 mg (Moderate Hepatic Impairment) (n=8); Group 3: SPN-812 200 mg (Severe Hepatic Impairment) (n=8); Group 4a: SPN-812 400 mg (Healthy Matches to Mild Hepatic Impairment) (n=8); Group 4b: SPN-812 400 mg (Healthy Matches to Moderate Hepatic Impairment) (n=8); Group 4c: SPN-812 200 mg (Healthy Matches to Severe Hepatic Impairment) (n=7)

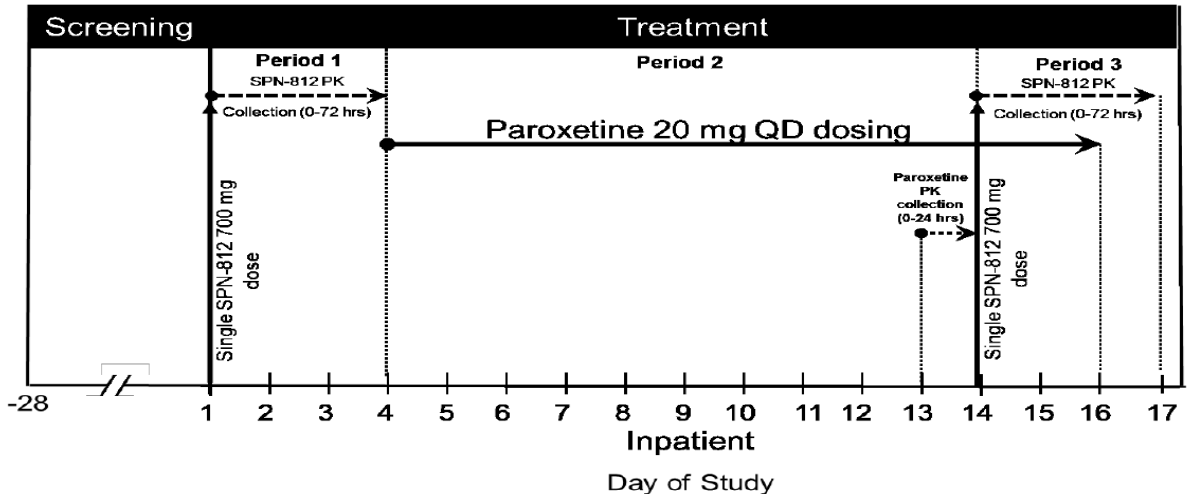
Source: Study 812P112.2 CSR, p. 100.

Viloxazine C_{max} was approximately 24% higher for subjects with mild hepatic impairment compared to matched healthy subjects; AUC_{0-t} and AUC_{inf} were approximately 21% higher for subjects with mild hepatic impairment compared to matched healthy subjects. Viloxazine geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{inf} were approximately 5%, 6%, and 3% lower, respectively, for subjects with moderate hepatic impairment compared to matched healthy subjects. Viloxazine C_{max} was approximately 15% lower for subjects with severe hepatic impairment compared to matched healthy subjects and viloxazine AUC_{0-t} and AUC_{inf} were approximately 23% and 25% higher, respectively, for subjects with severe hepatic impairment compared to healthy subjects. Median viloxazine T_{max} occurred approximately 2 hours later for subjects with mild hepatic impairment compared to matched healthy subjects, approximately 1 hour later for subjects with moderate hepatic impairment compared to matched healthy subjects, and approximately 5 hours later for subjects with severe hepatic impairment compared to healthy subjects. Differences in median T_{max} for the comparisons of subjects with mild and moderate hepatic impairment to matched healthy subjects were not statistically significant (p=0.3706 and p=0.5216, respectively). The difference in median viloxazine T_{max} for the comparison of subjects with severe hepatic impairment to matched healthy subjects was statistically significant (p=0.0164). Mean viloxazine $T_{1/2}$ values were similar for subjects with mild hepatic impairment (7.56 hours) and matched healthy subjects (6.73 hours), were approximately 3.3 hours longer for subjects with moderate hepatic impairment compared to matched healthy subjects and were approximately 7.1 hours longer for subjects with severe hepatic impairment compared to matched healthy subjects. The difference in median $T_{1/2}$ for the comparisons of subjects with mild hepatic impairment to matched healthy subjects was not statistically significant (p=0.7183). The differences in median viloxazine $T_{1/2}$ for the comparison of subjects with moderate hepatic impairment (8.39 hours) versus matched healthy subjects and subjects with severe hepatic impairment versus matched healthy subjects were statistically significant (p=0.0480 and p=0.0325, respectively).

15.3.2. **Effect of Paroxetine on the Pharmacokinetics of Viloxazine**

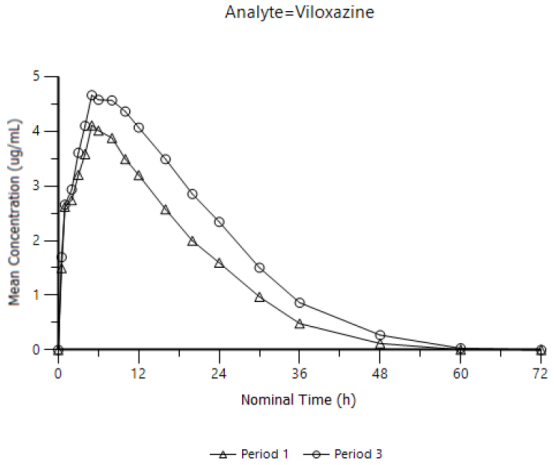
Study 812P113.4 evaluated the effect of multiple dose paroxetine on the pharmacokinetics of viloxazine after administration of viloxazine ER with and without paroxetine under fasted conditions (See Figure 5).

Figure 5. Drug-Drug Interaction Study Schematic



Source: Study 812P113.4 CSR, p. 4.

Figure 6. Mean Viloxazine Concentration-Time Profiles after Viloxazine ER 700 mg Alone (Period 1, Day 1) and SPN-812 700 mg + 20 mg Paroxetine QD (Period 3, Day 14)



Source: Study 812P113.4 CSR, p. 62.

Table 21. Statistical Analysis of Viloxazine Pharmacokinetic Parameters following Administration of Viloxazine ER Alone and Coadministration with Paroxetine after Multiple Doses

Dependent Variable (n=22)	GeoMean[a]		Ratio (%)[b] (Period 3/Period 1)	90% CI [c] Lower	90% CI [c] Upper
	Period 3	Period 1			
C_{max}	4.79	4.13	116.04	109.49	122.99
AUC_{0-t}	109	81.1	134.65	127.65	142.03
AUC_{inf}	111	82.0	134.80	127.94	142.03

[a] Geometric Mean for (Period 3; Test); (Period 1; Reference) based on Least Squares Mean of log-transformed parameter values
[b] Ratio (%) = Geometric Mean (Period 3)/Geometric Mean (Period 1)
[c] Confidence Interval
Source: Study 812P113.4 CSR, p. 66.

Table 22. Statistical Analysis of Viloxazine Metabolite (5-OH-viloxazine-gluc (5-HVLX-gluc)) Pharmacokinetic Parameters following Administration of Viloxazine ER Alone and Coadministration with Paroxetine after Multiple Doses of Paroxetine

Dependent Variable (n=22)	GeoMean[a]		Ratio (%)[b] (Period 3/Period 1)	90% CI [c] Lower	90% CI [c] Upper
	Period 3	Period 1			
C_{max}	2.81	3.38	83.05	78.52	87.85
AUC_{0-t}	60.1	67.8	88.75	84.20	93.55
AUC_{inf}	60.3	67.9	88.77	84.20	93.60

[a] Geometric Mean for (Period 3; Test); (Period 1; Reference) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Period 3)/Geometric Mean (Period 1)
[c] Confidence Interval
Source: Study 812P113.4 CSR, p. 66.

Median viloxazine T_{max} was delayed by approximately 1 hour after viloxazine ER + paroxetine compared to that after viloxazine ER alone. Mean viloxazine $T_{½}$, CL/F, and Vd/F were approximately similar across treatment periods. Co-administration of a single dose of viloxazine ER 700 mg with 20 mg paroxetine daily for 10 days increased viloxazine C_{max}, AUC_{0-t}, and AUC_{inf} by approximately 16%, 35%, and 35%, respectively, compared to that after viloxazine ER alone.

5-HVLX-gluc exposure was lower after vilozazine + paroxetine than after viloxazine ER alone. Median Tmax was 10 hours and 7 hours after viloxazine ER + paroxetine and after viloxazine ER alone, respectively. Mean $T_{½}$ was 6.38 hours after viloxazine ER + paroxetine and 5.7 hours after viloxazine alone. A decrease of approximately 17% in 5-HVLX-gluc C_{max} was observed following the co-administration of viloxazine ER and paroxetine. 5-HVLX-gluc AUCs decreased by about 11%.

15.3.3. Pharmacometric Review

Applicant's Analysis

Population PK Analysis

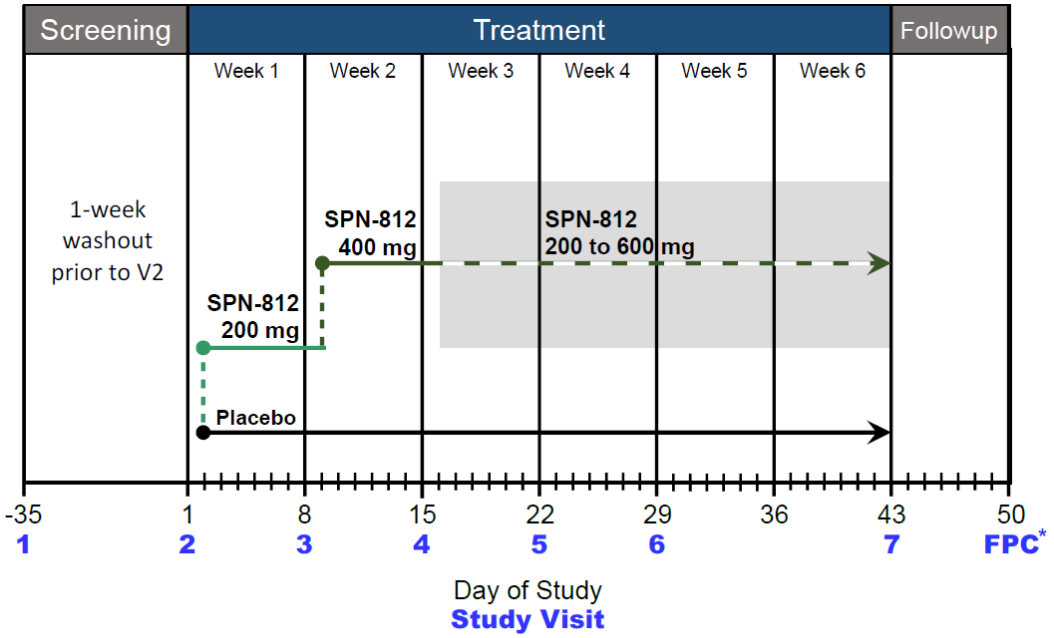
The PK data of 37 subjects collected from an optional PK sub-study of the Phase III study 812P306 were used for the population PK (popPK) analysis. 261 evaluable plasma concentrations (129 viloxazine (VLX) concentrations and 132 5-hydroxy-viloxazine glucuronide (5-HVLX-gluc) concentrations) were included to quantitatively describe the clinical PK of VLX and its major metabolite 5-HVLX-gluc and identify sources of interindividual variability in adult subjects. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4 (ICON, Maryland) was used for the popPK analysis.

Study 812P306 was a randomized, double-blind, placebo-controlled, multicenter, parallel group, flexible dose study of viloxazine in adults diagnosed with ADHD per DSM-5 criteria. Approximately 366 subjects were randomized in a 1:1 ratio (183 subjects per arm): viloxazine (200 mg to 600 mg) or placebo. Following up to 5 weeks of screening, subjects were treated with study medication (SM) for 6 weeks.

An optional PK sub-study was conducted within the study. A maximum of five separate blood samples (4 mL each) were drawn to assess the PK characteristics of VLX and its metabolite 5-HVLX-gluc in the study population. All five blood samples were either collected at one single study visit (Visit 5, 6, or 7) at the predetermined time points relative to dosing (pre-dose and 1, 2, 4, and 6 hours post-dose) or the five blood samples were collected over Visit 5, 6, and 7 (e.g., Visit 5: at pre-dose; Visit 6: at 1 and 2 hours post-dose; Visit 7: at 4 and 6 hours post-dose). The study schematic is presented in Figure 7.

Thirty-seven subjects who received viloxazine and had at least one measurable PK sample drawn were included in the popPK analysis. A listing of the baseline demographics for these subjects is given in Table 23 and Table 24.

Figure 7. Schematic of the Study 812P306



*A safety follow-up phone call will be performed 1 week after EOS Visit only for those subjects who do not enroll/rollover into the Open-Label Extension study

Source: Applicant's popPK report 812p306: Figure 1, p. 11.

Table 23. Summary Statistics of the Continuous Covariates in the Analysis Dataset

Variable	Label	N	Mean	Std Dev	Median	Min	Max	Q1	Q3
AGE	Age (Year)	37	33.22	9.03	35	18	58	27	37
HT	Height (cm)	37	174.43	10.69	175	155.5	198	165.1	182
WT	Weight (kg)	37	83.27	18.36	81.1	50.6	136.1	71.7	96.7
BMI	BMI(kg/m^2)	37	27.16	4.31	26.43	18.56	34.72	23.8	30.88
ALT	Alanine aminotransferase (U/L)	37	30.49	17.09	25	16	98	19	32
AST	Aspartate transaminase (U/L)	37	25.27	6.97	23	14	45	21	30
CREAT	Creatinine (µmol/L)	37	78.11	13.75	78	55	112	67	86

Q1 and Q3 represent the first and the third quartiles

Source: Applicant's popPK report 812p306: Table 3, p. 18.

Table 24. Distribution of Categorical Covariates in the Analysis Dataset

Categorical Covariates	Levels	Frequency	Percent	Cumulative Frequency	Cumulative Percentage
Gender	**Male**	27	73	27	73
	Female	10	27	37	100
Race	**White**	32	86.5	32	86.5
	Black or African American	3	8.1	35	94.6
	Asian	2	5.4	37	100
Ethnicity	**Not Hispanic or Latino**	28	75.7	28	75.7
	Hispanic or Latino	9	24.3	37	100

Source: Adapted from Applicant's popPK report 812p306: Table 4-6, pp. 18-19.

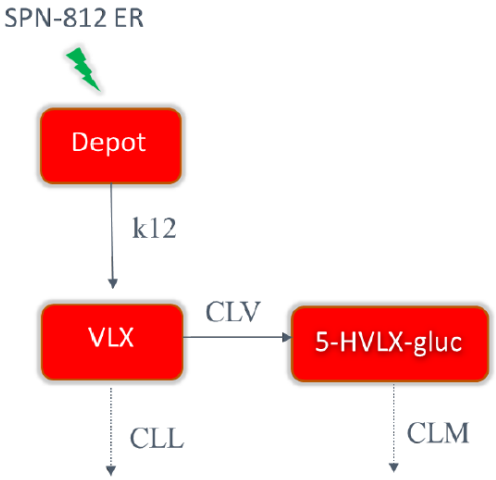
Population PK Model

Structural Model:

The PK of viloxazine was described by one compartment model with first-order absorption and elimination of parent drug, and first-order metabolite formation and elimination (Figure 8). Body weight was added on viloxazine metabolite clearance.

Figure 8. Schematic Representation of the PopPK Model for VLX and 5-HVLX-gluc

- *V2/F : Apparent Volume of distribution for VLX*
- *V3/F: Apparent volume of distribution of 5-HVLX-gluc*
- *k12 : VLX absorption rate constant*
- *CLL : VLX clearance*
- *CLV: Metabolic clearance*
- *CLM: 5-HVLX-gluc Clearance*



Source: Applicant's popPK report 812p306: Figure 4, p. 23.

The popPK model was parameterized in terms of VLX clearance (CLL), metabolic clearance (CLV), 5-HVLX-gluc(CLM), apparent volume of distribution for VLX(V2/F), apparent volume of distribution of 5-HVLX-gluc(V3/F), and first-order absorption rate constant (K12) for VLX.

To solve the identifiability issues in simultaneous PK model for parent and metabolite, the same modeling assumptions applied to the Pop PK model developed in the pediatric population were used as the same structural model was used in adult and pediatric populations.

Because the fraction of VLX converted to 5-HVLXgluc, and the fraction of VLX eliminated by other pathways are unknown, the Applicant considered using two different models with distinct assumptions to identify the model parameters:

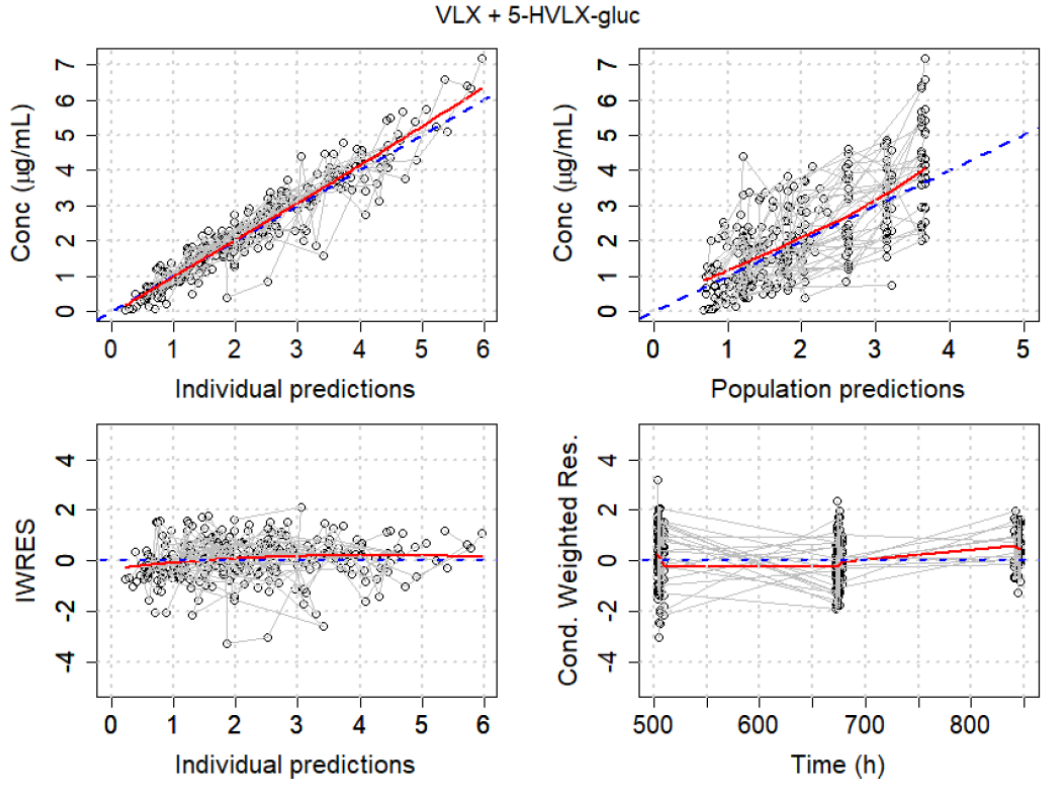
1. (b) (4)

2. Set V3=V2 (the volume of distribution of 5-HVLX-gluc is fixed to the value of the volume of distribution of VLX) then all the other parameters will be identifiable

The Applicant selected the second modeling option considering the poor plausibility of the first modeling option.

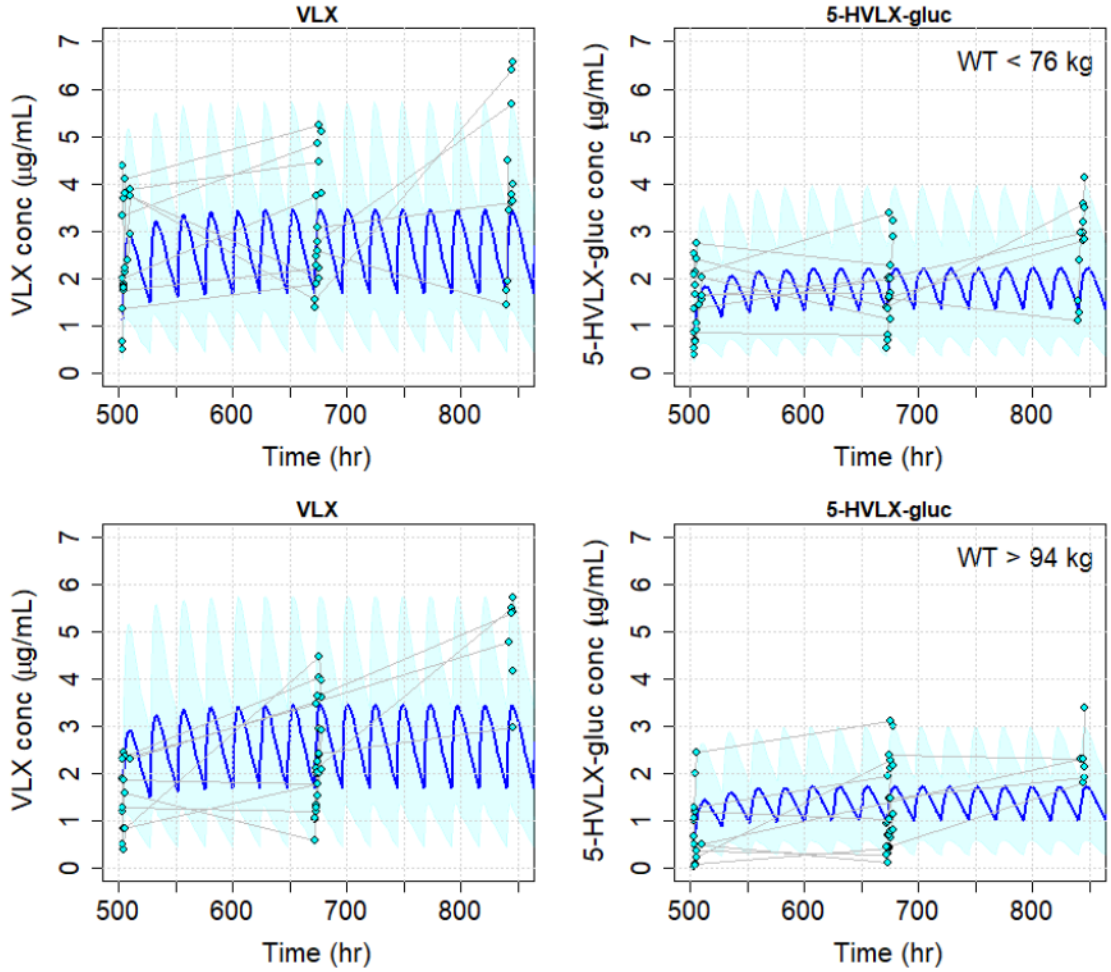
The final PK model for VLX and 5-HVLX-gluc was assessed with diagnostics plots including goodness-of-fit (Figure 9) and pcVPC (Figure 10). The parameter estimates of the final PopPK model for viloxazine in pediatric and adult population are shown in Table 25 and Table 26, respectively.

Figure 9. Goodness-of-fit Plots for the Final PopPK Model- VLX and 5-HVLX-gluc



Source: Applicant's popPK report 812p306: Figure 8, p. 30.

Figure 10. Visual Predictive Check for the Final PopPK Model for VLX and 5-HVLX-Gluc by Low and High Body Weight at 600 mg Dose



Source: Applicant's popPK report 812p306: Figure 10, p. 32.

For a typical pediatric patient (body weight: 36.35 kg) and typical adult patient (body weight: 81.1 kg), the estimated volume of distribution (V2) was 14.6 and 25.1 L, the estimated VLX clearance (CLL) was 0.865 and 2.92 L/hr, the estimated 5-HVLX-gluc clearance (CLM) was 6.75 and 9.68 L/hr, the estimated metabolic clearance was 6.75 and 9.68 L/hr, respectively.

The comparison of the popPK results indicated that V2, CLL, CLM, and CLV were lower in the pediatric population with respect to the adult population.

Table 25. Population Parameter Estimates of the Final PopPK Model in the Pediatric Population

	Parameter	Estimate	SE	RSE	CV%
Fixed	V2/F(L)	14.6	0.665	4.60%	
Effect	CLL(L/h)	0.865	0.184	21.30%	
	k12(1/h)	0.068	0.0028	4.10%	
	CLV(L/h)	4.72	0.209	4.40%	
	CLM(L/h)	6.75	0.308	4.60%	
	WT(V)	0.78	0.0809	10.40%	
	WT(CLV)	0.585	0.0704	12%	
	WT(CLM)	0.699	0.066	9.40%	
Random	V2/F(L)	0.102	0.0286	28%	31.94
Effect	CLL(L/h)	3.03	0.496	16.40%	174.07
	k12(1/h)	0.17	0.0266	15.60%	41.23
	CLV(L/h)	0.114	0.013	11.40%	33.76
	CLM(L/h)	0.0787	0.0117	14.90%	28.05
Residual	error_ad	0.121	0.0066	5.50%	
Error	error_prop	0.288	0.0102	3.50%	

Source: Applicant's popPK report 812p306: Table 14, p. 35.

Table 26. Population Parameter Estimates of the Final PopPK Model in the Adult Population

	Parameter	Estimate	SE	RSE	CV%
Fixed	V2/F(L)	25.10	3.63	14.50%	
Effect	CLL(L/h)	2.92	0.80	27.40%	
	k12(1/h)	0.05	0.01	11.70%	
	CLV(L/h)	5.84	0.63	10.80%	
	CLM(L/h)	9.68	1.26	13.00%	
	WT(CLM)*	0.59	0.22	36.70%	
Random	V2/F(L)	0.49	0.31	63.20%	70.14
Effect	CLL(L/h)	1.43	0.42	29.00%	119.58
	k12(1/h)	0.21	0.10	50.70%	45.28
	CLV(L/h)	0.05	0.02	37.30%	21.42
	CLM(L/h)	0.03	0.03	88.70%	18.08
Residual	error_ad	0.28	0.06	20.20%	
Error	error_prop	0.19	0.02	12.50%	

**WT(CLM) represents the shape of the allometric response (i.e., the parameter g in the allometric scaling model used in the covariate analysis).*

Source: Applicant's popPK report 812p306: Table 15, p. 36.

The Applicant used the popPK model developed in the pediatric population to estimate the steady state exposure at the dose of 600 mg/day in the adult population.

The parameters derived from final pediatric popPK model were used in the simulations with an adjustment to the typical body weight of 81.1 kg of the adult population. The adjusted parameters in the adults were estimated using the allometric relationship between the typical values of model parameters (V2, CLM, and CLV) and covariate (WT) estimated in the pediatric population. The estimated steady state parameters at the dose of 600 mg/day are presented in Table 27.

Table 27. Comparison of the Estimated and Extrapolated Steady State Parameters in the Adult Population at 600 mg/day Dose

	Variable	Mean	Std Dev	CV%	Median	Lower 95% CL for Mean	Upper 95% CL for Mean
Estimated parameters from the adult PopPK model	Cmax (µg/mL)	3.6	1.18	32.7	3.53	3.21	4
	Ctrough(µg/mL)	1.75	0.96	55	1.45	1.43	2.07
	Cave (µg/mL)	2.74	1.05	38.2	2.55	2.39	3.09
	Tmax(h)	5.03	1.72	34.29	5	4.45	5.6
	AUC_{0-t} (µg*h/mL)	65.77	25.12	38.2	61.1	57.39	74.14
	t1/2(h)	16.65	6.8	40.84	14.9	14.38	18.91
	Kel(1/h)	0.05	0.02	36.91	0.05	0.04	0.05
	CL/F(L/h)	6.89	3.39	49.15	6.7	5.76	8.02
	V/F(L)	148.22	69.5	46.89	131	125.05	171.39
	Fluctuation(%)	73.21	28.12	38.41	73.16	63.84	82.59
Extrapolated parameters from the pediatric PopPK model	Cmax (µg/mL)	5.41	2.18	40.36	5.43	4.96	5.86
	Ctrough(µg/mL)	1.09	0.69	63.82	1	0.95	1.23
	Cave (µg/mL)	2.89	1.27	44.11	2.85	2.63	3.15
	Tmax(h)	5.2	2.73	52.56	4	4.64	5.76
	AUC_{0-t} (µg*h/mL)	69.32	30.58	44.11	68.5	63.06	75.59
	t1/2(h)	10.27	6.63	64.61	7.92	8.91	11.62
	Kel(1/h)	0.09	0.05	52.01	0.09	0.08	0.1
	CL/F(L/h)	9.65	11.49	119	6.79	7.3	12.01
	V/F(L)	141.04	246.75	174.95	93.45	90.5	191.58
	Fluctuation(%)	161.57	53.73	33.26	152.6	150.56	172.57

Source: Applicant's popPK report 812p306: Table 16, p. 37.

The Applicant conducted simulation to explore the relationship between body weight and exposure. Steady-state C_{max} and AUC_{0-t} of VLX and 5-OH-VLX-gluc at the dosage of 200 mg/day and 400 mg/day, at the median body weight values in children, adolescents and adults (i.e., 31.5 kg, 57.25 kg, and 81.1 kg) are presented in Table 28.

The results indicate that the estimated steady-state C_{max} and AUC_{0-t} of viloxazine and its major metabolite, at doses ranging from 200 mg to 400 mg, were approximately 130 to 250% and 60 to 140% higher in a typical pediatric subject 6 to 11 years of age (31.5 kg) and 12 to 17 years of age (57.25 kg), respectively, compared to a typical adult subject (81.1 kg).

Table 28. Estimated Steady-State PK Parameters of Viloxazine and 5-HVLX-glu by Age Group from Simulation

Viloxazine										
Dose (mg)	Cmax					AUC_{0-t}				
	Adult	Pediatric				Adult	Pediatric			
	18-65 yo (81.1 kg)	6-11yo (31.5 kg)		12-17yo (57.25 kg)		18-65 yo (81.1 kg)	6-11yo (31.5 kg)		12-17yo (57.25 kg)	
	ug/mL	ug/mL	%	ug/mL	%	ug*h/mL	ug*h/mL	%	ug*h/mL	%
200	1.68	4.04	140.5	2.89	72.0	22.68	71.45	215.0	52.41	131.1
400	3.01	8.15	170.8	5.77	91.7	44.02	143.61	226.2	105.51	139.7
5-HVLX-gluc (major metabolite)										
Dose (mg)	Cmax					AUC_{0-t}				
	Adult	Pediatric				Adult	Pediatric			
	18-65 yo (81.1 kg)	6-11yo (31.5 kg)		12-17yo (57.25 kg)		18-65 yo (81.1 kg)	6-11yo (31.5 kg)		12-17yo (57.25 kg)	
	ug/mL	ug/mL	%	ug/mL	%	ug*h/mL	ug*h/mL	%	ug*h/mL	%
200	1.13	2.66	135.4	1.79	58.4	13.92	47.8	243.4	32.36	132.5
400	1.87	5.17	176.5	3.49	86.6	27.05	93.72	246.5	63.94	136.4

% = percent change adult vs pediatric;
Note: Median body weight (kg) for age group is indicated in parentheses under the age range.

Source: Applicant's Response to Clin Pharm IR dated 3/10/2022, Table 4, p. 2.

Biometric Reviewer's Comment: *Overall, the Applicant's popPK model adequately characterized the PK profiles of viloxazine in adult ADHD patients. In general, the estimated PK parameters in adults at steady state indicated that the volume of distribution, the clearance, the average concentration, and the steady state AUC agree with the values extrapolated from the pediatric population despite the fact that the C_{max} value is higher compared to the extrapolated value.*

Reviewer's Analysis

Data Sets

Data set used is listed in Table 29.

Table 29. Analysis Data Sets

Study	Name	Link to EDR
Study 812P301, 812P302, 812P303, and 812P304	pk_all.csv	\\CDSESUB1\evsprod\nda211964\0003\m5\datasets\integrated-poppk\analysis\adam\datasets\pk-all.csv
Optional PK sub-study from Study 812P306	Data.csv	\\CDSESUB1\evsprod\nda211964\0082\m5\datasets\812p306-pop-pk\analysis\adam\datasets\data.csv

Software

PopPK model fitting was performed in NONMEM 7.4.3 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.2.

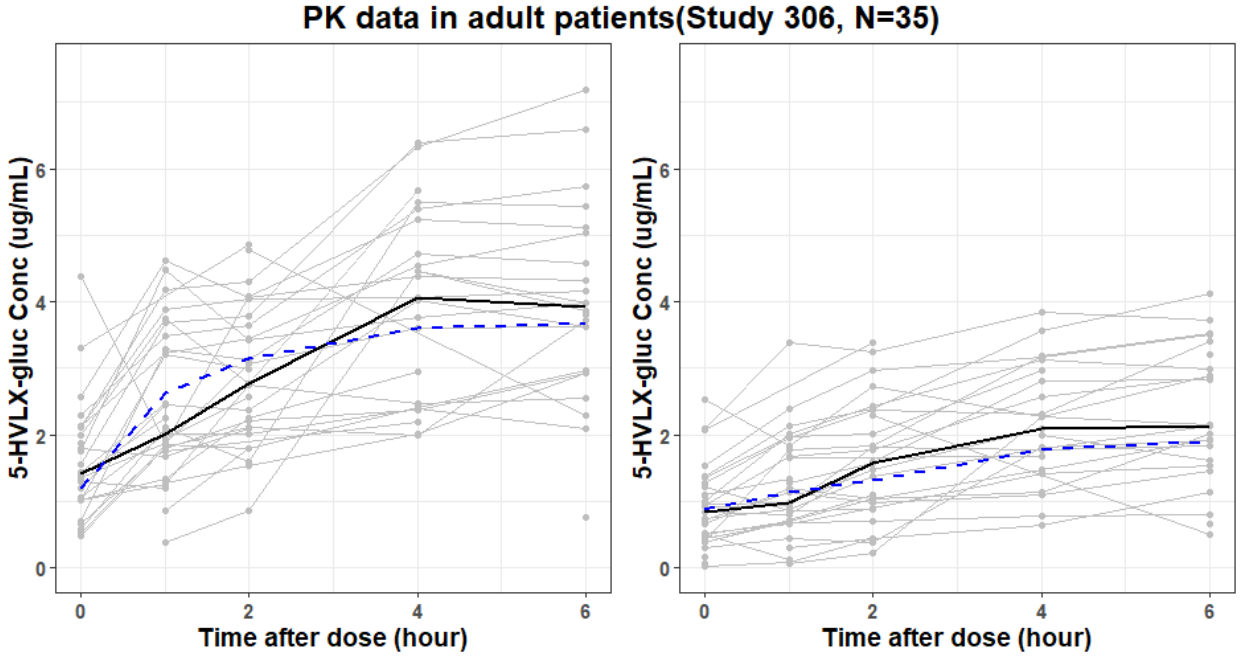
Results

The reviewer was able to reproduce the Applicant's popPK results with NONMEM (version:7.4.3). The Applicant's popPK analysis appears adequate for characterizing the PK profiles for VLX and 5-HVLX-gluc.

Overview of Observed Data

Figure 11 presents PK profiles of VLX and 5-HVLX-gluc for patients from 200 mg to 600 mg dose levels. Overall, the population predicted medians overlay well with the observed medians of VLX and 5-OH-VLX-gluc plasma concentrations.

Figure 11. Observed VLX and 5-HVLX-gluc Concentration versus Time after Dose in Patients in Study 812P306



Note: Observed values are indicated by solid grey circles, the black solid lines represent the observed medians, and the blue dashed lines represent the population predicted medians.
Source: Reviewer's Analysis.

The impact of age, bodyweight, BMI, ALT, AST, creatine, sex, and race on the PK of VLX and 5-HVLX-gluc was not reviewed due to small sample size (N=35). See Sections 5 and 14 of the integrated review for the original submission (archived November 6, 2020) for more information.

Listing of Analyses Codes and Output Files

File Name	Description	Location
Pk_analysis_viloxazine.R	PK and PopPK analysis file	M:\Review\NDA211964_S3_Viloxazine ER\PPK_Analyses\Rscript

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/s/

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