CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211964Orig1s000

INTEGRATED REVIEW

Joint Supervisory Memo

Date	April 2, 2021
From	Valerie Amspacher, PharmD—Cross-Discipline Team Lead Tiffany R Farchione, MD—Director, Division of Psychiatry Eric Bastings, MD—Deputy Director, Office of Neuroscience
Subject	Summary Review
NDA/BLA # Supp #	211964
Proprietary / Established (USAN) names	Qelbree (viloxazine) capsules
Dosage forms / strength	Capsule; 100, 150, 200 mg strength
Proposed Indication(s)	Treatment of attention deficit/hyperactivity disorder (ADHD) in children ages 6 to 17
Recommended Action:	*Approval*

1. Introduction

This NDA resubmission seeks approval for Qelbree (viloxazine) extended-release capsules at 100, 150, and 200 mg strengths. In the first review cycle, the Agency identified manufacturing facility deficiencies. As a result, a Complete Response Letter (CRL) was issued on November 6, 2020. The application was otherwise considered approvable by all disciplines; however, agreement on final labeling was not reached during the initial review cycle. This review will focus only on new information submitted to resolve the deficiencies stated in the CRL and the outstanding labeling issues.

2. Complete Response

The CRL cited objectionable conditions at a manufacturing facility and noted that satisfactory resolution (e.g., preapproval inspection or adequate facility responses addressing these conditions) of these objectionable conditions would be required. The Office of Pharmaceutical Quality (OPQ) team concluded the following:

- General product quality considerations
  All drug quality issues have been resolved. All disciplines recommend approval.

- Facilities review/inspection
  Facilities are adequate. To resolve the facilities issues the sponsor withdrew the out-of-compliance facility from the application. This is acceptable.

- Other notable issues *(resolved or outstanding)*
  N/A

3. Labeling

Unresolved issues from the first review cycle included the description of viloxazine's mechanism of action, language related to effects on weight, and the addition of a boxed warning for suicidal ideation and behavior. The mechanism of action was discussed during a Type A after action meeting; the Applicant's resubmission aligned with the Agency's recommendation. Viloxazine's effect on weight is described in Section 6 – Adverse Reactions. The final Boxed Warning language includes data from the viloxazine clinical development program and is similar to Boxed Warning language in the atomoxetine label, a mechanistically similar drug.

4. Conclusions and Recommendations

The concerns outlined in the CRL have been resolved and OPQ recommends approval for this application based on drug substance, drug product, process/facilities and biopharmaceutics reviews. We will issue an approval letter for this application.

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/s/

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CLINICAL REVIEW

Application Type	Class I Resubmission
Application Number(s)	211964
Submit Date(s)	February 3, 2021
Received Date(s)	February 3, 2021
PDUFA Goal Date	April 3, 2021
Division/Office	Division of Psychiatry/Office of Neuroscience
Reviewer Name(s)	Martine Solages, MD
Team Lead Name	Bernard Fischer, MD
Review Completion Date	March 10, 2021
Established/Proper Name	Viloxazine Extended Release (ER)
(Proposed) Trade Name	Quelbree
Applicant	Supernus Pharmaceuticals, Inc.
Dosage Form(s)	Extended-release capsule
Dosing Regimen(s)	Patients ages 6 to 11 years: 100 mg to 400 mg once daily Patients ages 12 to 17 years: 200 mg to 400 mg once daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age

On November 8, 2019, the Applicant submitted a 505(b)(1) new drug application (NDA) for viloxazine ER for the treatment of ADHD in children and adolescents ages 6 to 17 years. A Complete Response (CR) letter was issued on November 6, 2020, because of manufacturing facility deficiencies. The Applicant completed a CR resubmission on February 3, 2021, and has resolved the deficiencies that precluded approval of the application during the initial cycle.

The Agency and the Applicant did not reach full agreement on labeling prior to the CR action. Labeling negotiations therefore resumed after resubmission of the application. The most notable unresolved labeling issues pertained to the description of viloxazine's mechanism of action and effects on weight and suicidal ideation.

During the initial review cycle, the Applicant disagreed with the Agency on the description of viloxazine's mechanism of action and advocated for (b) (4) . In a Type A meeting following the issuance of the CR letter, the Applicant proposed including language (b) (4) . The Agency noted (b) (4) the Applicant's proposed language would not be included in labeling. The Applicant submitted draft labeling with the CR resubmission that indicated acceptance of the Agency's position.

The Agency had initially proposed including information about effects on weight in Section 5 of labeling (Warning and Precautions). The Agency noted that in the short-term controlled studies (6 to 8 weeks), viloxazine ER-treated patients 6 to 11 years of age gained an average of 0.2 kg, compared to a gain of 1 kg in same-aged patients who received placebo. Viloxazine ER-treated patients 12 to 17 years of age lost an average of 0.2 kg, compared to a weight gain of 1.5 kg in same-aged patients who received placebo. However, upon further consideration of the data from the long-term safety extension study (Study 812P310), the Agency concluded that the clinical meaningfulness of the findings over time is unclear and that the observed changes in weight in the long-term study could represent regression to the mean or the influence of confounding factors. Given the limitations of the uncontrolled data, the Agency determined that inclusion of effects on weight in Section 5 was not warranted. Nonetheless, healthcare professionals should be aware of the short-term weight effects of viloxazine. Information about weight effects was therefore included in Section 6 of labeling (Adverse Reactions). At the time of this review, whether to include the open-label weight results in labeling was under discussion. If included, long-term data in Section 6 would be the mean change from baseline in weight-for-age z-score for patients exposed to viloxazine ER for at least 12 months.

The Division also drafted new language regarding the boxed warning for suicidal ideation and behavior. The language proposed during previous labeling negotiations (b) (4) [redacted] The updated boxed warning now describes data on suicidal ideation and behavior from the viloxazine ER studies and more closely aligns with the boxed warning language of atomoxetine, which shares the same mechanism.

Please see the integrated review of the NDA for full details. No additional clinical information was submitted with the CR resubmission. The assessment of the overall benefit and risk of viloxazine ER has not changed since the initial review. Viloxazine ER continues to have a favorable benefit:risk profile in pediatric patients ages 6 to 17 years with ADHD and we recommend approval.

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/s/

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Supervisory Physician

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	211964
Priority or standard	Standard
Submit date(s)	11/8/2019
Received date(s)	11/8/2019
PDUFA goal date	11/8/2020
Division/office	Division of Psychiatry Products (DPP)
Review completion date	7/8/2020
Established name	Viloxazine hydrochloride
(Proposed) trade name	Qelbree
Pharmacologic class	Norepinephrine reuptake inhibitor
Code name	SPN-812
Applicant	Supernus Pharmaceuticals, Inc.
Dose form/formulation(s)	Extended-release capsules
Dosing regimen	Patients ages 6-11 years: 100 mg to 400 mg once daily Patients ages 12-17 years: 200 mg to 400 mg once daily
Applicant proposed indication(s)/population(s)	Attention deficit hyperactivity disorder (ADHD)
Proposed SNOMED indication	Attention deficit hyperactivity disorder
Regulatory action	Complete response
Approved indication(s)/population(s) (if applicable)	Treatment of attention deficit hyperactivity disorder in pediatric patients 6 to 17 years of age
Approved SNOMED indication	Attention deficit hyperactivity disorder

Reference ID: 4698714

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Glossary

ADHD	attention deficit hyperactivity disorder
ADHD-RS	ADHD Rating Scale
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BMI	body mass index
CAARS	Conners' Adult ADHD Rating Scale
CDER	Center for Drug Evaluation and Research
CDTL	cross-discipline team leader
CFB	change from baseline
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRO	contract research organization
CSA	Controlled Substances Act
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DA	dopamine
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DP	Division of Psychiatry
DPMH	Division of Pediatrics and Maternal Health
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EM	extensive metabolizer
EOS	end of study
ER	extended-release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FMQ	FDA MedDRA Query
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
HD	high dose
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation

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IND	investigational new drug
ITT	intent-to-treat
IWRS	interactive web response system
LacD	lactation day
LC/MS/MS	liquid chromatography-tandem mass spectrometry
LD	low dose
LD_{50}	median lethal dose
LS	least square
MD	mid dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MNAR	missing not at random
MOA	mechanism of action
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NDA	new drug application
NE	norepinephrine
NET	norepinephrine transporter
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PK	pharmacokinetic
PM	poor metabolizer
PMR	postmarketing requirement
PND	postnatal day
QD	once daily
(Q)SAR	quantitative structure-activity relationship
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TK	toxicokinetic
ULN	upper limit of normal
WFIRS-P	Weiss Functional Impairment Rating Scale-Parent Report
5-HT	serotonin

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I. Executive Summary

1. Summary of Regulatory Action

Supernus Pharmaceuticals, Inc. (the Applicant) has submitted a 505(b)(1) new drug application (NDA) for viloxazine extended-release (ER) capsules for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients ages 6 to 17 years. Viloxazine is norepinephrine reuptake inhibitor that was marketed in Europe as an antidepressant from the 1970s until 2008 (when it was withdrawn for commercial reasons). In the United States, viloxazine is a new molecular entity (NME) never previously approved or marketed for any indication.

The Applicant submitted four randomized, placebo-controlled, double-blind studies in support of this NDA: 812P301, -302, -303, and -304. In subjects 6 to 11 years old, Study 301 (N=477) tested viloxazine ER 100 and 200 mg daily, and Study 303 (N=313) tested viloxazine ER 200 and 400 mg daily. In subjects 12 to 17 years old, Study 302 (N=310) tested viloxazine ER 200 and 400 mg daily, and Study 304 (N=297) tested viloxazine ER 400 and 600 mg daily. An open-label extension study, 812P310, provided long-term safety data. At the time of this review, Study 310 is ongoing, but there have been 687 exposures for at least 6 months and 347 exposures for at least 1 year; thus, ICH E1 guidelines have been satisfied.

The Applicant's development program provides substantial evidence of effectiveness for viloxazine for the treatment of ADHD in pediatric patients ages 6 to 17 years. Clinically meaningful improvements in ADHD symptoms were demonstrated for 100 mg, 200 mg, and 400 dosages of viloxazine ER in patients 6 to 11 years old, and for the 200 mg and 400 mg dosages of viloxazine ER in patients 12 to 17 years old. A 600 mg dosage of viloxazine ER was also tested in patients 12 to 17 years old. The 600 mg dosage was not shown to provide additional benefits, but is associated with a higher incidence of some adverse events (b) (4)

The key review issues associated with safety were evaluation of the risk of seizure, suicidal ideation and behavior (SI/B), weight and appetite effects, and cardiovascular effects.

Convulsions were observed in nonclinical studies at therapeutically-relevant viloxazine doses. However, the review team found no evidence that viloxazine is associated with seizures in humans. The nonclinical signal will be described in labeling.

There were higher rates of suicidal ideation with viloxazine ER compared to placebo, but the overall rates were low. This risk can be mitigated by labeling (patients on viloxazine should be monitored for the emergence of SI/B).

Viloxazine ER was associated with decreased appetite, decreased age-appropriate weight gain, increased heart rate, and increased diastolic blood pressure. However, those risks appear no worse than for most approved ADHD treatments (i.e., stimulants and atomoxetine), and can be managed by appropriate labeling (patients should have their weight and vital signs monitored before and during viloxazine ER treatment).

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There are no approvability issues with the drug substance, drug product, environmental impact, labeling, or biopharmaceutics information. The manufacturing facility was previously inspected, but not since relocating in February 2020. Because FDA inspectors could not travel for inspection (based on the Agency's global travel warning)—and the facility could not provide documentation of procedures for handling laboratory records or appropriate re-qualification of analytical instruments—the NDA will receive a Complete Response.

Postmarketing requirements (PMRs) will include a single-arm pregnancy study, a milk-only lactation study, and a hepatic impairment study. PMRs will also include the studies from the Applicant's agreed iPSP: a safety and efficacy study, and a long-term safety study of viloxazine ER in patients with ADHD ages 4 to less than 6 years old.

In summary, the Applicant has provided substantial evidence of effectiveness of viloxazine ER, and the risks of viloxazine ER are acceptable for the proposed indication. However, a Complete Response Letter will be issued because of the manufacturing deficiency described above.

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2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that is characterized by hyperactivity, impulsivity, or inattention severe enough to cause functional impairment. • ADHD is the most common neurodevelopmental disorder of childhood. • ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes.	• Effective treatment of ADHD reduces functional impairment in the short-term, and may result in long-term benefits, such as a reduced risk of substance abuse and reduced risk of injuries.
Current Treatment Options	• Stimulant medications are the first-line pharmacologic treatment for ADHD. • Stimulant medications carry potential risks of blood pressure and heart rate increases, psychiatric adverse reactions including psychosis and mania, growth suppression, lowered seizure threshold, insomnia, decreased appetite and weight, abuse, misuse, and diversion. • Available nonstimulant options for treatment of ADHD include atomoxetine and alpha agonists (guanfacine extended-release and clonidine extended-release). None of these nonstimulant medications is controlled under the Controlled Substances Act.	• Stimulant and nonstimulant treatment options are available for ADHD. Nonstimulant medications are frequently used when patients are unable to tolerate adverse reactions associated with stimulants or when patients prefer a nonstimulant treatment. Viloxazine ER would provide patients and healthcare professionals with an additional nonstimulant treatment option.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Atomoxetine is associated with risks of somnolence, decreased appetite, suicidal ideation, severe liver injury, serious cardiovascular events, increased heart rate and blood pressure, emergence of psychosis or mania, aggression, and growth effects. • Guanfacine extended-release and clonidine extended-release are associated with somnolence/sedation, bradycardia, syncope, cardiac conduction abnormalities, and rebound hypertension.	
Benefit	• The Applicant conducted four adequate and well-controlled studies to assess the efficacy of viloxazine ER for the treatment of ADHD in patients ages 6 to 17 years. • The primary efficacy endpoint in all four studies was the change from baseline in the ADHD Rating Scale–5 (ADHD-RS-5), an 18-question scale that measures the core symptoms of ADHD. A reduction in the ADHD-RS-5 total score indicates an improvement in ADHD symptoms. • The Clinical Global Impression-Improvement (CGI-I) scale was included as a key secondary endpoint in the studies. The CGI-I assesses whether a patient's illness has improved or worsened over time. Responses on the CGI-I are rated on a 7-point Likert scale. • Study 812P301 evaluated the efficacy of viloxazine ER 100 mg and 200 mg daily in patients ages 6 to 11 years. Both dosages were statistically significantly superior to placebo in the mean change from baseline in ADHD-RS-5 total score at the end of study, with a least square (LS) mean treatment difference to placebo of -5.8 for the 100 mg dose and -6.9 for the 200 mg dose. • Study 812P303 evaluated the efficacy of the 200 mg and 400 mg daily dosages in patients ages 6 to 11 years, and similarly demonstrated a statistically significant effect on the primary endpoint for both dosages. The LS mean difference to placebo was -6.0 for the 200 mg dose and -5.8 for the 400 mg dose.	• Viloxazine ER demonstrated statistically significant efficacy compared to placebo for the 100 mg, 200 mg, and 400 mg daily dosages in patients ages 6 to 11 years and for the 200 mg and 400 mg daily dosages in patients ages 12 to 17 years. The clinical meaningfulness of the results is supported by the positive findings on the CGI-I across dose groups. • There was no evidence that the 600 mg dosage of viloxazine provides benefit additional to that of lower dosages. • There is substantial evidence of effectiveness to support approval of viloxazine ER (100 mg, 200 mg, 400 mg) for the treatment of ADHD in pediatric patients ages 6 to 17 years. Viloxazine ER was well-tolerated in the patient population, and may have safety advantages when compared with stimulant medications (i.e., lack of human abuse liabilty and rare occurrence of psychosis).

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In both studies that evaluated viloxazine ER in the patients 6 to 11 years of age (812P301 and 812P303), a statistically significant improvement in the CGI-I was observed. • Study 812P302 evaluated the efficacy of the 200 mg and 400 mg doses in patients ages 12 to 17 years. The LS mean difference to placebo in ADHD-RS-5 was -4.5 for viloxazine ER 200 mg and -5.1 for viloxazine ER 400 mg. A statistically significant improvement was also observed in the CGI-I for both dosages, compared to placebo. • Study 812P304, which evaluated the efficacy of the 400 mg and 600 mg daily dosages of viloxazine ER in patients ages 12 to 17 years, did not demonstrate a statistically significant difference between viloxazine ER and placebo on the primary endpoint. This finding could be attributable to type II error, a robust placebo response in this study, or a lack of treatment effect. • In the controlled studies, a small proportion of patients (3.5%) discontinued with viloxazine ER because of adverse events, and few patients reported serious adverse events. Unlike stimulant medications, viloxazine ER was not associated with significant abuse liability or emergence of psychotic symptoms.	
Risk and Risk Management	• The most common treatment-emergent adverse events associated with viloxazine ER in pediatric patients with ADHD (and occuring more frequently than in placebo-treated patients) were somnolence/sedation (16.1%), headache (6.9%), decreased appetite (7.4%), fatigue (6.4%), abdominal pain (5.4%), nausea (4.6%), vomiting (4.2%), and irritability (3.3%). • Viloxazine ER was associated with higher rates of suicidal ideation and behavior, increases in heart rate and diastolic blood pressure, and decreased weight gain. • In animal studies, maternal deaths occurred in late pregnancy in rats and mice that were exposed to viloxazine.	• The submitted data were sufficient to assess the safety of viloxazine ER in pediatric patients ages 6 to 17 years with ADHD. None of the identified safety issues would preclude approval of viloxazine ER. The risks can be described adequately in labeling to allow for safe use of the drug. • The most common treatment-emergent adverse event was somnolence/sedation. Labeling will include a warning that alerts healthcare professionals to the potential risk to patients when operating machinery or driving. • A boxed warning indicating the risk of suicidal ideation and behavior will inform healthcare professionals of this serious

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Immediate-release viloxazine was previously authorized in Europe for the treatment of depression. Limited data about the safety of viloxazine in pregnancy are available in the literature or postmarketing databases. • Viloxazine ER increases the concentration of CYP1A2 substrates five-fold. • Seizures occurred in multiple animal species. No seizures occurred in the controlled clinical trials. Seizures were reported in an uncontrolled study of viloxazine ER and in postmarketing reports for immediate-release viloxazine, but the association between these events and viloxazine ER exposure is unclear. • Postmarketing databases include reports of liver injury associated with immediate-release viloxazine. Transaminase values were more likely to shift from within the reference range to above the reference range in patients receiving viloxazine ER in placebo-controlled studies; however, transaminase elevations were modest, and no cases of drug-induced liver injury were identified.	and possibly unexpected risk. • Labeling will advise healthcare professionals to monitor heart rate, blood pressure, and weight. • Use of viloxazine ER is not recommended in pregnancy. The Applicant should conduct a postmarketing single-arm pregnancy study as well as a milk-only lactation study to evaluate the potential risks to pregnant and lactating patients. • Viloxaxine will be contraindicated in patients receivig concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range. • Labeling will also detail the nonclinical findings of convulsions. • Routine postmarketing surveillance will provide further information about any potential risk of seizure or liver injury with viloxazine exposure.

Conclusions Regarding Benefit-Risk

ADHD is a common and impairing neurodevelopmental disorder of childhood. Viloxazine ER would provide another treatment option for patients who are unable to tolerate stimulant medications, patients for whom the risks of stimulants may outweigh the benefits, and patients who simply prefer a nonstimulant treatment. The applicant provided substantial evidence that viloxazine ER is effective for the treatment of ADHD in pediatric patients ages 6 to 17 years, at daily dosages between 100 and 400 mg in patients 6 to 11 years of age, and daily dosages between 200 and 400 mg in patients 12 to 17 years of age.

Overall, the safety profile of viloxazine ER is acceptable for the intended population, and the identified risks can be appropriately mitigated with strategies outlined in labeling. Viloxazine ER has some safety advantages when compared to stimulant medications—namely, low human abuse liability and no clear association with psychosis events. However, patients who received viloxazine ER did experience psychiatric adverse events (particularly irritability, insomnia, and suicidal ideation and behavior) at greater rates than those on placebo. Although no manic episodes have been reported in the development program, the safety of viloxazine ER exposure in patients with a bipolar diathesis is unknown. Viloxazine ER was associated with increased heart rate and diastolic blood pressure and decreased appetite and weight gain, as are stimulants and atomoxetine. Viloxazine ER, like the currently approved nonstimulant

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treatments for ADHD, was also associated with somnolence/sedation. Viloxazine ER does not appear to provide notable advantages over other nonstimulant ADHD medications, but is another safe and effective treatment option. As described in the proposed prescribing information, patients receiving viloxazine ER should be screened for risk of bipolar disorder and monitored for the emergence of suicidal ideation and behavior. Healthcare professionals should also measure weight and vital signs before and during viloxazine ER treatment.

The review team recommends approval of viloxazine ER for the proposed indication.

II. Interdisciplinary Assessment

3. Introduction

Supernus Pharmaceuticals, Inc. (the Applicant) has submitted a 505(b)(1) new drug application (NDA) for viloxazine extended-release capsules for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients ages 6 to 17 years.

ADHD is a childhood-onset neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity-impulsivity, or a combination thereof that interferes with functioning or development. Symptoms must persist for at least 6 months and at least some symptoms must have been present prior to the age of 12 years (American Psychiatric Association 2013) to meet diagnostic criteria. According to data from the National Center for Health Statistics (NCHS), the prevalence of diagnosed ADHD in U.S. children and adolescents ages 3 to 17 years has increased over the last decade. The prevalence of ADHD in this population was 8.5% in the years 2009 to 2011, and 9.5% in the years 2015 to 2017 (Zablotsky et al. 2019). ADHD may persist into adulthood. The prevalence of ADHD among U.S. adults has also increased from 3.4% in 2007 to 4.3% in 2012 (London and Landes 2019). ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes (Chan et al. 2016).

Stimulant medications are the first-line pharmacologic treatments for ADHD. Stimulant medications carry potential risks of blood pressure and heart rate increases, psychiatric adverse reactions, growth suppression, lowered seizure threshold, insomnia, and decreased appetite and weight. Stimulants are Schedule II/IIN controlled substances with significant human abuse liability potential; abuse, misuse, and diversion can occur.

Patients who are unable to tolerate adverse effects of stimulant medications, particularly appetite suppression, insomnia, and psychiatric adverse reactions, may benefit from nonstimulant treatment options. Nonstimulant medications may also be considered in clinical scenarios in which there are concerns about potential abuse or diversion of stimulants or when patients express a preference for nonstimulants. Three nonstimulant medications—atomoxetine, guanfacine extended-release, and clonidine extended-release—have been approved for the treatment of ADHD to date.

Atomoxetine is a norepinephrine reuptake inhibitor that is indicated for use in children, adolescents, and adults. Atomoxetine labeling includes a boxed warning regarding the potential risk of suicidal ideation. Other warnings and precautions outlined in its labeling include severe liver injury, serious cardiovascular events, anaphylaxis, urinary hesitancy and retention, priapism, increased heart rate and blood pressure, emergent psychotic or manic symptoms, aggressive behavior and hostility, and growth effects.

Guanfacine extended-release and clonidine extended-release are centrally acting α2 adrenergic receptor antagonists that are indicated for the treatment of ADHD as monotherapy or as adjunctive therapy to stimulant medications. Warnings and precautions for guanfacine extended-release and clonidine extended-release include: hypotension, bradycardia, syncope, sedation/somnolence, cardiac conduction abnormalities, and rebound hypertension.

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All three approved nonstimulant treatments for ADHD are unscheduled.

Buproprion, immediate-release guanfacine and clonidine, tricyclic antidepressants, venlafaxine, and modafinil have been used as off-label pharmacological treatments for ADHD. Pediatric data on the use of these medications for ADHD are limited.

Patients with ADHD may also benefit from non-pharmacologic interventions such as behavioral therapy, parent guidance, and educational modifications. However, data suggest that pharmacological treatment results in greater short-term symptomatic improvement than intensive behavioral therapy (Molina et al. 2009). Pharmacological treatment of ADHD may also result in a lower risk of substance-use disorder and injuries; however, data on the long-term benefits and risks of pharmacological treatment for ADHD are limited and frequently confounded (Chang et al. 2019).

In the NDA submission, the Applicant describes viloxazine extended-release as a norepinephrine reuptake inhibitor, 5HT2B serotonin receptor antagonist, and 5HT2C serotonin receptor agonist. The Applicant reports that viloxazine extended-release also potentiates serotonergic activity by mechanisms other than serotonin reuptake. The Applicant emphasizes the role of the noradrenergic and serotonergic systems in regulating executive functioning, attention, and behavior, and posits that the effects of viloxazine extended-release on these systems will lead to improvement in ADHD symptoms. Based on published nonclinical studies that did not find evidence of reinforcing effects, withdrawal, or other signs typically associated with abuse, the Applicant has concluded that viloxazine extended-release has low potential for abuse in humans.

The immediate-release formulation of viloxazine was initially marketed in Europe as an antidepressant in the late 1970s, and subsequently withdrawn in 2008 for commercial reasons. Although viloxazine was previously marketed in Europe, it has never been approved or marketed in the United States for any indication.

Prior to NDA submission, the Agency interacted with the Applicant in two pre-IND meetings (March 2010 and June 2013), an End-of-Phase 2 meeting (July 2017), a CMC End-of-Phase 2 meeting (July 2017), a pre-NDA meeting (July 2019), as well as via advice letters and other communications. The Applicant and the Agency came to agreement on the use of the ADHD Rating Scale–5 (ADHD-RS-5) as the primary efficacy endpoint in the phase 3 safety and efficacy studies. The Agency expressed reservations about the Applicant's planned use of the Clinical Global Impressions-Improvement (CGI-I) scale as a secondary endpoint because of the susceptibility of this scale to recall bias. The Agency expressed concern about the lack of a safety margin between the no observed adverse effect level (NOAEL) exposures for seizures in animals and the blood levels already attained in clinical trials. After review of published data submitted by the Applicant, the Agency agreed that there did not appear to be a clear seizure risk associated with viloxazine in humans. Please see the detailed Summary of Regulatory History in Appendix III.12.

3.1. Review Issue List

- Review issue 1
  - (b) (4)
- Review issue 2

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  - Inclusion of CGI-I results in labeling
- Review issue 3
  - Clinical significance of seizures and convulsions in nonclinical studies
- Review issue 4
  - Risk of suicidal ideation and behavior
- Review issue 5
  - Risk of somnolence/sedation
- Review issue 6
  - Clinical significance of weight/appetite effects
- Review issue 7
  - Clinical significance of heart rate and blood pressure effects
- Review issue 8
  - Clinical significance of postmarketing reports of liver injury with immediate-release viloxazine
- Review issue 9
  - Applicant's (b) (4) proposal
- Review issue 10
  - Differences in animal and human drug metabolism
- Review issue 11
  - Concomitant administration of viloxazine with CYP1A2 substrates (e.g., theophylline)
- Review issue 12
  - Dosing of viloxazine in renal-impaired patients

3.2. Approach to the Review

The Applicant submitted four phase 3, double-blind, placebo-controlled studies (812P301, 812P302, 812P303, and 812P304) as evidence of efficacy and safety. Table 3 provides an overview of the patient populations, trial designs, endpoints, and enrollment for these studies. In addition, a phase 2 dose-ranging study (812P202) was considered as supportive evidence of efficacy and safety. Long-term safety data from an ongoing open-label extension study (812P310), including updated data on adverse events, vital signs, and laboratory assessments provided in the 120-day safety update, were also considered in the safety review.

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Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations[1] for Viloxazine Extended-Release

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
812P301	Subjects 6 to 11 years of age with ADHD	Control type: Placebo concurrent Randomization: Standard randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Viloxazine Dose: 100 mg QD; 200 mg QD; placebo Number treated: 154; 161; 159 Duration: approximately 10 weeks	Primary: CFB in the ADHD-RS-5 Total Score at EOS Secondary: CGI-I score at EOS; CFB in the Conners 3-Parent Composite T-Score at EOS; CFB in the WFIRS-P Total Average Score at EOS	Planned: 432 Actual: 477	Centers: 34 Countries: 1
812P302	Subjects 12 to 17 years of age with ADHD	Control type: Placebo concurrent Randomization: Standard randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Viloxazine Dose: 200 mg QD; 400 mg QD; placebo Number treated: 99; 105; 104 Duration: approximately 10 weeks	Primary: CFB in the ADHD-RS-5 Total Score at end of study (EOS) Secondary: CGI-I score at EOS; CFB in the Conners 3-Parent Composite T-Score at EOS; CFB in the WFIRS-P Total Average Score at EOS	Planned: 300 Actual: 310	Centers: 33 Countries: 1
812P303	Subjects 6 to 11 years of age with ADHD	Control type: Placebo concurrent Randomization: Standard randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Viloxazine Dose: 200 mg QD; 400 mg QD; placebo Number treated: 107; 100; 103 Duration: approximately 12 weeks	Primary: CFB in the ADHD-RS-5 Total Score at EOS Secondary: CGI-I score at EOS; CFB in the Conners 3-Parent Composite T-Score at EOS; CFB in the WFIRS-P Total Average Score at EOS	Planned: 300 Actual: 313	Centers: 28 Countries: 1

Reference ID: 4698714

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
812P304	Subjects 12 to 17 years of age with ADHD	Control type: Placebo concurrent Randomization: Standard randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Viloxazine Dose: 400 mg QD; 600 mg QD; placebo Number treated: 100; 99; 97 Duration: approximately 11 weeks	Primary: CFB in the ADHD-RS-5 Total Score at EOS Secondary: CGI-I score at EOS; CFB in the Conners 3-Parent Composite T-Score at EOS; CFB in the WFIRS-P Total Average Score at EOS	Planned: 300 Actual: 297	Centers: 29 Countries: 1

Source: CSR and adsl.xpt; Table created by the Clinical Data Scientist.
[1] Includes all phase 3 clinical trials.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CFB = change from baseline; CGI-I = Clinical Global Impression–Improvement scale; DB = double-blind; EOS = end of study; N=number of subjects; QD = once daily; RS = rating scale; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section **Error! Reference source not found.** Section II.6.4
☒	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

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5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Pharmacologic properties of viloxazine that are relevant to the interpretation of benefit and risk are summarized in Table 5. This includes information related to the viloxazine extended-release formulation. The major metabolite, 5-hydroxyviloxazine-gluconate, is not pharmacologically active; therefore, information related to it is not included in Table 5.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Mechanism of action	Norepinephrine reuptake inhibitor.
Active moieties	Viloxazine, the parent compound.
QT prolongation	At a dose three-fold the maximum recommended dose, viloxazine does not prolong the QT interval to any clinically relevant extent. There was no effect of viloxazine on the PR interval or QRS duration in healthy volunteers. However, nonclinical studies suggest a potential for viloxazine to inhibit cardiac sodium channels.
General Information	
Bioanalysis	A validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method was used to determine the concentrations of viloxazine and 5-hydroxyviloxazine glucuronide in plasma and urine. The accuracy, precision, sensitivity, stability, incurred sample reanalysis and reproducibility met the acceptance criteria. The analytical method and its validation are acceptable.
Healthy subjects versus patients	The PK for ADHD patients and healthy subjects is expected to be similar based on the population pharmacokinetic analysis.
Drug exposure at steady state following the therapeutic dosing regimen (or a single dose, if more relevant for the drug)	**Parameter** / **Mean ± SD*** AUC_{tau} / 24.7±8.52 µg*h/mL $C_{max,ss}$ / 1.66±0.50 µg/mL C_{min} / 0.39±0.23 µg/mL %FL / 128±27.8% Median T_{max} (range) / 5 (2, 9) hours *Viloxazine PK values at steady state after multiple doses of viloxazine ER 200 mg once daily. Source: Applicant's Study 812P103 page 46
Range of effective dose(s) or exposure	100 to 400 mg
Maximally tolerated dose or exposure	600 mg
Dose proportionality	100 to 600 mg dose range
Accumulation	No significant accumulation from single dose to steady state
Time to achieve steady state	After 2 days of once-daily dosing
Bridge between to-be-marketed and clinical trial formulations	To-be-marketed formulation was used in the pivotal phase 3 and key pharmacokinetic studies

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Characteristic	Drug Information
Absorption	
Bioavailability	Relative bioavailability with immediate release (IR) oral capsule as reference was about 87%
Median T_{max} (range)	Sprinkled, fed, and fasted 5 (3, 7), 7 (4,18), and 5 (4, 9) hours, respectively
Food effect (fed/fasted) Geometric least square mean ratio and 90% CI Food effect (sprinkled on applesauce/intact) fasted. Geometric least square mean ratio and 90% CI	Viloxazine (See Appendix III.14.3.1) $AUC_{0-\infty}$ 92.35% (86.96, 98.07) C_{max} 90.86% (84.05, 98.21) T_{max} 7 vs. 5 hours for fed and fasted, respectively $AUC_{0-\infty}$ 95.37% (89.80, 101.28) C_{max} 90.10% (83.35, 97.40) Fed state: Within 30 minutes after start of high-fat, high-calorie standard meal (800-1000 kcal) after an overnight fast of 10 hours
Distribution	
Volume of distribution	14.6 L (Based on the population pharmacokinetic analysis)
Plasma protein binding	76-82% bound to human plasma proteins over concentration range of 0.5 to 10 µg/mL
Drug as substrate of transporters	Not a substrate of transporters (Pgp, BCRP, OATiB1/3, OAT, OCT, MATE)
Elimination	
Mass balance results	Following administration of a single oral dose of [^{14}C]-viloxazine, a mean of about 103% of the radioactivity administered was recovered, with approximately 90% of the dose recovered within the first 24 hours of dosing. An average of 102% of the total radioactivity was recovered from the urine and 0.67% from the feces. Urinary excretion is the major route of elimination of viloxazine and its metabolites. Unchanged viloxazine and the 5-hydroxy glucuronide metabolite were the only moieties excreted in urine in amounts greater than 10% of total radioactivity. Unchanged viloxazine and 5-hydroxyviloxazine-glucuronide accounted for about 53.1% and 10.6% of total radioactivity in plasma, respectively.
Clearance	0.865 L/hour (based on the population pharmacokinetic analysis)
Half-life	7.02±4.74 hours
Metabolic pathway(s)	1) Hydroxylation by CYP2D6, then glucuronidation to 5-OH-viloxazine glucuronide; 2) N-carboxylation, then glucuronidation to a minor metabolite
Primary excretion pathways (% dose)	Renal. Less than 1% excreted via feces
Intrinsic Factors and Specific Populations	
Body weight	The population pharmacokinetic analysis indicated that exposure (C_{max} and AUC) increases with decreasing weight. Exposures in children 6 to 11 years are 40-50% higher than in adolescents ages 12 to 17 years at the same dose.
Age	The population pharmacokinetic analysis indicated that pharmacokinetics of viloxazine is not affected by age
Renal impairment	AUC is about 90% higher in severely renal-impaired patients. A maximum dose of 200 mg is recommended in patients with severe renal impairment.

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Characteristic	Drug Information
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Viloxazine is a strong inhibitor of CYP1A2 substrates, increasing exposure of CYP1A2 by about 5-fold. Viloxazine is a weak (<2-fold increase) inhibitor of CYP2D6 and CYP3A4
Inhibition/induction of transporter systems	No clinically significant inhibition or induction of transporters

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AUC = area under the curve; FL = peak-to-trough fluctuation; PK = pharmacokinetics

5.1. Nonclinical Assessment of Potential Effectiveness

In in vitro and in vivo nonclinical studies, viloxazine increased noradrenergic neurotransmission by inhibiting the reuptake of norepinephrine. Specifically:

- In in vitro assays, viloxazine bound to the norepinephrine transporter (NET) with a K_i of 0.63µM;
- In cell-based functional assays, viloxazine inhibited the reuptake of norepinephrine with a half maximal inhibitory concentration (IC_{50}) of 0.2µM;
- In vivo administration of viloxazine to the rat increased brain norepinephrine levels, as well as serotonin (5-HT) and dopamine (DA) levels.

In addition to the noradrenergic mechanism of action, viloxazine also demonstrated weak binding affinity for a few serotonin receptors. However, when tested in in vitro functional assays, viloxazine showed both weak agonist and antagonist activity for the same 5-HT receptors. (b) (4) (see Section III.13.2.2 Pharmacology).

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Dose selection for the phase 3 studies was based on the findings from Studies 812P201and 812P202.

Study 812P201 was a phase 1/2a, randomized, double-blind, multicenter, placebo-controlled, parallel-group study of the safety and efficacy of viloxazine (SPN-812V) in adults with ADHD. Immediate-release capsules, 50 mg, were used in the study. At treatment Week 1, subjects received viloxazine at a dose of 50 mg three times daily (150 mg/day); from Weeks 2 to 6, subjects received viloxazine at a dose of 100 mg three times daily (300 mg/day). The study enrolled 52 subjects and the primary efficacy endpoint was the change from baseline in the investigator-rated Conners' Adult ADHD Rating Scale (CAARS) total ADHD symptom score. The median reduction from baseline in the investigator-rated CAARS total score after one week of treatment at a daily dose of 150 mg was 5.0 points in the viloxazine group and 2.0 points in the placebo group; the difference was not statistically significant (p=0.0803). The median change in the investigator-rated CAARS total score at each weekly visit during the treatment period (i.e.,

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at the target daily dose of 300 mg) showed a gradually widening difference between the viloxazine and placebo groups. Eight (30.8%) subjects in the viloxazine group and 1 (4.0%) subject in the placebo group reduced the dosage to 150 mg/day due to adverse events (AEs). The most common AEs in viloxazine-treated patients were nausea (38.5%), decreased appetite (30.8%), headache (30.8%), insomnia (30.8%), and dry mouth (23.1%).

Study 812P202 was a randomized, double-blind, placebo-controlled, multicenter, 5-arm, parallel-group, dose-ranging study to evaluate the efficacy, safety, and tolerability of viloxazine ER as monotherapy for ADHD in children. The study enrolled 200 subjects aged 6 to 12 years, who were randomized at a 1:2:2:2:2 ratio to placebo or active treatment (viloxazine ER 100, 200, 300, or 400 mg). When compared to placebo, doses of 200 to 400 mg showed a statistically significant effect on ADHD Rating Scale IV (ADHD-RS-IV) total score. A reduction of about 8 units from baseline in the ADHD-RS-IV total score was observed for doses of 200 to 400 mg. However, the 100 mg dose showed a reduction of 6.2 units from baseline in the ADHD-RS-IV total score, which was not statistically significant when compared to placebo.

Based on the findings discussed above and considering the differences in body weight across age groups (6 to 11 and 12 to 17 years), the Applicant selected a dosage range of 100 to 600 mg viloxazine ER capsules to evaluate in the phase 3 studies.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial Design

The Applicant conducted four phase 3, multicenter, randomized, double-blind, three-arm, placebo-controlled studies to evaluate the safety and efficacy of viloxazine ER in the pediatric population—Studies 812P301, 812P302, 812P303, 812P304. Studies 812P301 and 812P303 evaluated viloxazine ER in children ages 6 to 11 years. Studies 812P302 and 812P304 evaluated viloxazine ER in adolescents ages 13 to 17 years. Doses ranged from 100 mg to 400 mg once daily in patients ages 6 to 11 years, and from 200 mg to 600 mg once daily in patients ages 12 to 17 years. Each study included a screening phase, a dose-titration phase, and a 5-week, fixed-dose, maintenance phase. All four studies were conducted entirely in the United States.

Figure 1 depicts the design of Study 812P301. The designs of the other phase 3 studies mirrored that of Study 812P301, except for differences in age, dose range, and duration of the titration period. See Appendix III.15 for a more complete description of the phase 3 studies.

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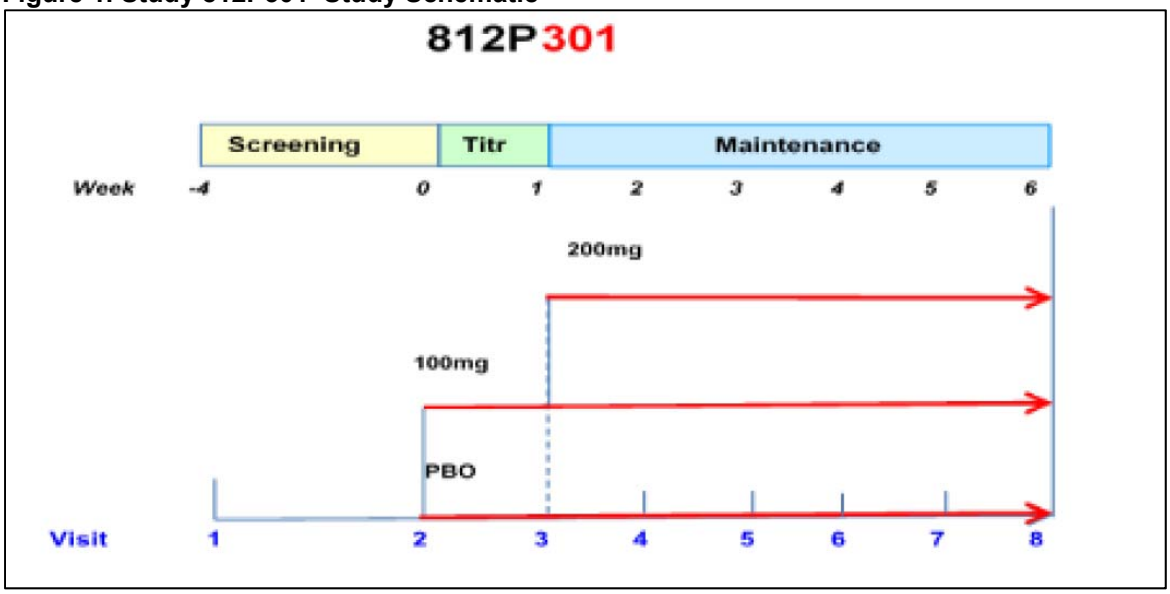
Figure 1. Study 812P301–Study Schematic



Source: Applicant's Clinical Study Protocol, Figure 1: Study Schematic, page 19
Abbreviations: PBO = placebo; Titr = titration

The primary efficacy endpoint in each phase 3 study was the change from baseline (CFB) in the ADHD-RS-5 total score at the end of study (EOS). The studies used the ADHD-RS-5 Home Version: Child Instrument, which was completed at each weekly visit by the Investigator from baseline to EOS.

The secondary endpoints for which type I error was controlled were the CGI-I scale score at EOS, the CFB in the Conners 3-Parent Composite T-Score at EOS, and the CFB in the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) total average score at EOS.

Safety endpoints included adverse events, clinical laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Overall, the studies were appropriately designed to meet their stated objectives. The design is typical of studies used to evaluate the safety and efficacy of psychiatric drugs and did not include any novel elements. The Applicant and the Agency reached agreement on the primary endpoint prior to submission of the NDA. However, the Agency did not agree with the use of the CGI-I as a key secondary endpoint because of its vulnerability to recall bias.

The Applicant has also submitted Study 812P202, a phase 2 dose-ranging study, as supportive evidence. See Appendix III.15 for further details on the design of Study 812P202.

6.2.2. Eligibility Criteria

Patients with a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents, were eligible to enroll in the phase 3 studies. In addition, a baseline ADHD-RS-5 score of at least 28 and a baseline Clinical Global Impression-Severity (CGI-S) score of at least 4 (moderately ill) were required. Patients entering the studies had to be free of medication for the treatment of ADHD for at least one week prior to randomization, and be

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considered medically healthy by the investigator (as assessed by physical examination, medical history, clinical laboratory tests, vital signs, and ECG). Female patients of childbearing potential had to either practice abstinence or agree to use effective methods of birth control throughout the study. The exclusion criteria included the presence of major psychiatric, neurological, or other physical health conditions. Patients with a personal history or family history of seizure disorders were specifically excluded.

The inclusion and exclusion criteria were appropriate to select a representative patient population and to mitigate potential risks to patients in the studies. ADHD diagnosis in clinical practice is based on application of the DSM-5 criteria, which were also used in the phase 3 studies. Participants had prominent ADHD symptoms at baseline based on ADHD-RS-5 scores. The study excluded patients with a known history of seizure disorder or high risk for seizures given that the risk of seizures in humans was unknown (convulsions occurred in multiple species in nonclinical studies). The protocols required reporting of seizures and seizure-like events as adverse events of special interest. The protocols also included appropriate prospective monitoring for potential safety signals of interest in this population, including cardiovascular adverse events, negative impacts on growth, and suicidal ideation. The inclusion and exclusion criteria for Study 812P202 were similar to those for the phase 3 studies. Patients from Studies 812P202, 812P301, 812P302, 812P303, and 812P304 were eligible to enroll in Study812P310, the long-term safety extension.

6.2.3. Statistical Analysis Plan

In each study, important design features, such as endpoints, primary analysis methods, multiplicity adjustment method, and sample size were prespecified in the statistical analysis plan. The primary efficacy outcome was the change from baseline to EOS in ADHD-RS-5 total score, which was the measure used in all of the other studies. The primary endpoint was targeted on the highest dose first, followed by lower doses, in sequence (e.g., 200 mg/day, 100 mg/day in Study 301). A similar hierarchy was used for the secondary endpoints. The proposed key secondary efficacy endpoints were:

- CGI-I score at EOS.
- Change from baseline in the Conners 3-Parent Composite T-Score at EOS.
- Change from baseline in the WFIRS-P total average score at EOS.

Multiplicity adjustment: To account for potential type I error inflation caused by comparisons of multiple dose-groups to placebo, a sequential testing procedure was used to assess the primary (high, low doses) and secondary endpoints (high, low doses) in all four trials.

Protocol amendments: (i) Study 301; the original protocol, which was issued on 11 July 2017, was amended three times: 14 August 2017, 7 September 2017, and 17 September 2017. (ii) Study 302; the original protocol, which was issued on 11 July 2017, was amended three times: 14 August 2017, 7 September 2017, and 18 September 2018. (iii) Study 303; the original protocol, which was issued on 11 July 2017, was amended three times: 14 August 2017, 7 September 2017, and 22 August 2018. (iv) Study 304; the original protocol, which was issued on 11 July 2017, was amended three times: 14 August 2017, 7 September 2017, and 12 October 2018.

Analysis method: The prespecified primary efficacy analysis model, mixed model repeated

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measures (MMRM), was used to evaluate the treatment effect in the studies. The model, which assesses the change from baseline in ADHD-RS-5, comprises the baseline ADHD-RS-5 total score, age group category, treatment, visit (in weeks), and treatment-by-visit interaction as fixed independent variables. MMRM assumes a missing at random missing data mechanism. The model parameters were to be estimated using the restricted maximum-likelihood method, with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

Sample size and power: The sample size calculation was based on a two-sample *t*-test and treatment effect assumptions from previously completed phase 2b trials. Below are the sample size and power calculation, which are extracted from the Applicant's statistical analysis plan.

Study 301: One hundred and four subjects per treatment group in the intent-to-treat (ITT) population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample *t*-test with equal allocation to the treatment groups. This assumes an effect size of 0.453, observed in the comparison of SPN-812 100 mg and placebo in the SPN-812 phase 2b study (based on the CFB to endpoint in the ADHD-RS-IV total score). A total of 432 subjects (144 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.

Study 302 and Study 303: Seventy-two subjects per treatment group in the ITT population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample *t*-test with equal allocation to the treatment groups. This assumes an effect size of 0.547, as observed in the comparison of SPN-812 200 mg and placebo in the SPN-812 phase 2b study (based on the CFB to endpoint in the ADHD-RS-IV total score). A total of 300 subjects (100 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.

Study 304: Seventy-two subjects per treatment group in the ITT population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample *t*-test with equal allocation to the treatment groups. This assumes an effect size of 0.547, which was observed in the comparison of SPN-812 200 mg and placebo in the SPN 812 phase 2b study (based on the CFB to endpoint in the ADHD-RS-IV total score) and will maintain consistency in the sample size assumption used between this clinical trial and the SPN-812 P302 study in the adolescent population. A total of 300 subjects (100 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.

6.2.4. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Efficacy

This section summarizes the baseline demographics and disease characteristics, patient dispositions, and primary efficacy results to support the use of viloxazine ER in the treatment of pediatric ADHD.

Overall, the baseline demographics and disease characteristics were well-balanced in patients receiving viloxazine ER and patients receiving placebo. The studies were conducted entirely in the United States. Greater than 60% of the patients were male, which is consistent with the gender ratios observed in clinical practice (Ramtekkar et al. 2010). The study population was

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ethnically diverse, although patients of Asian, Alaskan Native, Pacific Islander, and Native Hawaiian heritage were underrepresented. Black and Latino children and adolescents were over-represented in the sample; although a body of literature suggests that minority children are less likely to receive an ADHD diagnosis, more recent data indicate that Black children may be diagnosed with ADHD more frequently than those of other ethnicities (Morgan et al. 2013; Zablotsky and Alford 2020). Although the study population may differ somewhat from the general clinical population, the treatment groups had similar racial and ethnic compositions, making it unlikely that sociodemographic factors influenced the study results. Table 6 summarizes the baseline demographic characteristics of the phase 3 controlled studies.

Table 6. Baseline Demographic Characteristics, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 Years		Ages 12 to 17 Years		Total	
Characteristic	**Treatment N=522**	**Placebo N=262**	**Treatment N=403**	**Placebo N=201**	**Treatment N=925**	**Placebo N=463**
Sex, n (%)						
Male	335 (64)	166 (63)	276 (69)	119 (59)	611 (66)	285 (62)
Female	187 (36)	96 (37)	127 (32)	82 (41)	314 (34)	178 (38)
Age, years, n (%)						
Mean (SD)	8.5 (2)	8.5 (2)	13.9 (2)	13.8 (2)	10.9 (3)	10.8 (3)
Median (min, max)	8.0 (6.0, 11.0)	8.0 (6.0, 11.0)	14.0 (12.0, 17.0)	14.0 (12.0, 17.0)	11.0 (6.0, 17.0)	11.0 (6.0, 17.0)
Age group, years, n (%)						
6–9	356 (68)	175 (67)	0	0	356 (39)	175 (38)
10–11	166 (32)	87 (33)	0	0	166 (18)	87 (19)
12–14	0	0	267 (66)	134 (67)	267 (29)	134 (29)
15–17	0	0	136 (34)	67 (33)	136 (15)	67 (15)
Race, n (%)						
American Indian or Alaska Native	2 (0.4)	3 (1)	4 (1)	1 (1)	6 (1)	4 (1)
Black or African American	226 (43)	111 (42)	142 (35)	64 (32)	368 (40)	175 (38)
Multiple	22 (4)	11 (4)	11 (3)	8 (4)	33 (4)	19 (4)
White	272 (52)	135 (52)	243 (60)	128 (64)	515 (56)	263 (57)
Asian	0	2 (1)	2 (1)	0	2 (0.2)	2 (0.4)
Native Hawaiian or other Pacific Islander	0	0	1 (0.2)	0	1 (0.1)	0
Ethnicity, n (%)						
Hispanic or Latino	152 (29)	68 (26)	125 (31)	63 (31)	277 (30)	131 (28)
Not Hispanic or Latino	369 (71)	194 (74)	278 (69)	137 (68)	647 (70)	331 (72)
Missing	1 (0.2)	0	0	1 (1)	1 (0.1)	1 (0.1)
Country of participation, n (%)						
United States	522 (100)	262 (100)	403 (100)	201 (100)	925 (100)	463 (100)

Source: adsl.xpt; Software, Python. Created by the Clinical Data Scientist and Clinical Review Team.
Abbreviations: Max = maximum; min = minimum; N=number of subjects in treatment group; N=number of subjects with a given characteristic; SD = standard deviation

The mean baseline weight in patients ages 6 to 11 years was 32 kg in the viloxazine ER treatment groups and 30.9 in the placebo groups. The mean baseline weight in patients ages 12 to

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17 years was 57.9 kg in the viloxazine ER treatment groups and 55.9 kg in the placebo groups. Similar proportions of patients in the viloxazine ER and placebo groups were taking psychostimulants or other agents used for ADHD (i.e., alpha agonists or atomoxetine) at screening (28.3% and 28.8% of patients respectively).

The baseline ADHD-RS-5 score in viloxazine ER–treated patients was 42.5 (SD 7.4), compared to 41.8 (SD 7.4) in placebo-treated patients.

Table 7 and Table 8 summarize the patient disposition and reasons for study discontinuation in the phase 3 controlled studies. Patients who received viloxazine ER were more likely than patients receiving placebo to discontinue the studies because of adverse events. However, only approximately 3.5% of viloxazine ER–treated patients dropped out because of adverse events.

Table 7. Patient Screening and Randomization (Studies 812P301, 812P302, 812P303, and 812P304)

Screening Disposition	Study 812P301	Study 812P302	Study 812P303	Study 812P304
Patients screened	587	379	393	417
Patients not randomized	110	69	80	120
Screening failures	110	69	80	120
Patients randomized	477	310	313	297

Source: adds.xpt; Software, R. Table created by the Clinical Data Scientist.
In Study 812P301, 3 patients were randomized but not treated
In Study 812P302, 2 patients were randomized but not treated
In Study 812P303, 3 patients were randomized but not treated
In Study 812P304, 1 patient was randomized but not treated

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Table 8. Patient Disposition (Studies 812P301, 812P302, 812P303, and 812P304)

	Study 812P301			Study 812P302			Study 812P303			Study 812P304		
Disposition Outcome	**100 mg N=154 n (%)**	**200 mg N=161 n (%)**	**Placebo N=159 n (%)**	**200 mg N=99 n (%)**	**400 mg N=105 n (%)**	**Placebo N=104 n (%)**	**200 mg N=107 n (%)**	**400 mg N=100 n (%)**	**Placebo N=103 n (%)**	**400 mg N=100 n (%)**	**600 mg N=99 n (%)**	**Placebo N=97 n (%)**
Discontinued study												
Adverse event	5 (3)	2 (1)	2 (1)	4 (4)	2 (2)	0	6 (6)	4 (4)	3 (3)	4 (4)	5 (5)	1 (1)
Lost to follow-up	9 (6)	6 (4)	3 (2)	6 (6)	4 (4)	2 (2)	7 (7)	8 (8)	10 (10)	5 (5)	4 (4)	5 (5)
Subject noncompliant	1 (1)	1 (1)	1 (1)	2 (2)	0	0	3 (3)	1 (1)	1 (1)	0	1 (1)	2 (2)
Withdrawal by parent/guardian	8 (5)	10 (6)	19 (12)	4 (4)	7 (7)	1 (1)	2 (2)	9 (9)	2 (2)	1 (1)	5 (5)	4 (4)
Withdrawal by subject	1 (1)	0	1 (1)	3 (3)	1 (1)	2 (2)	0	1 (1)	0	2 (2)	2 (2)	0
Noncompliance with study drug	1 (1)	0	0	0	0	0	0	0	0	0	0	0
Other	3 (2)	1 (1)	1 (1)	1 (1)	0	3 (3)	1 (1)	0	1 (1)	0	1 (1)	0

Source: adds.xpt; Software, R. Created by the Clinical Data Scientist.
Abbreviations: N = number of subjects in treatment arm; N = number of subjects in a specified population or group

Primary Efficacy Results

The four pivotal studies evaluated the efficacy of fixed doses of SPN-812 ER, compared to placebo, in patients with ADHD: Study 301–SPN-812 ER 100 mg/day, 200 mg/day; Study 302–SPN-812 ER 200 mg/day, 400 mg/day; Study 303–SPN-812 ER 200 mg/day, 400 mg/day; and Study 304–SPN-812 ER 400 mg/day, 600 mg/day.

The primary efficacy endpoint was the ADHD-RS-5 total score and was tested hierarchically, with the higher dose first. A reduction in the ADHD-RS-5 total score is evidence of improvement in ADHD symptoms. The primary objective was met in three studies (301, 302, and 303), but not in the fourth (Study 304), in which the comparison of SPN-812 ER 600 mg vs. placebo failed to reach statistical significance after adjusting for multiplicity (p=0.071). In that study, however, the comparison of SPN-812 ER 400 mg vs. placebo was nominally significant (p=0.0082). (b) (4)

In addition to the primary efficacy endpoints, key secondary endpoints were also tested in all four trials. To adjust for multiplicity, the trials utilized a sequential testing procedure to control the overall type I error rate. The multiple hypotheses involved one primary endpoint (high, low doses) and three key secondary endpoints (high, low doses). Below are the key secondary endpoints in the order in which they were tested, from highest to lowest, within each endpoint:

- CGI-I score at EOS (Week 6).
- Change from baseline in the Conners 3-Parent Composite T-score at EOS.
- Change from baseline in the WFIRS-P total average score at EOS.

A statistically significant improvement in the CGI-I was observed in Study 301 (doses 100 mg and 200 mg) and Study 303 (doses 200 mg and 400 mg), which evaluated viloxazine ER in patients ages 6 to 11 years. Similarly, a statistically significant improvement was observed on the CGI-I in doses 200 mg and 400 mg compared to placebo in Study 302, which evaluated patients ages 12 to 17 years. A statistically significant improvement was observed on the Conners 3-Parent Composite T-score and the WFIRS in Study 301 (in both dose groups). No statistically significant change on the Conners or the WFIRS was observed in the other studies.

6.2.4.1. Study 301

Primary Endpoint

The statistical reviewer confirmed the Applicant's efficacy findings (Table 9). Fixed 100 mg/day and 200 mg/day dosages of SPN-812 ER were statistically significantly superior to placebo in the mean change from baseline in ADHD-RS-5 total score at Week 6, with least square (SE) mean treatment differences to placebo of -5.8 (1.61) (100 mg/day; p=0.0004) and -6.9 (1.58) (200 mg/day; p<0.0001), respectively.

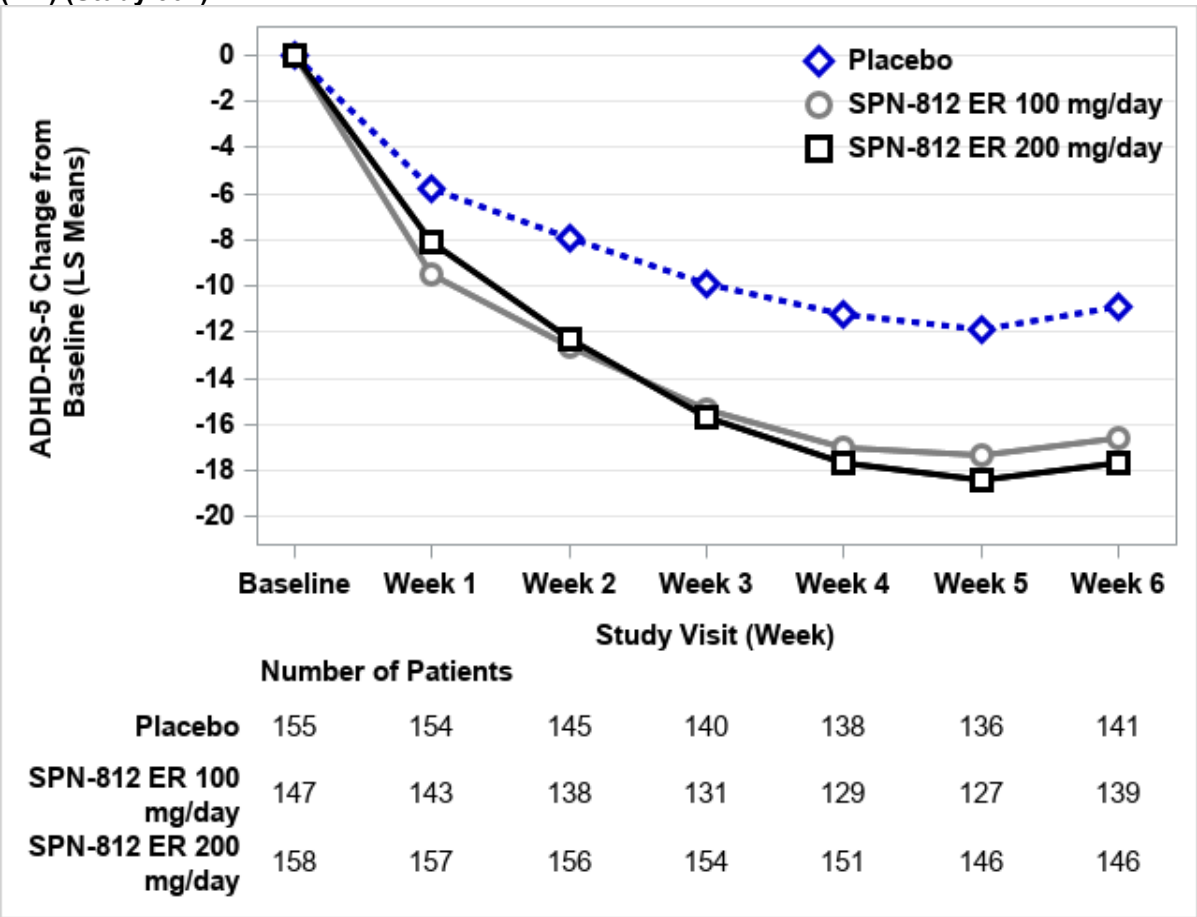
Reference ID: 4698714

Table 9. Change from Baseline at Week 6 (EOS) in ADHD-RS-5 Total Score (ITT; MMRM) (Study 301)

Visit	Statistic	Placebo N=155	SPN-812 ER 100 mg/Day N=147	SPN-812 ER 200 mg/Day N=158
Baseline	Mean ± SD	43.6±7.05	45.0±6.53	44.0±6.80
EOS	Mean ± SD (Week 6)	32.9±13.88	28.1±15.33	26.2±13.92
	Mean ± SD (CFB)	-10.7±12.98	-16.8±15.10	-17.4±13.53
EOS statistical results	LS mean ± SE (CFB)	-10.9±1.14	-16.6±1.16	-17.7±1.12
	Difference of LS mean ±SE (vs. placebo)	-	-5.8±1.61	-6.9±1.58
	95% CI of difference	-	(-8.9, -2.6)	(-10.0, -3.8)
	p-value (vs. placebo)	-	0.0004	<0.0001
	Adjusted p-value	-	0.0004	<0.0001

Source: Table 11-1 of the Sponsor's Clinical Study Report (page 62)
Mean denotes raw mean (second and third rows of the table)
MMRM models change from baseline in ADHD-RS-5 and comprises the baseline ADHD-RS-5 total score, age group, treatment, visit, and treatment-by-visit interaction as fixed independent variables.
Abbreviations: ADHD = attention deficit/hyperactivity disorder; CFB = change from baseline; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; MMRM = mixed effects model repeat measurement; N = total number of subjects; RS = rating scale; SPN = viloxazine

Figure 2. LS Mean Change from Baseline in ADHD-RS-5 Total Score by Visit and Treatment Group (ITT) (Study 301)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit/hyperactivity disorder; ER = extended release; LS = least squares; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

Key Secondary Endpoints

At the end of Week 6, a statistically significant improvement was observed on the CGI-I scale for the two SPN-812 ER dose levels (100 mg/day and 200 mg/day), compared to placebo (LS mean difference: -0.4±0.14, p<0.0001; -0.6±0.13, p=0.002).

Similarly, analysis of the other key secondary variables (Conners 3-Parent Composite T-score and WFIRS-P total average score) showed statistically significantly greater improvement in the changes from baseline for all dose levels, compared to placebo, at the end of the 6-week double-blind phase. That is, Conners 3-Parent Composite T-score LS mean (SE): -4.2 (1.16), p=0.0003; -4.3±1.15, p=0.0002 and WFIRS-P total average score LS mean (SE): -0.14 (0.047), p=0.0019; -0.17 (0.046), p=0.0002.

Table 10. Observed Global Severity Score (CGI-S) at Baseline and Observed Global Improvement Score (CGI-I) at Week 6 (EOS)–(ITT; ANCOVA) (Study 301)

Visit	Statistic	Placebo N=155	SPN-812 ER 100 mg/Day N=147	SPN-812 ER 200 mg/Day N=158
Baseline	Mean ± SD	4.8±0.68	4.8±0.76	4.8±0.66
EOS	Mean ± SD (Week 6)	3.1±1.14	2.7±1.19	2.5±1.11
EOS Statistical results	LS mean ± SE	3.1±0.10	2.7±0.10	2.6±0.09
	Difference of LS mean ±SE (vs. placebo)	-	-0.4±0.14	-0.6±0.13
	95% CI of difference	-	(-0.7, -0.2)	(-0.8, -0.3)
	p-value (vs. placebo)	-	0.0020	<0.0001
	Adjusted p-value	-	0.0020	<0.0001

Source: Table 11-4 of the Sponsor's Clinical Study Report (page 66)
95% CIs and p-values are from ANCOVA model with treatment as a fixed classification variable and baseline CGI-S as a covariate
Abbreviations: ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression – Improvement Scale; CGI-S = Clinical Global Impression – Severity of Illness Scale; CI = confidence interval; EOS = end of study; ER = extended release; LS = least square; N = total number of subjects; SPN = viloxazine

Table 11. Change from Baseline at Week 6 (EOS) in the Conners 3-Parent Report Composite T-Score–(ITT; ANCOVA) (Study 301)

Visit	Statistic	Placebo N=155	SPN-812 ER 100 mg/Day N=147	SPN-812 ER 200 mg/Day N=158
Baseline	Mean ± SD	75.9±8.87	77.4±7.84	75.5±9.32
EOS	Mean ± SD (Week 6)	71.2±11.36	2.7±1.19	2.5±1.11
	Mean ± SD (CFB)	-4.7±9.70	-9.4±11.05	-8.8±10.07
EOS statistical results	LS Mean ± SE (CFB)	-4.8±0.81	-9.1±0.83	-9.2±0.82
	Difference of LS mean ±SE (vs. placebo)	-	-4.2±1.16	-4.3±1.15
	95% CI of difference	-	(-6.5, -1.9)	(-6.6, -2.1)
	p-value (vs. placebo)	-	0.0003	0.0002
	Adjusted p-value	-	0.0003	0.0002

Source: Table 11-5 of the Sponsor's Clinical Study Report (page 68)
95% CIs and p-values are from the ANCOVA model with treatment as a fixed classification variable and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression–Improvement scale; CGI-S = Clinical Global Impression–Severity of Illness scale; CI = confidence interval; EOS = end of study; ER = extended release; LS = least square; N = total number of subjects; SPN = viloxazine

Reference ID: 4698714

Table 12. Change from Baseline at Week 6 (EOS) in WFIRS-P Total Average Score–Key Secondary Analysis–(ITT; ANCOVA) (Study 301)

Visit	Statistic	Placebo N=155	SPN-812 ER 100 mg/day N=147	SPN-812 ER 200 mg/day N=158
Baseline	Mean ± SD	1.08±0.460	1.15±0.453	1.10±0.457
EOS	Mean ± SD (Week 6)	0.88±0.522	0.77±0.486	0.71±0.401
	Mean ± SD (CFB)	-0.21±0.431	-0.38±0.467	-0.38±0.407
EOS statistical results	LS Mean ± SE (CFB)	-0.22±0.033	-0.36±0.033	-0.39±0.032
	Difference of LS mean (±SE) (vs. placebo)	-	-0.14±0.047	-0.17±0.046
	95% CI of difference	-	(-0.24, -0.05)	(-0.26, -0.08)
	p-value (vs. placebo)	-	0.0019	0.0002
	Adjusted p-value	-	0.0019	0.0002

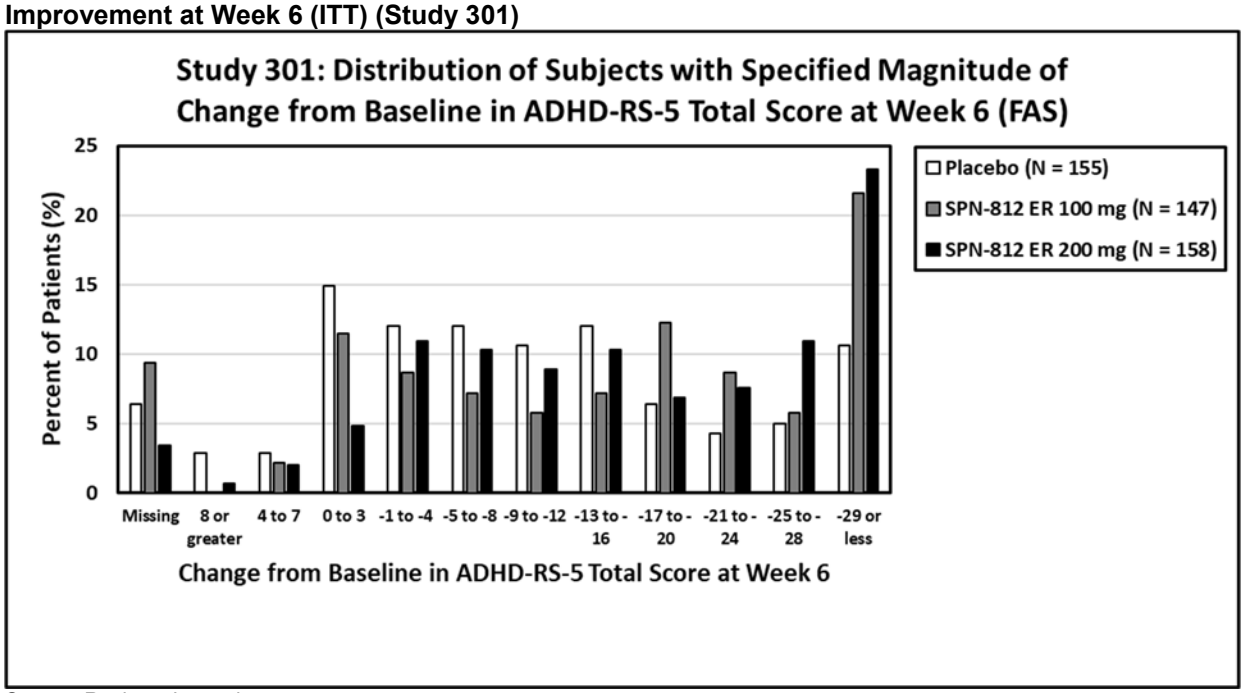
Source: Table 11-6 of the Sponsor's Clinical Study Report (page 69)
95% CIs and p-values are from ANCOVA model with treatment as a fixed classification variable and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EOS = end of study; ER = extended release; LS = least square; N = total number of subjects; SPN = viloxazine; WFIRS-P = Weiss functional impairment rating scale–parent report

Consistent results were seen for the sensitivity analyses of the primary endpoint based on multiple imputation with the missing not at random (MNAR) missing data mechanism.

Reviewer's note: This reviewer has included two figures to visualize the distribution of change in ADHD-RS-5 total score and percentage of improved subjects (Figure 3, Figure 4).

Figure 3 captures the distribution of change from baseline in the ADHD-RS-5 total score. With increasing magnitude of change, there is an increasing trend in the proportion of improved subjects in the placebo group. The proportion of subjects with a treatment change of greater than -17 units in either dose group is larger than that in the placebo group.

Figure 3. Percentage of Patients with a Specified Magnitude of ADHD-RS-5 Total Score Improvement at Week 6 (ITT) (Study 301)

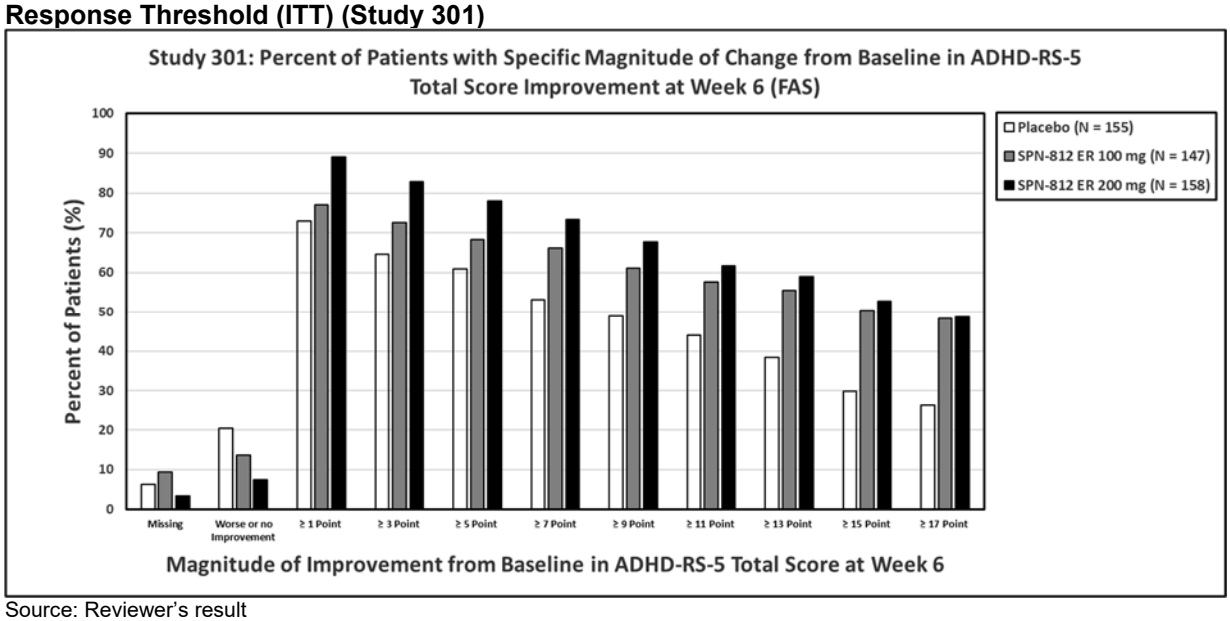


Source: Reviewer's result
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

Figure 4 shows a trend of improvement in the change from baseline in ADHD-RS-5 total score at Week 6 according to various subjective response cutoffs. Approximately 64.5%, 72.7%, and 82.9% of the patients improved at least by 3 units in the placebo, SPN-812 ER 100 mg, and 200 mg groups, respectively.

Figure 4. Percentage Response (ADHD-RS-5 Total Score) for Each Treatment Group at Week 6 by Response Threshold (ITT) (Study 301)



Source: Reviewer's result
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

6.2.4.2. Study 302

Primary Endpoint

The reviewer confirmed the Applicant's efficacy findings for this study. The results of the primary efficacy analysis are presented in Table 13. Adjusting for multiple-dose comparison, fixed 200 mg/day and 400 mg/day dosages of SPN-812 ER were statistically significantly superior to placebo in the mean change from baseline in ADHD-RS-5 total score at Week 6. At Week 6, the LS mean (SE) difference from placebo in the ADHD-RS-5 score was -4.5 (1.98) for SPN-812 ER 200 mg/day (p=0.0232), and -5.1 (1.93) for SPN-812 ER 400 mg/day (p=0.0091).

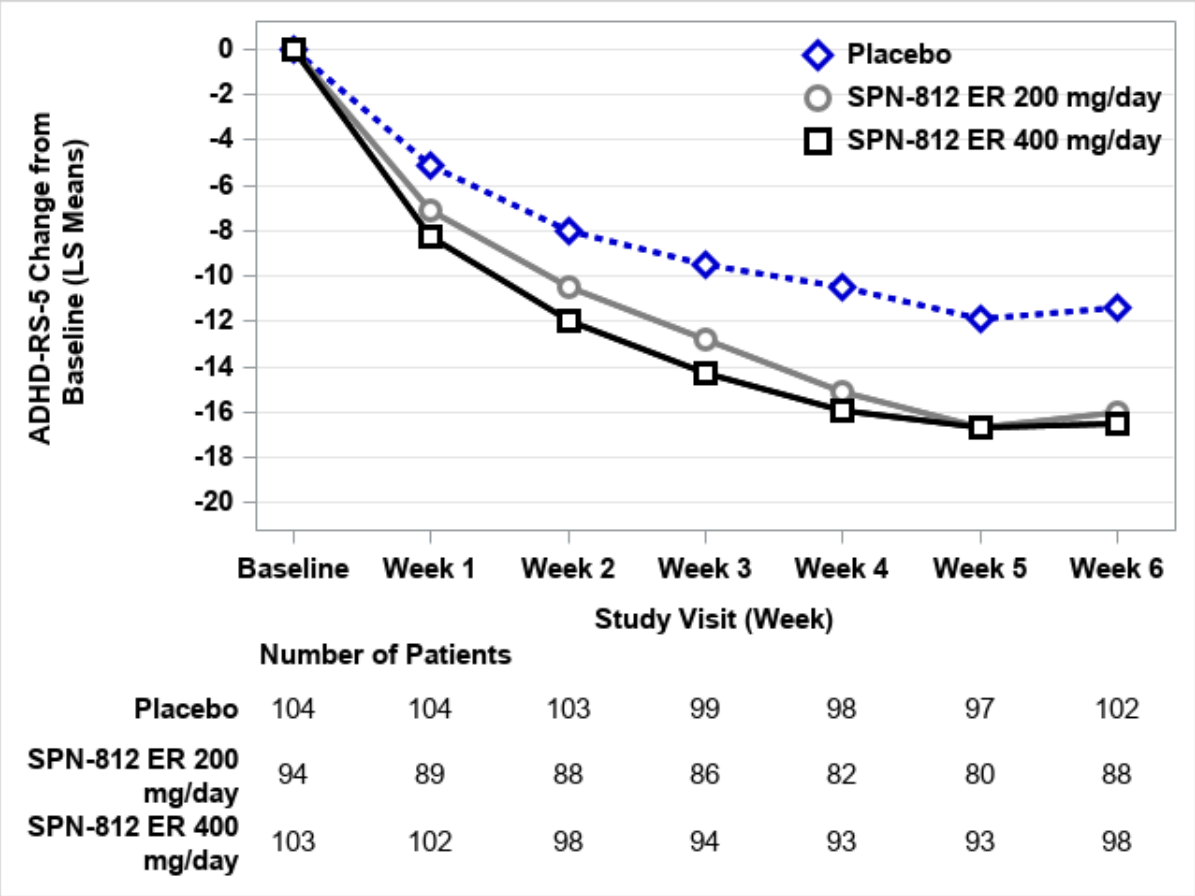
Reference ID: 4698714

Table 13. Change from Baseline at Week 6 (EOS) in ADHD-RS-5 Total Score (ITT; MMRM) (Study 302)

Visit	Statistic	Placebo N=104	SPN-812 ER 200 mg/Day N=94	SPN-812 ER 400 mg/Day N=103
Baseline	Mean ± SD	40.5±6.79	39.9±7.22	39.4±7.59
EOS	Mean ± SD (Week 6)	29.2±14.74	23.4±14.17	22.8±13.78
	Mean ± SD (CFB)	-11.3±14.14	-16.5±14.09	-16.6±13.23
EOS statistical results	LS mean ± SE (CFB)	-11.4±1.37	-16.0±1.45	-16.5±1.38
	Difference of LS mean ±SE (vs. placebo)	-	-4.5±1.98	-5.1±1.93
	95% CI of difference	-	(-8.4, -0.6)	(-8.9, -1.3)
	p-value (vs. placebo)	-	0.0232	0.0091
	Adjusted p-value	-	0.0232	0.0091

Source: Table 11-1 of the Sponsor's Clinical Study Report (page 66).
Mean denotes raw mean (second and third rows of the table); MMRM models change from baseline in ADHD-RS-5 and contains baseline ADHD-RS-5 total score, age group, treatment, visit, and treatment-by-visit interaction as fixed independent variables.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CFB = change from baseline; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; MMRM = mixed effect model repeat measurement; N = total number of subjects; RS = rating scale; SPN = viloxazine

Figure 5. LS Mean Change from Baseline in ADHD-RS-5 Total Score by Visit and Treatment Group (ITT) (Study 302)



Source: Reviewer's result
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; LS = least square; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

Key Secondary Endpoints

At the end of Week 6, a statistically significant improvement was observed on the CGI-I scale for the two SPN-812 ER doagse levels (200 mg/day and 400 mg/day), compared to placebo (LS mean: -0.5 [0.17], p<0.0042; -0.6±0.16, p=0.0003).

For the two other key secondary variables (Conners 3-Parent Composite T-score and WFIRS-P total average score), the difference between either of the SPN-812 ER dose levels and placebo failed to reach statistical significance, although strong trends were observed in the contrasts between SPN-812 ER 400mg/day and placebo.

Table 14. Observed Global Severity Score (CGI-S) at Baseline and Observed Global Improvement Score (CGI-I) at Week 6 (EOS), (ITT; ANCOVA) (Study 302)

Visit	Statistic	Placebo N=104	SPN-812 ER 200 mg/Day N=94	SPN-812 ER 400 mg/Day N=103
Baseline	Mean ± SD	4.6±0.65	4.6±0.70	4.6±0.64
EOS	Mean ± SD (Week 6)	3.0±1.17	2.5±1.15	2.4±1.16
EOS statistical results	LS mean ± SE	3.0±0.11	2.5±0.12	2.4±0.12
	Difference of LS mean (±SE) (vs. placebo)	-	-0.5±0.17	-0.6±0.16
	95% CI of difference	-	(-0.8, -0.2)	(-0.9, -0.3)
	p-value (vs. placebo)	-	0.0042	0.0003
	Adjusted p-value	-	0.0042	0.0003

Source: Table 11-4 of the Applicant's Clinical Study Report (page 70).
95% CIs and p-values are from ANCOVA model with treatment as a fixed classification variable and baseline CGI-S as a covariate
Abbreviations: ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression–Improvement scale; CGI-S = Clinical Global Impression–Severity of Illness scale; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; N = total number of subjects; SPN = viloxazine

Table 15. Change from Baseline at Week 6 (EOS) in the Conners 3-Parent Report Composite T-Score, (ITT; ANCOVA) (Study 302)

Visit	Statistic	Placebo N=104	SPN-812 ER 200 mg/Day N=94	SPN-812 ER 400 mg/Day N=103
Baseline	Mean ± SD	74.6±8.17	72.0±9.11	73.4±8.97
EOS	Mean ± SD (Week 6)	68.3±12.06	66.2±11.44	64.7±11.53
	Mean ± SD (CFB)	-6.3±11.63	-5.7±10.79	-8.6±10.68
EOS statistical results	LS Mean ± SE (CFB)	-5.7±1.04	-6.4±1.12	-8.6±1.07
	Difference of LS mean (±SE) (vs. placebo)	-	-0.6±1.54	-2.9±1.49
	95% CI of difference	-	(-3.6, 2.4)	(-5.8, 0.0)
	p-value (vs. placebo)	-	0.6854	0.0518
	Adjusted p-value	-	0.6854	0.0518

Source: Table 11-5 of the Applicant's Clinical Study Report (page 71).
95% CIs and p-values are from the ANCOVA model with fixed effects for treatment and baseline score as a covariate
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; N = total number of subjects; SPN = viloxazine

Reference ID: 4698714

Table 16. Change from Baseline at Week 6 (EOS) in WFIRS-P Total Average Score–Key Secondary Analysis, (ITT; ANCOVA) (Study 302)

Visit	Statistic	Placebo N=104	SPN-812 ER 200 mg/Day N=94	SPN-812 ER 400 mg/Day N=103
Baseline	Mean ± SD	1.06±0.487	1.03±0.513	1.03±0.490
EOS	Mean ± SD (Week 6)	0.86±0.535	0.75±0.469	0.72±0.50
	Mean ± SD (CFB)	-0.20±0.492	-0.25±0.430	-0.30±0.471
EOS statistical results	LS Mean ± SE (CFB)	-0.19±0.041	-0.27±0.045	-0.31±0.042
	Difference of LS mean (±SE) (vs. placebo)	-	-0.08±0.061	-0.11±0.059
	95% CI of difference	-	(-0.20, 0.04)	(-0.23, 0.00)
	p-value (vs. placebo)	-	0.2062	0.0519
	Adjusted p-value	-	--	0.0519

Source: Table 11-6 of the Applicant's Clinical Study Report (page 72).
95% CIs and p-values are from the ANCOVA model with fixed effects for treatment and baseline score as a covariate
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; N = total number of subjects; SPN = viloxazine; WFIRS-P = Weiss functional impairment rating scale–parent report

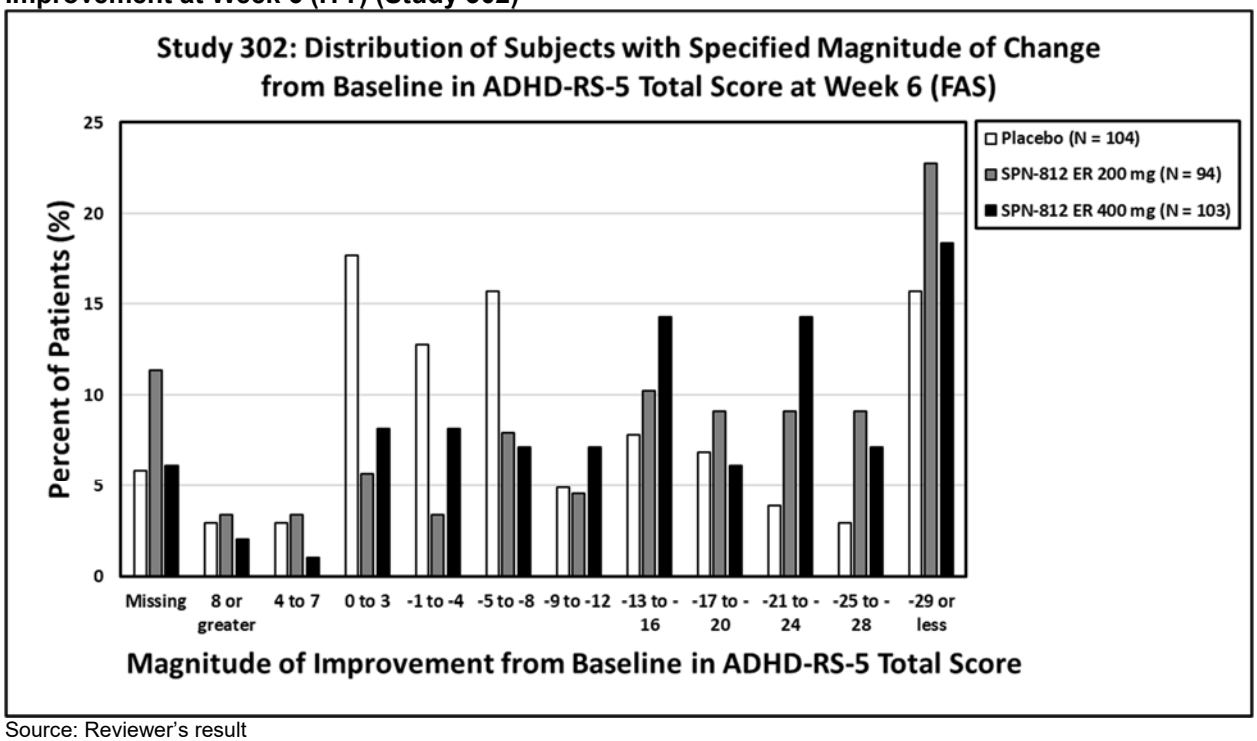
Sensitivity analysis of the primary endpoint based on multiple imputation with the MNAR missing data mechanism were consistent with the main efficacy conclusions.

Reviewer's note: As shown in Figure 6, with increased change from baseline in ADHD-RS-5, more subjects are allocated in either dose groups (SPN-812 200 mg or 400 mg).

Figure 7 presents the empirical percentage response for each treatment group at Week 6 by various response cutoffs. There was a consistent improvement trend in the change from baseline in ADHD-RS-5 total score at Week 6 for several arbitrary response magnitudes. Approximately 64.7% (placebo), 73.9% (SPN-812 200 mg), and 79.6% (SPN-812 400 mg) of subjects in the ITT population exhibited a greater than 3-point improvement in response.

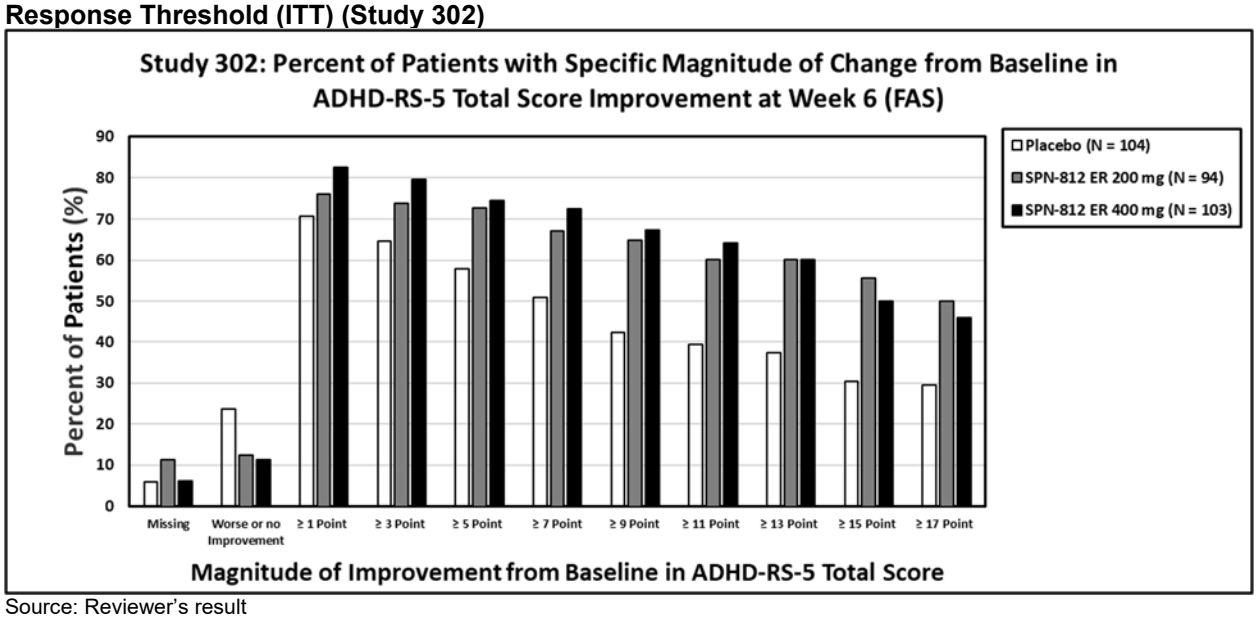
Reference ID: 4698714

Figure 6. Percentage of Patients with a Specified Magnitude of ADHD-RS-5 Total Score Improvement at Week 6 (ITT) (Study 302)



Source: Reviewer's result
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Figure 7. Percentage Response (ADHD-RS-5 Total Score) for Each Treatment Group at Week 6 by Response Threshold (ITT) (Study 302)



Source: Reviewer's result
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

6.2.4.3. Study 303

Primary Endpoint

The reviewer confirmed the Applicant's efficacy findings for this study. The results of the primary efficacy analysis are presented in Table 17. Adjusting for multiple-dose comparison, fixed 200 mg/day and 400 mg/day dosages of SPN-812 ER were statistically significantly superior to placebo in the mean change from baseline in ADHD-RS-5 total score at Week 6 (LS mean difference -6.0 [2.05], 0.0063; -5.8 [2.11], p=0.0063).

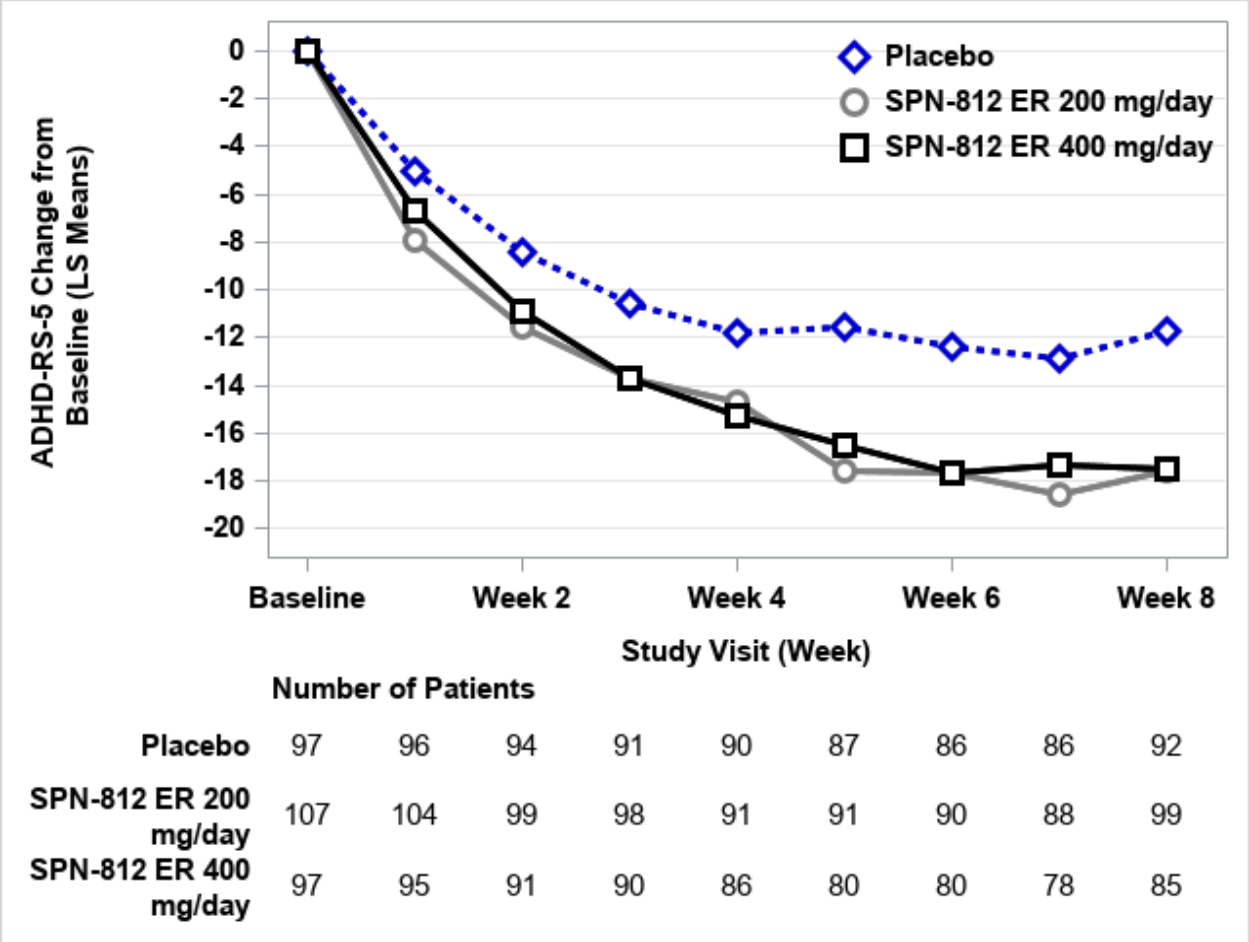
Table 17. Change from Baseline at Week 8 (EOS) in ADHD-RS-5 Total Score (ITT; MMRM) (Study 303)

Visit	Statistic	Placebo N=97	SPN-812 ER 200 mg/Day N=107	SPN-812 ER 400 mg/Day N=97
Baseline	Mean ± SD	43.5±6.79	43.8±6.54	45.0±6.55
EOS	Mean ± SD (Week 8)	32.8±15.10	26.5±14.96	27.3±15.02
	Mean ± SD (CFB)	-11.0±13.64	-17.1±14.89	-17.6±14.36
EOS statistical results	LS mean ± SE (CFB)	-11.7±1.48	-17.6±1.43	-17.5±1.52
	Difference of LS mean (±SE) (vs. placebo)	-	-6.0±2.05	-5.8±2.11
	95% CI of difference	-	(-10.0, -1.9)	(-9.9, -1.7)
	p-value (vs. placebo)	-	0.0038	0.0063
	Adjusted p-value	-	0.0063	0.0063

Source: Table 11-1 of the Sponsor's Clinical Study Report (page 65)
Mean denotes raw mean (second and third rows of the table)
MMRM models change from baseline in ADHD-RS-5 and contains baseline ADHD-RS-5 total score, age group, treatment, visit, and treatment-by-visit interaction as fixed independent variables.
Abbreviations: ADHD = attention-deficit hyperactivity disorder; CFB = change from baseline; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least square; MMRM = mixed effect model repeat measurement; N = total number of subjects; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

Figure 8. LS Mean Change from Baseline in ADHD-RS-5 Total Score by Visit and Treatment Group (ITT) (Study 303)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; LS = ; RS = rating scale; SPN = viloxazine

Key Secondary Endpoints

At the end of Week 6, a statistically significant improvement was observed on the CGI-I scale for the two SPN-812 ER dose levels (200 mg/day and 400 mg/day), compared to placebo (LS mean [±SE] -0.5±0.17, p=0.0009; -0.4±0.17, p=0.0009).

The SPN-812 ER 200 mg/day group showed numerical improvement compared to placebo (LS mean -3.8 (1.39); p=0.0064) in the change from baseline in Conners 3-Parent Composite T-score at Week 8, but the change failed to reach statistical significance when adjusted for multiplicity (p=0.0917). No statistically significant change on the Conners 3-Composite T-score was observed for the 400 mg/day group.

The difference between either of the SPN-812 ER dose levels and placebo failed to reach statistical significance for the WFIRS-P total average score.

Reference ID: 4698714

Table 18. Observed Global Severity Score (CGI-S) at Baseline and Observed Global Improvement Score (CGI-I) at Week 8 (EOS), (ITT; ANCOVA) (Study 303)

Visit	Statistic	Placebo N=97	SPN-812 ER 200 mg/day N=107	SPN-812 ER 400 mg/day N=97
Baseline	Mean ± SD	4.8±0.69	4.8±0.70	4.8±0.74
EOS	Mean ± SD (Week 6)	3.1±1.26	2.6±1.17	2.6±1.08
EOS statistical results	LS mean ± SE	3.1±0.12	2.6±0.12	2.6±0.12
	Difference of LS mean (±SE) (vs. placebo)	-	-0.5±0.17	-0.4±0.17
	95% CI of difference	-	(-0.8, -0.2)	(-0.8, -0.1)
	p-value (vs. placebo)	-	0.0028	0.0099
	Adjusted p-value	-	0.0099	0.0099

Source: Table 11-4 of the Applicant's Clinical Study Report (page 69).
95% CIs and p-values are from the ANCOVA model with treatment as a fixed classification variable and baseline CGI-S as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression–Improvement Scale; CGI-S = Clinical Global Impression–Severity of Illness Scale; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine

Table 19. Change from Baseline at Week 8 (EOS) in the Conners 3–Parent Report Composite T-Score, (ITT; ANCOVA) (Study 303)

Visit	Statistic	Placebo N=97	SPN-812 ER 200 mg/Day N=107	SPN-812 ER 400 mg/Day N=97
Baseline	Mean ± SD	77.1±8.13	76.0±8.11	77.9±8.23
EOS	Mean ± SD (Week 6)	71.7±9.84	67.2±10.26	69.6±11.31
	Mean ± SD (CFB)	-5.3±10.08	-8.6±10.60	-8.2±10.22
EOS statistical results	LS Mean ± SE (CFB)	-5.3±1.00	-9.1±0.96	-7.8±1.06
	Difference of LS mean (±SE) (vs. placebo)	-	-3.8±1.39	-2.5±1.46
	95% CI of difference	-	(-6.5, -1.1)	(-5.3, 0.4)
	p-value (vs. placebo)	-	0.0064	0.0917
	Adjusted p-value	-	0.0917	0.0917

Source: Table 11-5 of the Applicant's Clinical Study Report (page 70).
95% CIs and p-values are from the ANCOVA model with fixed effects for treatment and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine

Table 20. Change from Baseline at Week 8 (EOS) in WFIRS-P Total Average Score–Key Secondary Analysis, (ITT; ANCOVA) (Study 303)

Visit	Statistic	Placebo N=97	SPN-812 ER 200 mg/Day N=107	SPN-812 ER 400 mg/Day N=97
Baseline	Mean ± SD	1.11±0.457	1.08±0.493	1.17±0.482
EOS	Mean ± SD (Week 6)	0.87±0.469	0.74±0.464	0.82±0.517
	Mean ± SD (CFB)	-0.23±0.485	-0.33±0.470	-0.34±0.429
EOS statistical results	LS Mean ± SE (CFB)	-0.24±0.042	-0.35±0.041	-0.33±0.044
	Difference of LS mean (±SE) (vs. placebo)	-	-0.11±0.059	-0.08±0.061
	95% CI of difference	-	(-0.22, 0.01)	(-0.20, 0.04)
	p-value (vs. placebo)	-	0.0651	0.1680
	Adjusted p-value	-	--	--

Source: Table 11-6 of the Applicant's Clinical Study Report (page 72).
95% CIs and p-values are from the ANCOVA model with fixed effects for treatment and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CBF = change from baseline; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report;

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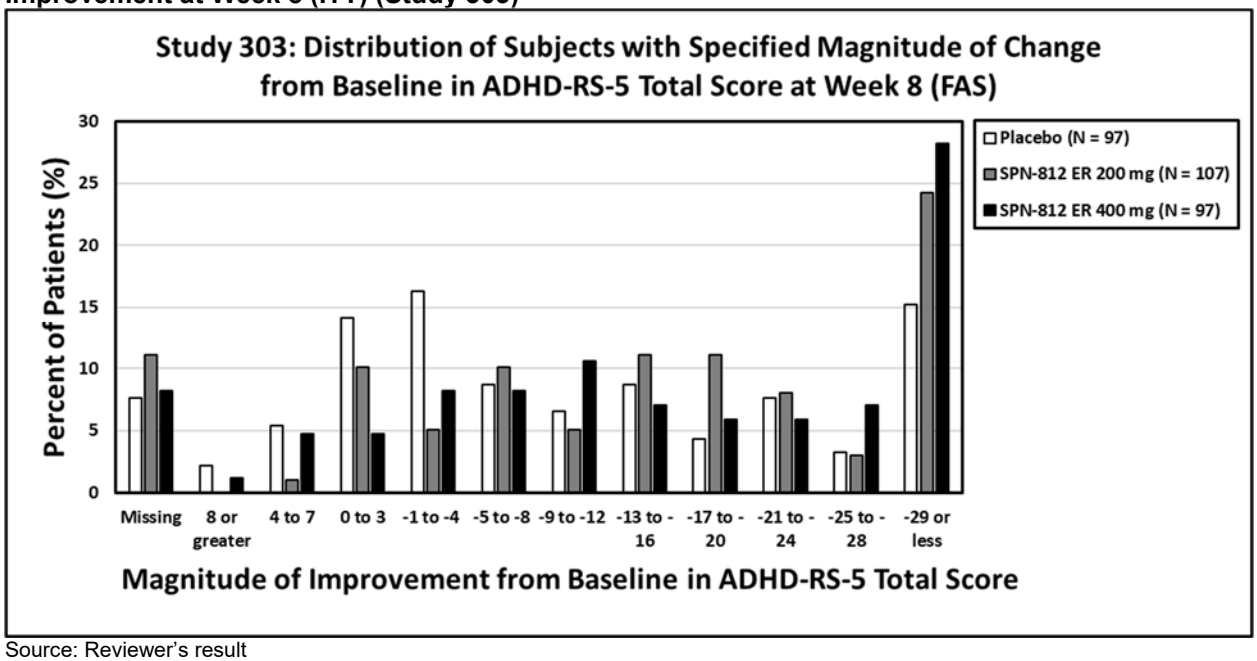
The results of the sensitivity analysis (multiple imputation based on MNAR) of the primary endpoint yielded the same conclusions as those of the primary efficacy analysis.

Reviewer's note: Figure 9 shows the distribution of the magnitude of change in ADHD-RS-5. The proportion of subjects who experienced improvement in ADHD-RS-5 scores in the SPN-812 200 mg and 400 mg dose groups was greater than that in the placebo group.

Figure 10 shows the proportion of patients who had an improvement based on various ADHD-RS-5 response thresholds across the treatment groups at Week 6. For example, approximately 60.9% (placebo), 73.7% (SPN-812 200 mg), and 76.5% (SPN-812 400 mg) of subjects showed a greater than 3-point improvement in ADHD-RS-5 score.

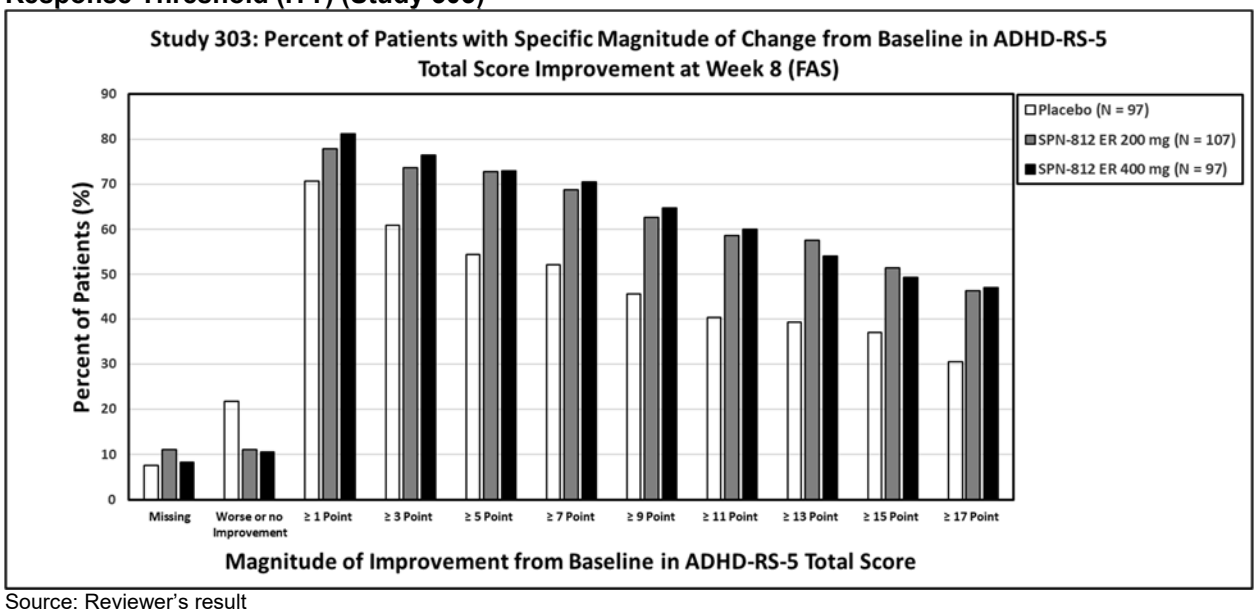
Figure 9. Percentage of Patients with a Specified Magnitude of ADHD-RS-5 Total Score Improvement at Week 8 (ITT) (Study 303)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit hyperactivity disorder; ER = extended release; FAS = full analysis set; ITT = intent-to-treat; N = total number of subjects; RS = rating scale; SPN = viloxazine

Reference ID: 4698714

Figure 10. Percentage Response (ADHD-RS-5 Total Score) for Each Treatment Group at Week 8 by Response Threshold (ITT) (Study 303)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit/hyperactivity disorder; ER = extended release; FAS = full analysis set; ITT = intent-to-treat; N = total number of subjects; RS = rating scale; SPN = viloxazine

6.2.4.4. Study 304

Primary Endpoint

The reviewer confirmed the Applicant's efficacy findings for this study. The results of the primary efficacy analysis are presented in Table 21. Adjusting for multiple comparisons (through the prespecified testing sequence starting with the high dose), none of the SPN-812 ER dosing group was statistically significantly better than placebo in the change from baseline in ADHD-RS-5 total score at end of treatment (Week 7). A nominally significant improvement was, however, observed for the 400 mg/day dosing group, compared to placebo. At Week 7, the LS mean (SE) difference from placebo in ADHD-RS-5 score was -5.1 (1.93) for SPN-812 ER 400 mg/day (p=0.071) and -3.5 (1.93) for SPN-812 ER 600 mg/day (p=0.071).

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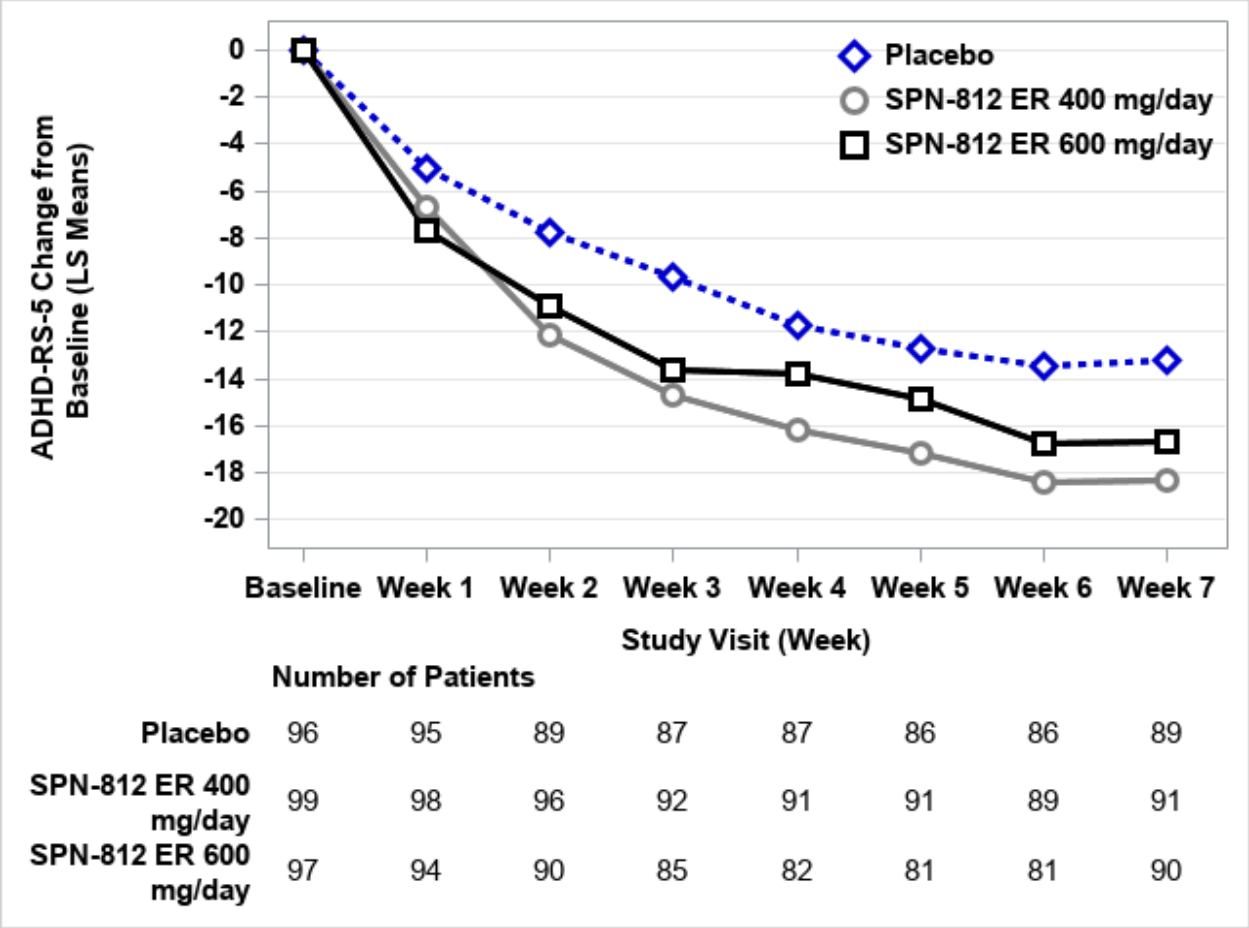
Table 21. Change from Baseline at Week 7 (EOS) in ADHD-RS-5 Total Score (ITT; MMRM) (Study 304)

Visit	Statistic	Placebo N=96	SPN-812 ER 400 mg/Day N=99	SPN-812 ER 600 mg/Day N=97
Baseline	Mean ± SD	38.8±8.06	41.2±7.80	39.8±8.34
EOS	Mean ± SD (Week 7)	25.5±12.95	21.8±13.60	23.2±13.15
	Mean ± SD (CFB)	-13.0±13.07	-19.1±13.77	-16.3±14.06
EOS statistical results	LS mean ± SE (CFB)	-13.2±1.38	-18.3±1.36	-16.7±1.39
	Difference of LS mean (±SE) (vs. placebo)	-	-5.1±1.93	-3.5±1.93
	95% CI of difference	-	(-8.9, -1.3)	(-7.3, 0.3)
	p-value (vs. placebo)	-	0.0082	0.071
	Adjusted p-value	-	0.071	0.071

Source: Table 14 of the Applicant's Clinical Study Report (page 93).
Mean denotes raw mean (second and third rows of the table)
MMRM models change from baseline in ADHD-RS-5 and comprises baseline ADHD-RS-5 total score, age group, treatment, visit, and treatment-by-visit interaction as fixed independent variables.
Abbreviations: ADHD = attention deficit/hyperactivity disorder; CBF = change from baseline; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; MMRM = mixed effect model repeat measurement; N = total number of subjects; SPN = viloxazine

Figure 11. LS Mean Change from Baseline in ADHD-RS-5 Total Score by Visit and Treatment Group (ITT) (Study 304)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit hyperactivity disorder; ER = extended release; ITT = intent-to-treat; LS = least squares; MMRM = mixed effect model repeat measurement; RS = rating scale; SPN = viloxazine

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Key Secondary Endpoints

At Week 7, patients in the SPN-812 ER 400 mg/day dosing group experienced a nominally statistically significantly greater improvement on the CGI-I scale, compared to placebo (LS mean -0.5 [0.17]; p=0.0051), but this endpoint was lower in the testing hierarchy than the first key secondary endpoint (CGI-I for SPN-812 ER 600 mg/day).

The difference between either of the SPN-812 ER dose levels and placebo failed to reach statistical significance for the Conners 3-Parent Composite T-score and the WFIRS-P total average score.

Table 22. Observed CGI-S at Baseline and Observed CGI-I at Week 8 (EOS), (ITT; ANCOVA) (Study 304)

Visit	Statistic	Placebo N=96	SPN-812 ER 400 mg/Day N=99	SPN-812 ER 600 mg/Day N=97
Baseline	Mean ± SD	4.5±0.66	4.8±0.69	4.6±0.69
EOS	Mean ± SD (Week 6)	2.9±1.11	2.3±1.17	2.6±1.16
EOS statistical results	LS mean ± SE	2.9±0.12	2.4±0.12	2.6±0.12
	Difference of LS mean (±SE) (vs. placebo)	-	-0.5±0.17	-0.3±0.17
	95% CI of difference	-	(-0.8, -0.1)	(-0.6, 0.1)
	p-value (vs. placebo)	-	0.0051	0.0995
	Adjusted p-value	-	--	--

Source: Table 11-4 of the Applicant's Clinical Study Report (page 68).
95% CIs and p-values are from the ANCOVA model with treatment as a fixed classification variable and baseline CGI-S as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression–Improvement Scale; CGI-S = Clinical Global Impression–Severity of Illness Scale; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine

Table 23. Change from Baseline at Week 8 (EOS) in the Conners 3-Parent Report Composite T-Score, (ITT; ANCOVA) (Study 304)

Visit	Statistic	Placebo N=96	SPN-812 ER 400 mg/Day N=99	SPN-812 ER 600 mg/Day N=97
Baseline	Mean ± SD	73.1±8.91	73.2±8.87	73.9±8.82
EOS	Mean ± SD (Week 6)	67.4±9.48	65.7±10.28	66.7±9.96
	Mean ± SD (CFB)	-5.4±9.04	-7.3±8.97	-7.1±8.97
EOS statistical results	LS Mean ± SE (CFB)	-5.6±0.89	-7.5±0.87	-6.9±0.88
	Difference of LS mean (±SE) (vs. placebo)	-	-1.9±1.26	-1.3±1.25
	95% CI of difference	-	(-4.3, 0.6)	(-3.7, 1.2)
	p-value (vs. placebo)	-	0.1377	0.3130
	Adjusted p-value	-	--	--

Source: Table 11-5 of the Applicant's Clinical Study Report (page 70).
95% CIs and p-values are from ANCOVA model with fixed effects for treatment and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CBF = change from baseline; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine

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Table 24. Change from Baseline at Week 8 (EOS) in WFIRS-P Total Average Score–Key Secondary Analysis, (ITT; ANCOVA) (Study 304)

Visit	Statistic	Placebo N=96	SPN-812 ER 400 mg/Day N=99	SPN-812 ER 600 mg/Day N=97
Baseline	Mean ± SD	0.97±0.480	0.96±0.442	0.99±0.450
EOS	Mean ± SD (Week 6)	0.72±0.427	0.63±0.341	0.74±0.419
	Mean ± SD (CFB)	-0.22±0.419	-0.29±0.340	-0.23±0.417
EOS statistical results	LS Mean ± SE (CFB)	-0.23±0.035	-0.32±0.034	-0.23±0.035
	Difference of LS mean (±SE) (vs. placebo)	-	-0.09±0.049	0.00±0.050
	95% CI of difference	-	(-0.19, 0.01)	(-0.10, 0.10)
	p-value (vs. placebo)	-	0.0698	0.9756
	Adjusted p-value	-	--	--

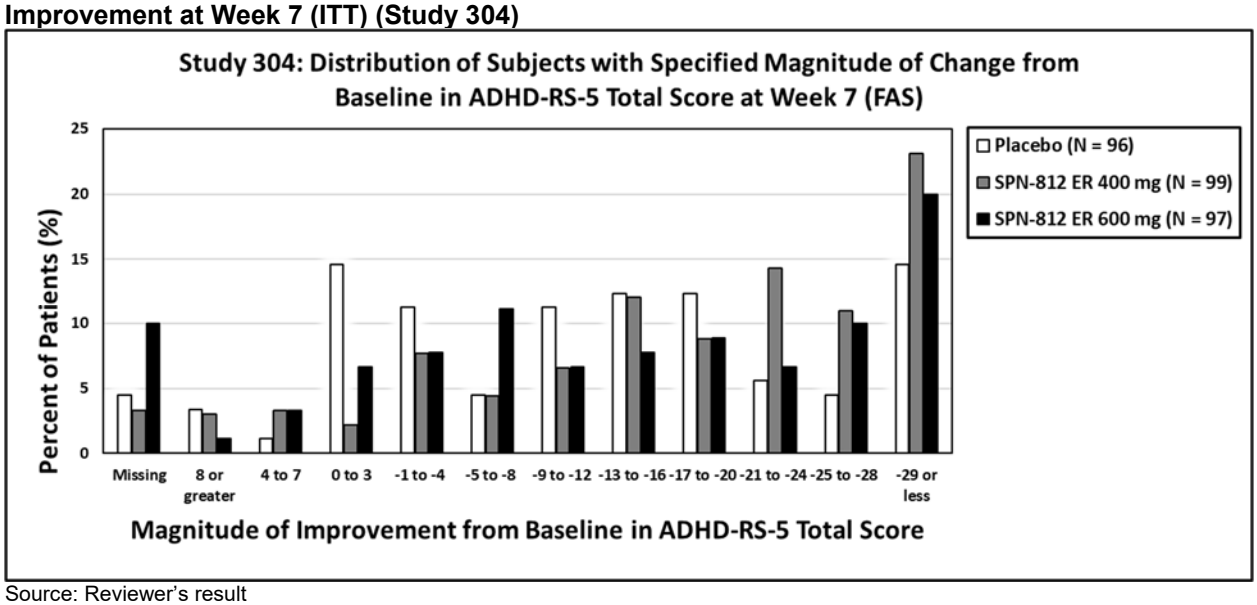
Source: Table 11-6 of the Applicant's Clinical Study Report (page 71).
95% CIs and p-values are from the ANCOVA model with fixed effects for treatment and baseline score as a covariate.
Abbreviations: ANCOVA = analysis of covariance; CBF = change from baseline; CI = confidence interval; EOS = end of study; ER = extended release; ITT = intent-to-treat; LS = least squares; N = total number of subjects; SPN = viloxazine; WFIRS-P = Weiss functional impairment rating scale–parent report

The sensitivity analysis (multiple imputation based on MNAR) of the primary endpoint yielded the same conclusions as the primary efficacy analysis result.

Reviewer's note: Figure 12, an exploratory plot of the distribution of the magnitude of change in ADHD-RS-5 score, shows a high proportion of subjects in the placebo group with improved ADHD-RS-5 scores at Week 7.

Figure 13 displays the proportion of subjects who met a specific threshold (greater than or equal to a response cutoff). Approximately 72% (placebo), 85.7% (SPN-812 400 mg), and 79% (SPN-812 600 mg) of subjects showed a greater than 3-point improvement in ADHD-RS-5 score at Week 7. More subjects in the SPN-812 400 mg group than in the placebo group or the SPN-812 600 mg group showed a consistent improvement in ADHD-RS-5 score.

Figure 12. Percentage of Patients with a Specified Magnitude of ADHD-RS-5 Total Score Improvement at Week 7 (ITT) (Study 304)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit hyperactivity disorder; ER = extended release; FAS = full analysis set; ITT = intent-to-treat; N = total number of subjects; RS = rating scale; SPN = viloxazine

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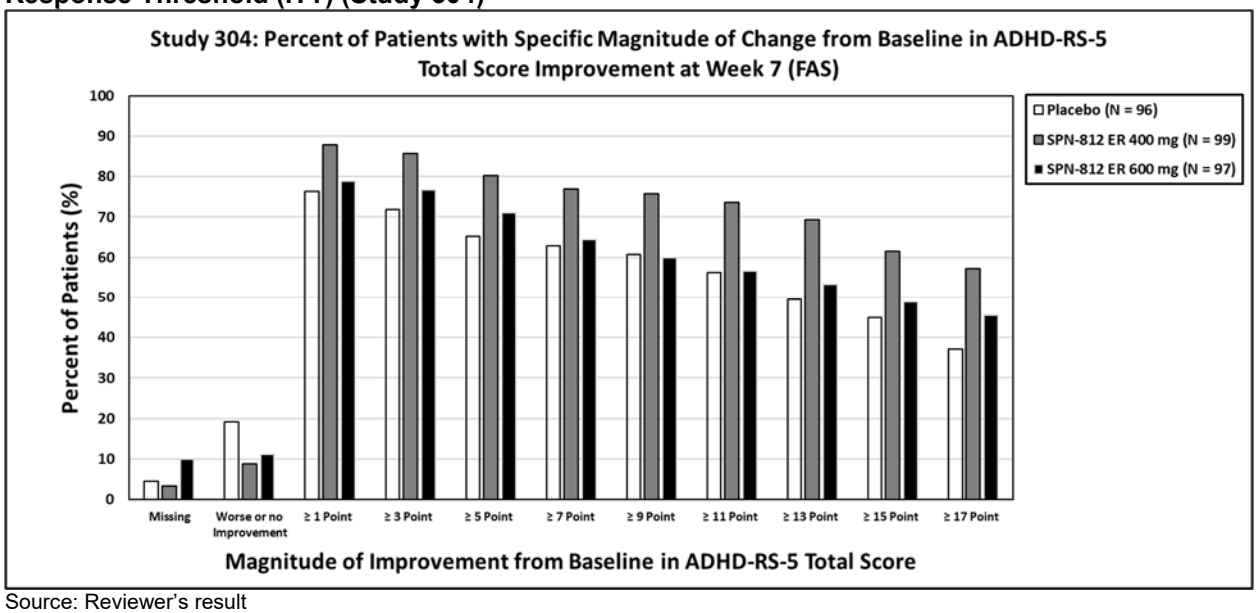
Figure 13. Percentage Response (ADHD-RS-5 Total Score) for Each Treatment Group at Week 7 by Response Threshold (ITT) (Study 304)



Source: Reviewer's result
Abbreviations: ADHD = attention deficit hyperactivity disorder; ER = extended release; FAS = full analysis set; ITT = intent-to-treat; N = total number of subjects; RS = rating scale; SPN = viloxazine

6.2.5. Integrated Assessment of Effectiveness

The controlled phase 3 studies provide evidence of effectiveness for the 100 mg, 200 mg, and 400 mg doses of viloxazine in pediatric patients ages 6 to 11 years, and for the 200 mg and 400 mg doses of viloxazine in patients ages 12 to 17 years. There is no evidence of a greater efficacy of the 600 mg dose of viloxazine (b) (4) Although the CGI-I may be vulnerable to recall bias, the positive CGI-I results across dose groups in Studies 812P301, 812P302, and 812P303 provide additional support for the clinical meaningfulness of the primary efficacy results.

6.3. Key Review Issues Relevant to the Evaluation of Benefit

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(b) (4)

6.4. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Viloxazine ER is a norepinephrine reuptake inhibitor. As described in Section 3, another norepinephrine reuptake inhibitor, atomoxetine, is indicated for the treatment of ADHD. Safety concerns associated with atomoxetine include cardiovascular adverse events, suicidal ideation and other psychiatric adverse events, negative effects on growth, and liver injury. The safety review included an assessment of these safety concerns with use of viloxazine ER.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety studies in this application included in vitro and in vivo pharmacology and pharmacokinetic studies, genotoxicity studies, single- and multiple-dose toxicity studies, reproductive/developmental studies, and carcinogenicity studies. The major safety-related findings are summarized below. The detailed evaluation of risk is discussed in Section 7.6. Full reviews for all nonclinical studies are located in Section III.13.2.

Pharmacology

Viloxazine is a norepinephrine reuptake inhibitor (see Sections **Error! Reference source not found.** and III.14.2). Based on its pharmacology, viloxazine could induce noradrenergic effects in the cardiovascular system. See Section 7.6.4 for a detailed evaluation of the risk of heart rate and blood pressure changes.

Pharmacokinetics

There are substantial species differences in the metabolism of viloxazine between the nonclinical species (rats and dogs) and humans. In primary hepatocytes, viloxazine is extensively metabolized in rat hepatocytes, moderately metabolized in dog hepatocytes, and minimally metabolized in human hepatocytes. There are no unique human metabolites. The *in vivo* metabolic profile was quantitatively compared between the rat and human. In rat, viloxazine is extensively metabolized, with desethyl viloxazine as the major circulating metabolite, accounting for up to 60% of total drug-related exposure; the parent drug accounts for only ~10% to 20% of total drug-related exposure. In contrast, in human, there is limited metabolism and unchanged viloxazine is the major circulating entity in plasma, accounting for ~60% of total drug-related exposure, as well as glucuronidated 5-hydroxy-viloxazine, which accounts for ~10% to 16%. (The latter is present as a minor metabolite in rat). Other minor human metabolites of viloxazine include unconjugated 4- and 5-monohydroxylated viloxazine and glucuronidated N-carboxylated-viloxazine, accounting for <10% of total drug-related exposure.

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It should be noted that despite the differences in the metabolic profiles, the exposure level to both the parent drug and its major human metabolite (glucuronidated-5-hydroxy-viloxazine) are adequately represented and characterized in rat (for a detailed comparison, see Section III.13.2.3 Pharmacokinetics).

General Toxicology

Drug-related Convulsions

In general toxicology and/or carcinogenicity studies in all species tested (rat, mouse, and dog), viloxazine caused multiple central nervous system (CNS) effects, ranging from clinical signs consistent with CNS depression and ataxia at lower doses, to tremors and convulsions or even deaths at higher doses. Specifically, viloxazine caused convulsions at doses approximately equal to or slightly higher than the maximum recommended human dose (MRHD) of 400 mg, based on mg/m^2 body surface area in children[1], and the threshold for convulsions decreased with repeated viloxazine treatment. These CNS effects are likely associated with the adrenergic pharmacology of the drug; these effects did not cause histopathology lesions in the brain. See Section 7.1 Risk of Seizure for details of the safety evaluation.

Drug-related Liver Findings

In all three species (rat, mouse, and dog), repeat administration of viloxazine caused dose-dependent hepatocellular hypertrophy and/or vacuolation in the liver. In addition, viloxazine caused hepatocellular eosinophilic bodies or inclusion bodies in dog. Vacuolation was due to lipid accumulation, and inclusion bodies were likely due to hypertrophic endoplasmic reticulum. These changes were reversible. See Section 7.6.5 Risk of Liver Injury for a detailed safety evaluation.

Drug-related Decreases in Body Weight, Weight Gain, and Food Consumption

Viloxazine treatment caused dose-dependent decreases in body weight, weight gain, and/or food consumption. The decreases were more profound at higher doses, particularly during the first few weeks after treatment initiation and were mostly reversible after dose was reduced or stopped (recovery). These effects are likely associated with the adrenergic pharmacology of the drug. Body weight and food consumption are clinically monitorable; therefore, moderate decreases in body weight and food consumption do not represent an unacceptable risk.

Genotoxicity and Carcinogenicity

Viloxazine was not genotoxic in a battery of genotoxicity tests. It was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro mammalian chromosomal aberration assay (human peripheral blood) or the in vivo rat bone marrow micronucleus assay.

[1] Because the proposed indication is for pediatric population only (ADHD patients ages 6 to 17 years), body surface area (mg/m^2)-based safety margins are calculated using average child body weight of 20 kg and conversion factor Km of 25.

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Viloxazine did not increase the incidence of tumors in rats treated orally for 2 years at doses of 22, 43, and 87 mg/kg/day. The highest dose of 87 mg/kg/day is approximately equal to the MRHD of 400 mg, based on mg/m^2 in children.

Viloxazine did not increase the incidence of tumors in Tg.rasH2 mice treated orally for 26 weeks at doses of 4.3, 13, and 43 mg/kg/day.

7.2. Potential Safety Concerns Identified Through Postmarket Experience

Immediate-release viloxazine was authorized as a treatment for depression in the European Union from 1976 to 2008. The team reviewed available postmarketing information from EudraVigilance, the European Medicines Agency's publicly available system for tracking suspected adverse drug reactions, and from Vigibase, the World Health Organization's global Individual Case Safety Report database. Although viloxazine has never been approved or marketed in the United States, the FDA Adverse Event Reporting System (FAERS) was also queried for any relevant case reports. The Division of Pharmacovigilance assisted with identifying postmarketing adverse drug reaction reports.

EudraVigilance

A total of 37 individual case reports is included in the European Database of Suspected Adverse Drug Reactions (EudraVigilance) as of April 25, 2020. Males accounted for 20 cases and females for 17 cases. No pediatric cases were reported. Most (34/37) cases originated in France. The most common system organ classes (SOCs) represented were Nervous System Disorders and Hepatobiliary Disorders (Figure 17).

Among patients who reported Nervous System Disorders, the event terms included somnolence, balance disorder, cerebrovascular accident, dizziness, headache, serotonin syndrome, and Wernicke's encephalopathy. Of note, there were also two reports of epilepsy. In addition, there were reports of coma in 3 patients; 1 of these cases was fatal.

Among patients who reported Hepatobiliary Disorders, the event terms included cholestasis, hepatitis, hepatitis cholestatic, hepatitis toxic, hepatocellular injury, and hyperbilirubinemia. Two of the reported cases of hepatitis were fatal.

Cardiac disorders and hypertension were not reported. Hypotension was reported in 3 cases.

One completed suicide was reported. No other reports of suicidal ideation or behavior are included in the database.

Interpretation of the data from the EudraVigilance database is hampered by several factors. First, clinical narratives were not available for the case reports included in the EudraVigilance database. Second, the database may contain duplicate reports. In addition, the total number of patients exposed to immediate-release viloxazine is not known, so the true frequency of adverse reactions cannot be calculated. Finally, adverse reactions associated with the immediate-release formulation of viloxazine may not necessarily occur with viloxazine extended-release. However, given the reports of hepatobiliary adverse reactions, including of fatal cases, data related to the effect of viloxazine ER on liver assessments were specifically reviewed and are summarized in

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Section 7.6.5. Seizures were reported in the postmarketing period; Section 7.6.1 also includes a review of the data related to the risk of seizure with viloxazine ER exposure. Despite the limitations of the available data, the fact that suicidal behavior was rarely reported is reassuring given the concern about the higher rate of suicidal ideation and behavior in the viloxazine ER clinical trials.

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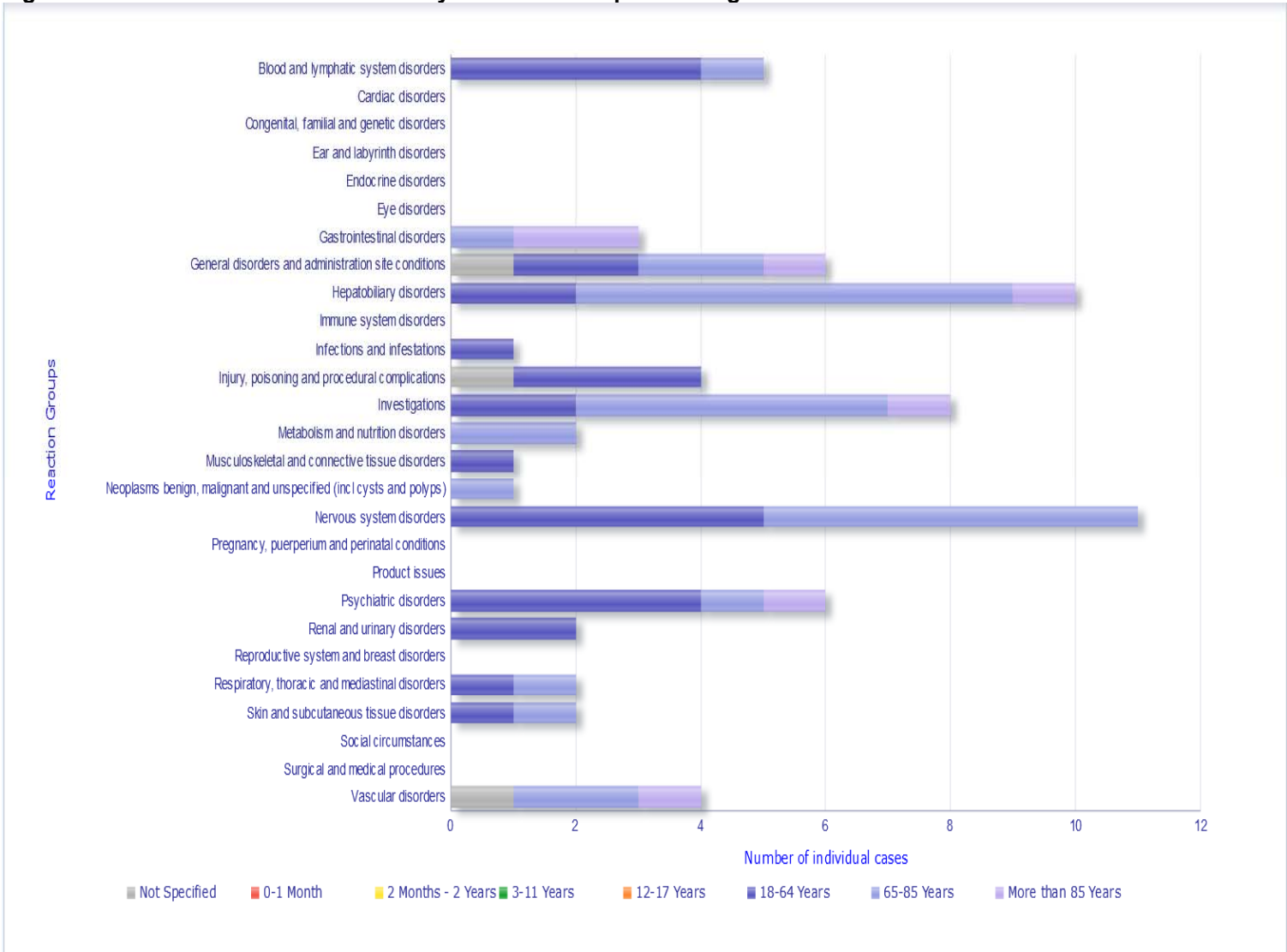
Figure 17. Number of Individual Cases by Reaction Group–EudraVigilance Database



Source: EudraVigilance Database - http://www.adrreports.eu

Vigibase

Vigibase contains 440 adverse drug reaction reports from the years 1976 to 2014. Female patients accounted for 59% of the reports. In total, three pediatric reports are included in the database (one report in a patient 0 to 27 days of age and two reports in patients ages 12 to 17 years). Nervous system disorders, Gastrointestinal disorders, Psychiatric disorders, Skin and subcutaneous tissue disorders, and Hepatobiliary disorders were most common (Figure 18).

Figure 18. Adverse Drug Reactions Reported to Vigibase–1976 to 2014

Adverse drug reactions (ADRs)

- Blood and lymphatic system disorders (25)
- Cardiac disorders (18)
- Congenital, familial and genetic disorders (2)
- Ear and labyrinth disorders (8)
- Endocrine disorders (2)
- Eye disorders (6)
- Gastrointestinal disorders (81)
- General disorders and administration site conditions (38)
- Hepatobiliary disorders (53)
- Immune system disorders (1)
- Injury, poisoning and procedural complications (6)
- Investigations (38)
- Metabolism and nutrition disorders (16)
- Musculoskeletal and connective tissue disorders (5)
- Nervous system disorders (115)
- Pregnancy, puerperium and perinatal conditions (1)
- Psychiatric disorders (70)
- Renal and urinary disorders (19)
- Reproductive system and breast disorders (8)
- Respiratory, thoracic and mediastinal disorders (3)
- Skin and subcutaneous tissue disorders (59)
- Vascular disorders (25)

Source: http://www.vigiaccess.org

Adverse events of special interest in this application include seizures, cardiovascular effects, and psychiatric adverse events. The Vigibase database contains a total of 31 reports of seizure, including the following event terms: seizure (19 reports), epilepsy (6 reports), generalized tonic clonic seizure (5 reports), and petit mal seizure (1 report). The most commonly reported psychiatric adverse event was confusional state (35 reports), followed by agitation (12 reports). Of note, the database includes one report of suicide attempt but no other reports of suicidal ideation or behavior. Tachycardia was the most commonly reported cardiac disorder (9 reports), and orthostatic hypotension was the most commonly reported vascular disorder (9 reports). Hypertension, hypotension, palpitations, and bradycardia were also reported.

Reference ID: 4698714

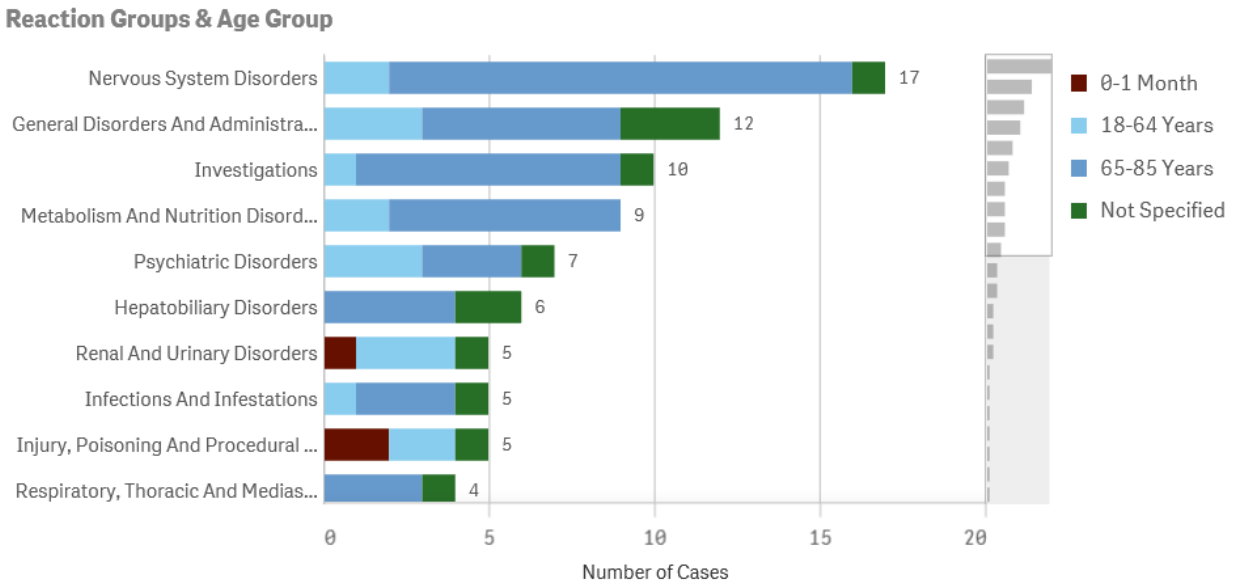
FAERS

From 1997 to 2016, a total of 35 reports involving viloxazine hydrochloride were included in the FAERS database, including 33 serious reports and 5 deaths. The FAERS database may contain duplicate reports. Suspected drug reactions in the Nervous System Disorders, General Disorders and Administration, and Investigations reaction groups were most common (Figure 19). However, although viloxazine is listed among the suspect product active ingredients in these 35 reports, viloxazine was not the suspect product in any report, or the sole suspect active ingredient in any report. In each report, multiple suspect active ingredients are listed.

In three of the reports of death, the suspect product was ceftriaxone. In the other two reports of death, the suspect products were chlorazepate and labetalol.

Of note, the database includes two reports of seizure and six reports of epilepsy. See Section 7.6.1 for a discussion of these cases. These case reports were confounded by the presence of other medications and medical illness; the seizure events could not clearly be attributed to viloxazine. Similarly, the reports of liver injury were also confounded; see Section 7.6.5 for a full discussion of data related to viloxazine ER exposure and hepatobiliary adverse events and laboratory assessments.

Figure 19. Suspected Adverse Reactions by Reaction Groups Reported to the FAERS Database–1997 to 2016



Source: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard
Abbreviation: FAERS = FDA Adverse Event Reporting System

Summary of Postmarketing Safety Signals

Although immediate-release viloxazine was authorized in Europe for more than 30 years for the treatment of major depressive disorder, few data about adverse reactions are available in worldwide postmarketing databases. The postmarketing reports include primarily adult data. Notable adverse events reported in the postmarketing period include seizures and liver injury.

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However, the available reports of these events are confounded by the presence of other possibly contributory factors. In addition, the true frequency of these events among patients exposed to viloxazine is unknown. Of note, there are few reports of suicidal ideation and behavior in the postmarketing databases, which may be somewhat reassuring given that patients with major depressive disorder could be more vulnerable to suicidal ideation. The limitations of the data nonetheless preclude any clear determination of the risk of suicidal ideation and behavior with viloxazine.

7.3. FDA Approach to the Safety Review

The safety review focused primarily on the four phase 3 placebo-controlled efficacy and safety studies (812P301, 812P302, 812P303, and 812P304). Adverse events were examined for two age groups (ages 6 to 11 and 12 to 17 years) and four dose arms (100 mg, 200 mg, 400 mg, and 600 mg). The vital signs, laboratory, electrocardiogram, and C-SSRS databases for the phase 3 trials were also analyzed.

Convulsions occurred in multiple species in nonclinical studies, and so seizures and seizure-like events were considered adverse events of special interest in the development program. Based on the mechanism of action and the potential for stimulation of the adrenergic system, cardiovascular adverse events were also examined closely. This drug is intended for use in the pediatric population, so effects on weight and growth, both short- and long-term, were investigated. Finally, given the frequent psychiatric comorbidities of ADHD, psychiatric adverse events were also analyzed.

In addition to data from the phase 3 studies, the safety review considered adverse events and other supporting safety data from Study 812P202, a phase 2 dose-finding study.

Study 812P310, an open-label safety extension, was the primary source of long-term safety data. Though this study did not include controlled data, long-term trends in vital signs, growth parameters, and laboratory assessments were examined.

Immediate-release viloxazine was previously approved in Europe for the treatment of depression. Therefore, publicly available European postmarketing data for viloxazine were also reviewed.

The Applicant submitted a thorough QT study, which was reviewed by the QT/IRT consultation team. In addition, the Controlled Substance Staff (CSS) reviewed the data for drug dependence and liability signals.

7.4. Adequacy of the Clinical Safety Database

The safety database was comprehensive, and adequate to assess the safety of viloxazine ER in pediatric patients ages 6 to 17 years with ADHD.

A summary of the exposures in the phase 3 controlled studies is shown in Table 28. The median duration of exposure in these studies was approximately 6 weeks. The duration of exposure to study drug was balanced between the viloxazine ER treatment groups and the placebo groups.

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Table 28. Duration of Exposure, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 Years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
Variable	**100 mg N=154**	**200 mg N=268**	**400 mg N=100**	**TX N=522**	**Placebo N=262**	**200 mg N=99**	**400 mg N=205**	**600 mg N=99**	**TX N=403**	**Placebo N=201**	**TX N=925**	**Placebo N=463**
Duration of exposure (weeks)												
Mean (SD)	7.0 (6.6)	6.5 (2.1)	6.9 (2.5)	6.7 (4.0)	6.5 (3.2)	5.3 (1.8)	6.1 (1.6)	6.2 (2.0)	6.0 (1.8)	6.2 (1.4)	6.4 (3.3)	6.4 (2.6)
Median	6.1	6.1	8.0	6.1	6.1	6.1	6.3	7.1	6.3	6.3	6.1	6.3
(min, max)	(0.1, 45.4)	(0.1, 20.4)	(0.1, 9.0)	(0.1, 45.4)	(0.1, 38.0)	(0.1, 7.0)	(0.1, 8.9)	(0.1, 8.4)	(0.1, 8.9)	(0.1, 8.4)	(0.1, 45.4)	(0.1, 38.0)
Subjects treated, by duration (weeks), n (%)												
<1	3 (2)	(2)	4 (4)	12 (2)	7 (3)	7 (7)	(2)	3 (3)	15 (4)	3 (2)	27 (3)	10 (2)
1 to <3	11 (7)	(3)	7 (7)	26 (5)	19 (7)	4 (4)	13 (6)	8 (8)	25 (6)	8 (4)	51 (6)	27 (6)
3 to <6	24 (16)	32 (12)	10 (10)	66 (13)	29 (11)	19 (19)	17 (8)	8 (8)	44 (11)	21 (10)	110 (12)	50 (11)
6 to <9	108 (70)	219 (82)	78 (78)	405 (78)	202 (77)	69 (70)	170 (83)	80 (81)	319 (79)	169 (84)	724 (78)	371 (80)
9 to <12	0	1 (0.4)	1 (1)	2 (0.4)	2 (1)	0	0	0	0	0	2 (0.2)	2 (0.4)
Missing TX end date	8 (5)	3 (1)	0	11 (2)	3 (1)	0	0	0	0	0	11 (1)	3 (1)

Source, adex.xpt; Software, Python. Created by the Clinical Data Scientist and Clinical Review Team.
Abbreviations: N = number of subjects in treatment arm; n = number of subjects with given treatment duration; TX = treatment

According to the International Conference on Harmonisation (ICH) EI Guidance, for chronically administered medications, the safety database should include at least 1500 individuals exposed to the investigational product in short-term trials, 300 to 600 individuals with at least 6 months of exposure, and 100 individuals with at least 1 year of exposure. At the time of the 120-day safety update, 1593 individuals had been exposed to viloxazine ER. Of the patients who received viloxazine ER in the long-term safety extension study (812P310), 429 were exposed for <6 months, 340 for 6 to 12 months, and 347 were exposed for ≥12 months. The duration of exposure was similar in the child and adolescent age groups (Table 29).

Table 29. Duration of Exposure to Viloxazine ER

Parameter	6-11 Years (N=668)	12-17 Years (N=448)	Total (N=1116)
Patients treated, by duration, n (%)			
<6 months	231 (35%)	198 (44%)	429 (38%)
6 to 12 months	203 (30%)	137 (31%)	340 (31%)
≥12 months	234 (35%)	113 (25%)	347 (31%)

Source: 812P310 adsl. Data cutoff March 5, 2020. Created by (b) (4) and the Clinical Reviewer.
Abbreviations: N = number of subjects in the group; n = number of subjects with a given treatment duration

7.5. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The submitted safety data for viloxazine ER in pediatric patients ages 6 to 17 years were adequate. The safety profile of viloxazine ER in this population is acceptable for the intended use. Rates of discontinuation because of adverse events and serious adverse events were low. No deaths occurred in the development program. The most common treatment-emergent adverse events were somnolence/sedation, headache, fatigue, decreased appetite, abdominal pain, upper respiratory infection, nausea, and vomiting. Transaminase values were more likely to shift from within the reference range to above the reference range in patients receiving viloxazine; however, transaminase elevations were modest, and no cases of drug-induced liver injury were identified. Viloxazine ER was otherwise not associated with other clinically meaningful changes in laboratory values. Viloxazine ER was associated with higher rates of suicidal ideation and behavior, increases in heart rate and diastolic blood pressure, and may be associated with slowed weight gain. These risks are reviewed more fully in Section 7.6 and can be described in labeling to support safe use of viloxazine in the intended population.

7.5.1. Overall Adverse Event Summary

Approximately 52% of viloxazine ER–treated patients experienced a TEAE, compared to approximately 37% of placebo-treated patients (Table 30). The incidence of treatment-emergent adverse events (TEAEs) was similar in the younger age group (6 to 11-year-olds) and the older age group (12 to 17-year-olds). Serious adverse events occurred in six patients in the younger age group, and four patients in the older age group, who received viloxazine ER; no serious adverse events were observed in the placebo group. Patients in both age groups appeared to be equally likely to experience a TEAE leading to discontinuation, dose modification, or dose interruption. Overall, serious adverse events and dose adjustments or discontinuation because of adverse events were uncommon, but did occur more frequently in the viloxazine ER group than in the placebo group.

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Table 30. Overview of Adverse Events, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 Years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
Event Category[1]	**100 mg N=154 %**	**200 mg N=268 %**	**400 mg N=100 %**	**Treatment N=522 %**	**Placebo N=262 %**	**200 mg N=99 %**	**400 mg N=205 %**	**600 mg N=99 %**	**Treatment N=403 %**	**Placebo N=201 %**	**Treatment N=925 %**	**Placebo N=463 %**
Any TEAE	48	50	58	51	36	43	56	56	53	38	52	37
Moderate or severe AEs	18	18	37	22	14	19	23	26	23	14	22	14
SAE	1	1	2	1	0	2	1	0	1	0	1	0
SAEs with fatal outcome	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to discontinuation of study drug	3	3	4	3	2	4	3	5	4	1	4	1
AE leading to dose modification of study drug	0	1	4	1	1	3	2	0	2	2	1	1
AE leading to interruption of study drug	0	1	4	1	1	3	2	0	2	2	1	1
AE leading to reduction of study drug	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to delay of study drug	0	0	0	0	0	0	0	0	0	0	0	0

Source: adae.xpt. Software, Python. Table created by the Clinical Data Scientist and Clinical Review Team.
[1] Treatment-emergent AEs are defined as AEs with onset or an increase in severity at any time from the first exposure to study drug.
Abbreviations: AE = adverse event; SAE = severe adverse event; TEAE = treatment-emergent adverse event

7.5.2. Deaths

No deaths occurred during the viloxazine extended-release development program.

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Serious Adverse Events

The most common serious adverse events (SAEs) in patients receiving viloxazine ER in the phase 3 placebo-controlled trials (812P301, 812P302, 812P303, and 812P304) were suicidal ideation or behavior (3 patients) and syncope (3 patients). Half of the SAEs in the phase 3 trials were in the Psychiatric Disorders SOC (Table 31). No SAEs were reported in Study 812P202, a phase 2 dose-ranging study. In the long-term safety extension study (812P310), 25 of 1097 patients who received study medication experienced SAEs. The most common SAEs reported in Study 812P310 were suicidal ideation, syncope, and seizure (Table 32).

Table 31. Serious Adverse Events, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 Years (Trials 812P301 and 812P303)					Ages 12 to 17 Years (Trials 812P302 and 812P304)					Total	
Serious Adverse Event[1,2]	**100 mg N=154 n (%)**	**200 mg N=268 n (%)**	**400 mg N=100 n (%)**	**Treatment N=522 n (%)**	**Placebo N=262 n (%)**	**200 mg N=99 n (%)**	**400 mg N=205 n (%)**	**600 mg N=99 n (%)**	**Treatment N=403 n (%)**	**Placebo N=201 n (%)**	**Treatment N=925 n (%)**	**Placebo N=463 n (%)**
Any serious TEAE	2 (1)	2 (1)	2 (2.0)	6 (1)	0	2 (2)	2 (1)	0	4 (1)	0	10 (1)	0
Conduct disorder	1 (1)		0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Pyromania	1 (1)	0	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Appendicitis	0	1 (0.4)		1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Suicidal ideation	0	1 (0.4)		1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Syncope	0	0	1 (1)	1 (0.2)	0	1 (1)	1 (0.5)		2 (0.5)	0	3 (0.3)	0
Suicidal behavior	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Thermal burn	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Suicide attempt	0	0	0	0	0	0	1 (0.5)		1 (0.2)	0	1 (0.1)	0

Source: adae.xpt. Software, Python. Created by the Clinical Data Scientist and Clinical Review Team.
[1] Serious adverse events are defined as those AEs resulting in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
[2] Terms included are those that occurred more often in the treatment than comparator group
Abbreviations: N = number of subjects in the group; n = number of subjects with the adverse event; TEAE = treatment-emergent adverse event

Table 32. Serious Adverse Events (Study 812P310)

Serious Adverse Event	Number of Patients	% of Total (N=1097)
Suicidal ideation	10	0.9%
Syncope	4	0.4%
Seizure (Epilepsy, Generalized tonic-clonic seizure, petit mal epilepsy)	3	0.3%
Intentional self-injury	2	0.2%
Major depression	2	0.2%
Suicide attempt	2	0.2%
Affective disorder	1	0.1%
Aggression	1	0.1%
Appendicitis	1	0.1%
Atrial septal defect	1	0.1%
Biliary colic	1	0.1%
Borderline personality disorder	1	0.1%
Burns second degree	1	0.1%
Dyspnea	1	0.1%
Hallucination, auditory	1	0.1%
Humerus fracture	1	0.1%
Palpitations	1	0.1%
Psychotic disorder	1	0.1%
Nonepileptiform seizure	1	0.1%
Type 1 diabetes mellitus	1	0.1%

Source: adae.xpt. Created by the Clinical Reviewer.

Patients receiving viloxazine ER were more likely than patients on placebo to report suicidal ideation and behavior in the controlled phase 3 studies. Two patients reported SAEs of suicidal behaviors in the controlled studies. In addition, suicidal ideation was classified as an SAE for one patient. Suicidal ideation, self-injury, and suicide attempts were also reported as SAEs in the long-term safety extension study. Adverse events of suicidal ideation and behavior, including case narratives, are discussed in detail in Section 7.6.2.

Seizures and adverse events that could represent seizure (syncope, syncopal episode, pseudoseizure, myoclonus, severe muscle spasm) were reported as adverse events of special interest in this development program. In the phase 3 short-term safety and efficacy studies, 3 viloxazine-treated patients (and no placebo-treated patients) reported syncope. In Study 812P310, four patients reported SAEs of syncope. As adverse events of special interest, these events were classified as serious, although no patients who reported syncope were hospitalized or experienced life-threatening symptoms. No other adverse events of special interest were reported in the short-term safety and efficacy studies. Three patients experienced seizures in Study 812P310. The details of these cases and the review issues relevant to the potential risk of seizures with viloxazine exposure are discussed in Section 7.6.1.

The clinical narratives for the syncope events in the controlled phase 3 trials are below:

- Patient 302-(b) (6): a 13-year-old female who was randomized to receive viloxazine ER 200 mg in Study 812P302. She had a syncopal episode 23 days after first intake of study medication. The episode was accompanied by lower abdominal pain, lightheadedness, and weakness. The patient was evaluated in an emergency department, where an electrocardiogram revealed an elevated QTc interval (472 msec) and laboratory assessments showed hyponatremia (serum sodium, 132 mmol/L). The patient was given intravenous fluids and referred for cardiology evaluation. Viloxazine ER was discontinued. During the

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cardiology evaluation, the patient's mother reported that the patient had previously experienced similar presyncopal and syncopal episodes. Her echocardiogram and electrocardiogram were within normal limits. Holter monitoring and increased fluid and salt intake were recommended.

- Patient 303-(b) (6): 9-year-old female who received viloxazine ER 400 mg in Study 812P303. The patient experienced a syncopal episode 17 days after first intake of study medication. The event occurred in the context of deliberate breath-holding at school; the patient reported that she was trying to turn her face red in view of her peers. No seizure-like activity occurred, and the patient immediately returned to her class activities.

- Patient 304-(b) (6): 12-year-old female who received viloxazine ER 400 mg in Study 812P304. The patient experienced nausea and diarrhea approximately 4 days after first intake of study medication. One week later, the patient had an episode of vomiting but felt well enough to go to school. While at school that day, the patient felt dizzy and fainted after standing up. She had reportedly been engaged in physical exercise in 104°F heat. Of note, her brother had been diagnosed with a viral illness 2 weeks earlier. The patient recovered and continued study medication.

The clinical narratives for the syncope events in Study 812P310 are below:

- Patient 304-(b) (6): 16-year-old female who received placebo in Study 812P304. Approximately 4 months after starting study medication, she reportedly had a syncopal episode with subsequent seizure-like activity versus myoclonus. Her mother reported that she was overheated after being outside, felt dizzy, fell, hit her head, and passed out while in a hot laundry room. The patient was evaluated at a hospital and discharged. The Principal Investigator assessed the clinical history to be inconsistent with a seizure occurring before or after the fall.

- Patient 302-(b) (6): 16-year-old female who was randomized to receive placebo in Study 812P302. She experienced an SAE of syncope approximately 4 months after enrollment in Study 812P310. Of note, this patient also experienced a suspected generalized tonic-clonic seizure while enrolled in 812P310. Additional details from the clinical narrative can be found in Section 7.6.1.

- Patient 304-(b) (6): 15-year-old male who received viloxazine ER 400 mg in Study 812P304. His medical history was remarkable for hypertension, episodes of dizziness upon standing, and a history of syncope while enrolled in a clinical trial for an antihypertensive medication. Eighty days after he began receiving study medication, he had a syncopal episode when moving from sitting to standing position. The episode lasted <1 minute. The patient recovered and the dose was unchanged.

- Patient 301-(b) (6): 10-year-old male who received viloxazine ER 200 mg in Study 812P301. Eighty-one days after exposure to study medication, his father reported that the patient had experienced cough, chest pain, and syncope. No details regarding the duration or quality of the symptoms were provided. A chest x-ray and electrocardiogram were within normal limits. The patient was evaluated and diagnosed with conversion disorder. Two

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weeks later, the patient experienced syncopal episodes accompanied by palpitations, shortness of breath, headache, and chest pain. The patient was evaluated in an emergency department, where his vital signs and physical examination findings were within normal limits. An ECG revealed left atrial enlargement but no other findings. The patient was diagnosed with panic disorder, conversion disorder, chest pain, and syncope. He was referred to a cardiologist for further work-up.

No syncopal events were reported in Study 812P302, the phase 2 dose-ranging study.

Reviewer's note:

Syncopal episodes were specifically tracked because they were considered adverse events of special interest that could represent seizure. However, the clinical narratives of the patients who experienced syncope in the controlled clinical trials do not appear to be consistent with seizure events. In the open-label study, one patient (304-[redacted] (b) (6)) experienced "seizure-like activity versus myoclonus" in the context of a syncopal episode, but the possible seizure-like activity occurred after hitting her head. Although it is possible that her symptoms of feeling dizzy and falling could have represented a seizure event related to drug exposure, syncope followed by a head injury could also have precipitated the reported "seizure-like activity." In addition, the case report suggests that the patient was overheated, which would make a syncopal event more likely. Of note, no electroencephalogram (EEG) was performed at the time of evaluation and, in the Principal Investigator's assessment, the clinical presentation was not consistent with seizure before or after the patient's fall. Another patient (302-1[redacted] (b) (6)) experienced a syncopal episode approximately 2 months prior to having a generalized seizure. It is not clear, however, that there was any relationship between the syncopal event or the seizure. See Section 7.6.1 for a full discussion of viloxazine ER and the risk of seizure.

In addition, the syncopal episodes were not clearly associated with viloxazine. Two patients (302-[redacted] (b) (6) and 304-[redacted] (b) (6)) had a premorbid history of similar events, another patient (303-[redacted] (b) (6)) fainted after intentional breath-holding, two patients (304-[redacted] (b) (6) and 304-[redacted] (b) (6)) likely had other predisposing factors (e.g., dehydration, possible hyperthermia, possible viral illness). Most of the syncopal episodes occurred weeks after introduction of study medication, making an adverse drug reaction less likely. Overall, the available safety data do not provide strong evidence of an association between viloxazine ER and syncope.

7.5.3. Dropouts and/or Discontinuations Due to Adverse Events

Treatment discontinuation due to TEAEs occurred in 3.5% of viloxazine ER–treated patients and 1.3% of placebo-treated patients (Table 33) in the phase 3 controlled trials. Using the FDA Medical Dictionary for Regulatory Activities (MedDRA) queries, which group like terms together to detect safety signals, the TEAEs that most commonly led to treatment discontinuation were somnolence, abdominal pain, fatigue, nausea, tachycardia, decreased appetite, dizziness, headache, insomnia, and irritability (Table 34). Patients ages 12 to 17 years were more likely than younger patients to discontinue treatment because of somnolence. Patients ages 6 to 11 years were more likely than older patients to discontinue because of irritability.

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Table 33. Adverse Events Leading to Discontinuation, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
Adverse Event[1,2]	**100 mg N=154 n (%)**	**200 mg N=268 n (%)**	**400 mg N=100 n (%)**	**Treatment N=522 n (%)**	**Placebo N=262 n (%)**	**200 mg N=99 n (%)**	**400 mg N=205 n (%)**	**600 mg N=99 n (%)**	**Treatment N=403 n (%)**	**Placebo N=201 n (%)**	**Treatment N=925 n (%)**	**Placebo N=463 n (%)**
Treatment discontinuation due to TEAEs	5 (3)	8 (3)	4 (4)	17 (3)	5 (1.9)	4 (4)	6 (3)	5 (5)	15 (4)	1 (1)	32 (4)	6 (1)
Somnolence	0	2 (1)	0	2 (0.4)	0	1 (1)	2 (1)	(2)	5 (1)	0	7 (1)	0
Fatigue	1 (1)	(0.4)	0	2 (0.4)	0	0	0	1 (1)	1 (0.2)	0	3 (0.3)	0
Nausea	0 1	2 (1)	0	2 (0.4)	0	0	1 (1) 2		1 (0.2)	0	3 (0.3)	0
Tachycardia	1 (1)	(0.4)	0	2 (0.4)	0	0	0	1 (1)	1 (0.2)	0	3 (0.3)	0
Decreased appetite	0 1	2 (1)	0	2 (0.4)	0	0	0 0	0	0	0	2 (0.2)	0
Irritability		2 (1)	0	2 (0.4)	0	0	0	0	0	0	2 (0.2)	0
Headache	0	1 (0.4)	0	1 (0.2)	0	0	1 (1)		1 (0.2)	0	2 (0.2)	0
Aggression	1 (1)		0	1 (0.2)	2 (1)	0	0	0	0	0	1 (0.1)	2 (0.4)
Conduct disorder	1 (1)		0	1 (0.2)		0	0 0	0	0	0	1 (0.1)	0
Dizziness	1 (1) 0		0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Electrocardiogram t-wave inversion	1 (1) 0 0	0	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Pyromania 0	1 (1)		0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Affect lability		1 (0.4)	0	1 (0.2)	1 (0.4)	0	0	0	0	0	1 (0.1)	1 (0.2)
Abdominal discomfort	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Erection increased	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Hot flush 0	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Hyperacusis	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Impulsive behavior 0	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Insomnia	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Mood swings	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Sleep terror	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Flat affect	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Gastroenteritis	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Mood altered	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Sedation	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Abdominal pain	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Anxiety	0			0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Diarrhea	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0

0 0

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	Ages 6 to 11 years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
Adverse Event[1,2]	100 mg N=154 n (%)	200 mg N=268 n (%)	400 mg N=100 n (%)	Treatment N=522 n (%)	Placebo N=262 n (%)	200 mg N=99 n (%)	400 mg N=205 n (%)	600 mg N=99 n (%)	Treatment N=403 n (%)	Placebo N=201 n (%)	Treatment N=925 n (%)	Placebo N=463 n (%)
Syncope	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Abdominal pain upper	0	0	0	0	0	0	1 (1)		1 (0.2)	0	1 (0.1)	0
Suicide attempt	0	0	0	0	0	0	1 (1)		1 (0.2)	0	1 (0.1)	0
Terminal insomnia	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Vomiting	0			0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Depressed mood	0	0	0	0	0	0	0	0 1 (1)	1 (0.2)	0	1 (0.1)	0
Dizziness postural	0	0	0	0	0	0	0	0 1 (1)	1 (0.2)	0	1 (0.1)	0
Vitiligo	0 0	0 0	0	0	0	0	0	1 (1)	1 (0.2)	0	1 (0.1)	0
Suicidal ideation	0	0	0	0	0	0	0	0	0	1 (0.5)	0	1 (0.2)
Agitation	0	0	0	0	1 (0.4)	0	0	0	0	0	0	1 (0.2)
Tic	0	0	0	0	1 (0.4)	0	0	0	0	0	0	1 (0.2)

Source: adae.xpt; Software, Python. Table created by the Clinical Data Scientist and Clinical Review Team.
[1] Treatment-emergent adverse events, defined as those AEs with onset or increase in severity at any time from the first exposure to study drug. Terms included are those that occurred more often in the treatment than comparator group.
[2] Coded as MedDRA preferred terms
Abbreviations: AE = adverse event; N = number of subjects in treatment arm; n = number of subjects with the adverse event; TEAE = treatment-emergent adverse event

Table 34. FDA MedDRA Queries (Narrow) Leading to Discontinuation, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Ages 6 to 11 Years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
FDA MedDRA Query[1]	100 mg N=154 n (%)	200 mg N=268 n (%)	400 mg N=100 n (%)	Treatment N=522 n (%)	Placebo N=262 n (%)	200 mg N=99 n (%)	400 mg N=205 n (%)	600 mg N=99 n (%)	Treatment N=403 n (%)	Placebo N=201 n (%)	Treatment N=925 n (%)	Placebo N=463 n (%)
Somnolence	0	2 (1)	1 (1)	3 (1)	0	1 (1)	2 (1)	2 (2)	5 (1)	0	8 (1)	0
Somnolence	0	2 (1)	0	2 (0.4)	0	1 (1)	2 (1)	2 (2)	5 (1)	0	7 (1)	0
Sedation	0	0	1 (1)	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0

Reference ID: 4698714

	Ages 6 to 11 Years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
FDA MedDRA Query[1]	**100 mg N=154 n (%)**	**200 mg N=268 n (%)**	**400 mg N=100 n (%)**	**Treatment N=522 n (%)**	**Placebo N=262 n (%)**	**200 mg N=99 n (%)**	**400 mg N=205 n (%)**	**600 mg N=99 n (%)**	**Treatment N=403 n (%)**	**Placebo N=201 n (%)**	**Treatment N=925 n (%)**	**Placebo N=463 n (%)**
Abdominal pain	0	1 (0.4)	0	1 (0.2)	0	1 (1)	1 (1)	0	2 (1)	0	3 (0.3)	0
Abdominal discomfort	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Abdominal pain	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Abdominal pain upper	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Fatigue	1 (1)	1 (0.4)	0	2 (0.4)	0	0	0	1 (1)	1 (0.2)	0	3 (0.3)	0
Nausea	0	2 (1)	0	2 (0.4)	0	0	1 (1)	0	1 (0.2)	0	3 (0.3)	0
Tachycardia	1 (1)	1 (0.4)	0	2 (0.4)	0	0	0	1 (1)	1 (0.2)	0	3 (0.3)	0
Decreased appetite	0	2 (1)	0	2 (0.4)	0	0	0	0	0	0	2 (0.2)	0
Dizziness	1 (1)	0	0	1 (0.2)	0	0	0	1 (1)	1 (0.2)	0	2 (0.2)	0
Dizziness postural	0	0	0	0	0	0	0	1 (1)	1 (0.2)	0	1 (0.1)	0
Dizziness	1 (1)	0	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Headache	0	1 (0.4)	0	1 (0.2)	0	0	1 (1)	0	1 (0.2)	0	2 (0.2)	0
Insomnia	0	1 (0.4)	0	1 (0.2)	0	0	1 (1)	0	1 (0.2)	0	2 (0.2)	0
Terminal insomnia	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Insomnia	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0

Reference ID: 4698714

	Ages 6 to 11 Years (812P301 and 812P303)					Ages 12 to 17 Years (812P302 and 812P304)					Total	
FDA MedDRA Query[1]	**100 mg N=154 n (%)**	**200 mg N=268 n (%)**	**400 mg N=100 n (%)**	**Treatment N=522 n (%)**	**Placebo N=262 n (%)**	**200 mg N=99 n (%)**	**400 mg N=205 n (%)**	**600 mg N=99 n (%)**	**Treatment N=403 n (%)**	**Placebo N=201 n (%)**	**Treatment N=925 n (%)**	**Placebo N=463 n (%)**
Irritability	0	2 (1)	0	2 (0.4)	1 (0.4)	0	0	0	0	0	2 (0.2)	1 (0.2)
Irritability	0	2 (1)	0	2 (0.4)	0	0	0	0	0	0	2 (0.2)	0
Agitation	0	0	0	0	1 (0.4)	0	0	0	0	0	0	1 (0.2)
Anxiety	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Depression	0	0	0	0	0	0	0	1 (1)	1 (0.2)	0	1 (0.1)	0
Depressed mood	0	0	0	0	0	0	0	1 (1)	1 (0.2)	0	1 (0.1)	0
Diarrhea	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Dyspepsia	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Abdominal pain upper	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Parasomnia	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Sleep terror	0	1 (0.4)	0	1 (0.2)	0	0	0	0	0	0	1 (0.1)	0
Self-harm	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Suicide attempt	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0
Syncope	0	0	0	0	0	1 (1)	0	0	1 (0.2)	0	1 (0.1)	0
Vomiting	0	0	0	0	0	0	1 (1)	0	1 (0.2)	0	1 (0.1)	0

Source: adae.xpt. Software, Python. Created by the Clinical Data Scientist and Clinical Review Team
[1] Terms included are those that occurred more often in the treatment than the comparator group.
Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects in the treatment arm; n = number of subjects with the adverse event

The phase 2 safety and efficacy study (812P202) included 193 patients exposed to viloxazine (doses ranging from 100 mg to 400 mg). No patient in the placebo group experienced adverse events that led to discontinuation. The adverse events that most commonly led to discontinuation in the viloxazine ER treatment groups were headache (4 patients) and irritability (2 patients). In Study 812P310, the adverse events that most frequently led to discontinuation were somnolence, suicidal ideation, fatigue, decreased appetite, and headache. See Appendix 17 for a description of additional safety findings from Studies 812P202 and 812P310.

7.5.4. Treatment-Emergent Adverse Events

Table 35 provides an overview of the treatment-emergent adverse events (TEAEs) that occurred in ≥2% of patients in the viloxazine ER treatment groups and occurred more frequently than in the placebo groups. The most common TEAEs were somnolence/sedation, headache, fatigue, decreased appetite, abdominal pain, upper respiratory infection, nausea, and vomiting.

Somnolence was the most commonly reported preferred term in the phase 3 placebo-controlled trials (13% of viloxazine-treated patients vs. 3.5% of placebo-treated patients, Table 35). In these studies, somnolence was the most commonly-reported TEAE in all age and dose groups and was the TEAE that most commonly led to discontinuation. Somnolence appeared to be dose related, occurring in 19% of patients in the 600 mg treatment group, 14% of patients in the 400 mg group, 12% of patients in the 200 mg group, and 10% of patients in the 100 mg group. Sedation was also reported more frequently in viloxazine ER–treated patients (3.5%) than placebo-treated patients (0.4%).

The FDA MedDRA Query (FMQ) of somnolence includes the preferred terms of somnolence, sedation, and lethargy. In the phase 3 trials, one of these three terms was reported in 16.9% of patients who were exposed to viloxazine ER and 0.9% of patients receiving placebo (Table 36).

Somnolence was reported in 21.2% of viloxazine-treated patients in Study 812P202, compared with 4.2% of placebo-treated patients. Sedation was reported in 2.1% of viloxazine ER patients and no placebo-treated patients.

The Applicant's draft labeling includes a warning about (b) (4), and advises to use caution when driving or operating (b) (4) machinery, though no formal driving study was conducted.

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Table 35. Adverse Events[1] Occurring at ≥2% and at a Higher Frequency in the Treatment Arm than the Comparator Arm, Phase 3 Safety Population

	Patients Aged 6 to 11 Years (812P301 and 812P303)					Patients Aged 12 to 17 Years (812P302 and 812P304)					Total	
Adverse Event[1,2]	100 mg N=154 %	200 mg N=268 %	400 mg N=100 %	Treatment N=522 %	Placebo N=262 %	200 mg N=99 %	400 mg N=205 %	600 mg N=99 %	Treatment N=403 %	Placebo N=201 %	Treatment N=925 %	Placebo N=463 %
Any TEAE	48	50	58	51	36	43	56	56	53	38	52	37
Somnolence	10	12	14	12	2	13	14	19	15	6	13	4
Headache	10	11	6	10	4	10	13	9	11	10	10	7
Decreased appetite	5	9	9	8	0	5	7	6	7	1	7	0.4
Fatigue	4	6	9	6	2	4	9	10	8	3	7	2
Nausea	1	3	2	3	2	7	9	9	8	4	5	3
Vomiting	5	3	7	4	2	2	5	4	4	2	4	2
Nasopharyngitis	3	5	6	5	4	2	4	4	4	4	4	4
Abdominal pain upper	3	4	6	4	2	3	3	4	4	3	4	2
Sedation	2	4	3	3	0	2	5	4	4	1	4	0.4
Irritability	3	2	6	3	2	3	4	5	4	1	4	1
Insomnia	1	3	3	3	1	1	2	4	2	0	2	0.4

Source: adae.xpt; Software, Python; modified by Clinical Review Team
[1] Treatment-emergent adverse events are defined as AEs with onset or an increase in severity at any time from the first exposure to study drug.
[2] Coded as MedDRA preferred terms
Abbreviations: N = number of subjects in the treatment arm; n = number of subjects with the adverse event; TEAE = treatment-emergent adverse event

Reference ID: 4698714

Table 36. FDA MedDRA Queries[1] Occurring at ≥2% and at a Higher Frequency in the Treatment Arm than the Comparator Arm, Phase 3 Safety Population

	Patients Aged 6 to 11 Years (812P301 and 812P303)					Patients Aged 12 to 17 Years (812P302 and 812P304)					Total	
FDA MedDRA Query[1,2]	100 mg N=154 %	200 mg N=268 %	400 mg N=100 %	Treatment N=522 %	Placebo N=262 %	200 mg N=99 %	400 mg N=205 %	600 mg N=99 %	Treatment N=403 %	Placebo N=201 %	Treatment N=925 %	Placebo N=463 %
Somnolence (narrow FMQ)	12	16	18	15	2	15	19	23	19	7	17	4
Headache (narrow FMQ)	10	11	7	10	5	10	14	9	12	10	11	7
Fatigue (narrow FMQ)	4	6	11	7	2	5	9	10	8	3	7	2
Decreased appetite (narrow FMQ)	5	9	9	8	0	5	7	6	7	1	7	0.4
Abdominal pain (narrow FMQ)	3	6	11	6	5	6	4	6	5	3	6	4
Nasopharyngitis (narrow FMQ)	4	7	9	7	6	2	5	5	4	4	6	5
Nausea (narrow FMQ)	1	3	2	3	2	7	9	9	8	4	5	3
Vomiting (narrow FMQ)	5	3	7	4	2	2	5	4	4	2	4	2
Insomnia (narrow FMQ)	2	6	7	5	2	2	3	4	3	1	4	1
Dyspepsia (narrow FMQ)	3	4	6	4	2	3	3	5	4	3	4	3
Irritability (narrow FMQ)	3	2	6	3	3	3	4	5	4	1	4	2

Source: adae.xpt; Software: Python. Created by the Clinical Data Scientist and Clinical Review Team.
[1] Treatment-emergent adverse event defined as those AEs with onset or increase in severity at any time from the first exposure to study drug.
[2] Coded as MedDRA preferred terms
Abbreviations: AE = adverse event; FMQ = FDA MedDRA Query; MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects in treatment arm; n = number of subjects with adverse event

Somnolence and sedation were frequently observed in clinical trials of other nonstimulant treatments for ADHD. Somnolence or sedation was reported in 11% of atomoxetine-treated patients and 4% of placebo-treated patients in child and adolescent studies. Somnolence was also one of the most common reasons for atomoxetine treatment discontinuation. No warning for somnolence or sedation is included in the atomoxetine labeling. In two fixed-dose studies that compared guanfacine ER to placebo, 38% of patients treated with guanfacine ER reported somnolence (including somnolence, sedation, and hypersomnia), compared with 11% of patients receiving placebo. Greater than 30% of patients treated with clonidine ER in fixed-dose studies reported somnolence or sedation, compared with 4% of placebo-treated patients. The approved labeling for guanfacine ER and clonidine ER contains a warning for somnolence/sedation. Patients are cautioned against operating heavy machinery or driving until they know how these medications will affect them. Healthcare professionals are advised to consider the potential of additive sedative effects and counsel patients to avoid use of alcohol.

Reviewer's note: Somnolence and sedation were commonly reported in patients receiving viloxazine ER. The functional impacts of these effects were not specifically studied, but they could potentially have clinically meaningful repercussions in a pediatric population (e.g., effects on school and social functioning and risks of falls and accidents). Somnolence and sedation were also relatively common in the atomoxetine program, suggesting the possibility of a class effect, although the atomoxetine labeling does not include this warning. Given how frequently somnolence and sedation occurred (almost 17% of patients receiving viloxazine ER), the apparent correlation with dose, and the potential clinical implications, the risk of somnolence and sedation should be described in Section 6 of the labeling. The potential risk of driving or operating (b) (4) machinery while receiving viloxazine ER treatment is appropriate for inclusion in Section 5 (Warnings and Precautions). Of note, higher rates of somnolence and sedation were reported in clinical trials of alpha agonists, which carry a related warning. However, no study directly compared these other drugs to viloxazine ER, so no firm conclusions about the relative frequency of somnolence and sedation in patients taking alpha agonists versus viloxazine ER can be made.

Decreased appetite was also reported more frequently in patients receiving viloxazine ER than in those receiving placebo. The review team evaluated data related to the short- and long-term effects of viloxazine ER on appetite and growth parameters. See Section 7.6.3 for a full discussion of this risk issue.

7.5.5. Laboratory Findings

No clinically meaningful differences in mean laboratory values were observed in viloxazine ER-treated patients, as compared to patients on placebo. Most laboratory values in the phase 3 controlled studies remained within the reference ranges for age. Patients receiving viloxazine ER were more likely than those on placebo to experience a shift in liver transaminases from within the normal ranges to above the upper limit of the reference ranges (Table 37). See Section 7.6.5 for a full discussion of the effect of viloxazine ER on hepatobiliary assessments. Otherwise, the frequency of out-of-range laboratory values at EOS or early termination visits was comparable in the viloxazine ER and placebo groups. See Appendix 17, Clinical Safety Assessment: Additional Information and Assessment, for details of laboratory findings in the clinical trials.

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Table 37. Liver Transaminases, Shifts from Normal to Elevated at End of Study Visit, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Viloxazine ER n (%)	Placebo n (%)
Alanine aminotransferase	N=816	N=421
>ULN	47 (6)	8 (2)
>2-fold ULN	6 (1)	0
Lab analysis B	N=817	N=423
>ULN	20 (2)	3 (1)
>2-fold ULN	2 (0.2)	0

Source: ad b.xpt. Includes end-of-study and early termination visits; modified by Clinical Review Team.
Abbreviations: ER = extended release; N = number of subjects; n = number of subjects with abnormality; ULN = upper limit of normal

7.6. Key Review Issues Relevant to the Evaluation of Risk

7.6.1. Risk of Seizure

Issue

Viloxazine caused seizures/convulsions in multiple animal species (rat, dog, and mouse) at therapeutically relevant doses, suggesting a potential risk for seizures with chronic use of viloxazine.

Background

In nonclinical safety studies, viloxazine, likely due to its adrenergic pharmacology, caused convulsions in multiple animal species at therapeutically relevant doses. Specifically, viloxazine caused convulsions at ≥130 mg/kg/day in rat, ≥173 mg/kg/day in mouse, and ≥39 mg/kg/day in dog, which are approximately 1.5-, 1-, and 1.5-fold the MRHD of 400 mg, based on mg/m^2 in children[2], respectively. More importantly, the threshold for convulsions decreased with repeat viloxazine treatment (Table 38). It should be noted that the decrease in the convulsion threshold was not due to drug accumulation because no significant changes in drug exposure were observed after repeat treatment.

Table 38. Summary of Viloxazine-Related Convulsion and CNS Findings in Nonclinical Studies

Study and Duration		Dose[a]	Convulsion-Related Findings	Safety Margin[b] mg/m^2	Safety Margin[b] C_{max}
Human, MRHD 400 mg, C_{max}: 3.9 µg/mL; AUC: 61.2 µg*hour/mL (from Studies 812P301 and 303 in children aged 6 to 11 years)					
Rat	Single dose	≥487	Ataxia, convulsions, and death	6x	NA
	7-day	≥433	Ataxia, tremors, convulsions, and deaths	5x	2–3×
	2-year[c]	≥130	Ataxia, tremors, and convulsions	1.5×	NA

[2] Because the proposed indication is for the pediatric population only (patients with ADHD ages 6 to 17 years), body surface area (mg/m^2)-based safety margins are calculated using the average child body weight of 20 kg and conversion factor K_m of 25.

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Study and Duration		Dose[a]	Convulsion-Related Findings	Safety Margin[b]	
				mg/m^2	C_{max}
Dog	7-day	87	Ataxia and convulsion, leading to early termination	3.5×	4×
	13-week	39	Impaired muscle coordination, tremors, and convulsions	1.5×	2×
Mouse	Single dose	434	Ataxia, convulsions, and death	2.5×	NA
	5-day	≥217	Recumbency and convulsions	1.5×	NA
	4-week	173	Convulsions	1×	2×

Source: Modified/reformatted based on the data in the Applicant's study reports
[a] mg/kg (single dose) or mg/kg/day (multi-dose)
[b] Exposure-based safety margins are calculated relative to the human C_{max} at the MRHD of 400 mg/day because convulsions are C_{max} related; mg/m^2-based safety margins calculated using an average child body weight of 20 kg and conversion factor K_m of 25
[c] Two-year rat carcinogenicity study;
Abbreviations: AUC = area under the curve; CNS = central nervous system; MRHD = maximum recommended human dose; NA = exposure data not available

The convulsion findings across multiple nonclinical species raise concerns for the potential seizure liability for long-term or chronic use of viloxazine. The Applicant argues that the convulsion findings in nonclinical studies have limited clinical relevance in that 1) the convulsions are likely due to animal-specific and CNS-active metabolite(s); 2) the convulsions are due to a kindling effect and have limited human relevance; and 3) there are no overt brain lesions in the animals that had convulsions. In addition, the Applicant argues that existing human experience from the clinical program under this application and from previous experience in Europe did not show an increased incidence of seizures or convulsions.

However, from a nonclinical perspective, the Applicant's arguments are not adequate for the following reasons:

- The Applicant has not identified the "presumed" animal-specific metabolite(s) present in all 3 nonclinical species and cause convulsions.

- Although kindling is often used as a model of epileptogenesis in nonclinical studies, it is not unique to animals. In fact, kindling has been observed in human; for example, in alcohol withdrawal leading to an increased risk (i.e., lower threshold) of seizures (Becker 1998).

- Lack of histopathology findings in the brain does not exclude the possibility of moderate and/or functional impairment associated with seizures/convulsions.

Although seizures were observed in nonclinical studies, no seizures or convulsions were reported in the controlled phase 2 or phase 3 clinical trials. The Division has previously expressed concern to the Applicant that a seizure risk may become more evident with long-term use. Seizures were reported in the long-term safety extension study.

The assessment of this review issue focused on characterizing the clinical significance of the findings in the nonclinical studies and the long-term clinical study. Of note, the long-term safety extension was uncontrolled and cannot provide information on the relative risk of seizure with viloxazine ER exposure compared to the background risk in the population. However, the clinical data were examined for any indicators of an association between viloxazine ER and the seizure events. The review also considered published literature and available European postmarketing data from use of immediate-release viloxazine as an antidepressant.

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Assessment

The population of patients enrolled in viloxazine ER clinical trials likely had a low baseline risk of seizure. The protocols for the phase 2 and 3 studies specifically excluded patients with seizures or a history of seizure disorder within the immediate family (siblings, parents), or a history of seizure-like events. Among the patients who enrolled in the studies, 8 had a reported history of febrile seizures and 1 had a history of "infantile seizures"; no other seizure disorders were reported. Patients with significant systemic disease or major neurologic disorders—which could theoretically increase the seizure risk—were also excluded. The submitted data therefore do not provide any information on the risk of viloxazine ER in patients who may be at higher risk for seizures.

Seizures and adverse events that may represent seizure (syncope, syncopal episode, pseudoseizure, myoclonus, and severe muscle spasm) were tracked as adverse events of special interest. No seizures were reported in the controlled phase 2 and phase 3 studies (812P202, 812P301, 812P302, 812P303, and 812P304). Syncope was reported in three patients in the phase 2 and phase 3 controlled studies. No patient in the placebo group reported syncope. No other adverse events of special interest were reported in the controlled studies.

Three patients experienced seizures during the open-label safety extension study (812P310):

- Patient 302-(b) (6): 16-year-old female who experienced a tonic-clonic seizure 5 months after starting open-label viloxazine treatment. The patient had received placebo during the double-blind treatment period. The patient's dosage was titrated to viloxazine ER 600 mg during the open-label extension. The patient also experienced a syncopal episode approximately 4 months after entering the open-label study. The seizure episode was characterized by jerking movements and tongue biting. No bowel or bladder incontinence was reported. The episode lasted approximately 1 minute and was followed by a 10-minute postictal period. The patient was evaluated in an emergency department and diagnosed with a tonic-clonic seizure. The patient was prescribed diazepam, referred to neurology, and discharged home. Awake and asleep EEGs performed 10 days later were reportedly normal. The patient was evaluated by a neurologist who considered possible diagnoses of syncope or epileptic seizure. Magnetic resonance imaging (MRI) was recommended but the results are not available in the case narrative.

- Patient 202-(b) (6): 8-year-old female with a history of muscle spasms who had a generalized tonic-clonic seizure 19 days after starting open-label viloxazine. The patient had received viloxazine ER 100 mg during the double-blind treatment period and the patient's dose of viloxazine was titrated to 300 mg in the open-label period. The episode was characterized by leg cramping, lower extremity tingling, screaming, kicking, rhythmic movements of the upper extremities, eye rolling, and jaw clenching. The episode lasted 45 to 90 sec and was followed by a postictal period. The patient did not have associated fever, traumatic injury, or stressors. The patient was evaluated by a neurologist approximately 1 week later and was diagnosed with benign rolandic epilepsy. Awake and asleep EEGs were reportedly normal. The patient had additional seizure episodes >30 days after study drug discontinuation and was started on levetiracetam. An MRI revealed scattered T2 hyperintensities.

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- Patient 303-(b) (6): 11-year-old female who reported episodes of staring and distractibility approximately one year after starting open-label treatment with viloxazine. The patient received viloxazine ER 200 mg in the double-blind study. In the open-label study, her dose was titrated to 600 mg, then decreased to 400 mg because of lack of improvement on the higher dose. An EEG was performed and reported to be consistent with absence seizures. The patient was started on treatment with ethosuximide. The parent reported that similar episodes may have occurred as early as (b) (6) A follow-up safety report provided an updated EEG result and indicated that no seizures were observed but that the EEG did reveal atypical spike and slow wave complexes suggestive of underlying seizure tendency.

No clear association between viloxazine ER and these seizure events can be deduced from the case narratives. The development of seizure in a 16-year-old female (302-(b) (6)) with no history of epilepsy is most suspicious for a drug-associated adverse event. However, the results of toxicology screening, other laboratory studies, and the recommended MRI were not provided, and so other contributory causes cannot be ruled out based on the available information. The neurologist who evaluated this patient was also reportedly considering nonepileptic etiologies (e.g., syncope) as an explanation for the patient's symptoms. The clinical history described for patient 202(b) (6) is plausibly consistent with benign rolandic epilepsy. In addition, this patient continued to have seizures even after the drug was withdrawn, making an association with the drug less likely. Finally, the symptoms that prompted the seizure evaluation for patient 303-(b) (6) may have preceded exposure to viloxazine ER.

One 7-year-old male patient (301-1(b) (6)) experienced a nonepileptiform seizure while enrolled in Study 812P310. Approximately 9 months after starting study medication, the patient exhibited whole-body shaking with his eyes closed. He immediately returned to his neurologic baseline. The event was witnessed by an emergency department physician. A computed tomography scan of the head was within normal limits. The patient was discharged from the emergency room. He had another event in the parking lot. Emergency Medical Services responded and indicated he was "faking" the events. The patient and his mother ultimately reported significant psychosocial strain, including parental conflict and an open child-abuse case. Viloxazine ER was stopped for 3 days. The patient did not have any further events after resuming the medication. The investigator assessed the event as unrelated to study medication. Based on the information available in the narrative, the categorization of the event as a nonepileptiform seizure appears reasonable. The patient did not appear to have movements typical of a generalized tonic clonic or focal seizure, he did not have postictal symptoms, he was experiencing psychosocial stressors that could increase the risk for conversion reactions, and he did not have any further events while still receiving the medication.

In Study 812P310, one patient (304-(b) (6)) experienced "seizure-like activity versus myoclonus" in the context of a syncopal episode. Another patient (302-(b) (6)) experienced a syncopal episode approximately 2 months prior to having a generalized seizure, though it is not clear that the syncopal episode and the seizure were related. See Section 7.5.4 for a discussion of these case narratives and other syncope events. The available clinical information does not support reclassification of these events as seizure events rather than syncopal events, although the possibility of seizure cannot be entirely excluded.

Viloxazine was previously authorized for treatment of depression in the EU. A review of the line listings of suspected adverse drug reactions in the publicly available EudraVigilance database

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(accessed February 10, 2020) found two reported cases of seizure. The World Health Organization's Vigibase database includes 31 reports of seizure events (seizure, generalized tonic clonic seizure, petit mal epilepsy, epilepsy). No additional clinical details about the EudraVigilance or Vigibase case reports were available. A review of the FAERS database identified the following 3 reported cases of seizure or possible seizure:

- 3003270: 63-year-old female who was admitted to a psychiatric unit where treatment with haloperidol, viloxazine, and clozepate was initiated. The patient experienced malaise with loss of consciousness. According to the report, "the hypothesis of convulsion was not dismissed." The patient's clinical presentation was remarkable for a serum sodium of 113 meq/L, worsening of renal insufficiency, and bacteremia with *Escherichia coli*. The patient recovered with antibiotic therapy, fluid restriction, and sodium supplementation.

- 3231774: 82-year-old male with a history of myocardial infarction and stroke who was started on labetalol, zopiclone, viloxazine, and paracetamol and subsequently developed tonic-clonic convulsions. The patient was also prescribed spironolactone. All drugs were withdrawn 1 day after the event. The patient's conditioned worsened and he died. The safety report indicates that the cause of death was unstated but that the following causes were considered: new stroke, epilepsy, cerebral metastases, or any of the drugs listed in the report.

- 5959260: 76-year-old male with a history of heart failure, abdominal aortic aneurysm, renal failure, hypertension, and tobacco use who was hospitalized for status epilepticus. The patient was prescribed risperidone, clonazepam, viloxazine, bisoprolol, dutasteride, acetylsalicylate lysine, tamsulosin hydrochloride, fluconazole, darbepoetin alfa, lactulose, furosemide, zopiclone, allopurinol, and simvastatin. The patient's serum sodium was 124 meq/L and a "tendency to water abuse was observed." All suspect drugs were discontinued. The patient recovered.

The Applicant has referenced a published review of seizure incidence with viloxazine (Edwards and Glen-Bott 1984) that found that the incidence of seizures associated with viloxazine treatment in nonepileptic populations was 1/7635 (0.01%). No other systematic reviews or clinical studies examining seizure incidence in viloxazine have been published. The yearly incidence of epilepsy in the general population is approximately 48 per 100,000 people or 0.04% (Medicine 2012). The prevalence of epilepsy in the U.S. population is approximately 1.2% (Zack and Kobau 2017).

The European labeling for immediate-release viloxazine includes the following warning:

> Convulsive events have been reported in patients that are treated for epilepsy or have a prior history of this condition or even outside the context of epilepsy. In addition, viloxazine enters into competition with certain anticonvulsive medications (carbamazepine, phenytoin) by inhibiting their hepatic metabolism, which leads to symptoms of overdose. Taking into account the epileptogenic potential of viloxazine, the classic precaution for use consists of reducing the dosage of the anticonvulsive, which requires close medical supervision.

The data from EudraVigilance and Vigibase are difficult to interpret given that the total number of patients exposed is unknown and the true incidence of these events among patients exposed to viloxazine is unclear. In addition, these databases may contain duplicate reports. Finally, the lack

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of clinical details accompanying the case reports precluded analysis of any confounding factors. Of note, the case reports of seizure events listed in FAERS all appear to be confounded by the presence of other medications and medical illnesses and do not clearly demonstrate an association between these events and viloxazine.

Conclusion

Viloxazine, likely due to its adrenergic pharmacology, caused convulsions across multiple nonclinical species in multiple studies, and the threshold for convulsion decreased with repeat treatment. Although nonclinical studies suggest that viloxazine may have epileptogenic potential, few seizures have been reported in clinical trials. The seizures reported in the long-term clinical trial were not clearly associated with viloxazine ER. Immediate-release viloxazine was authorized for the treatment of depression in the EU from 1976 to 2008, but the limited data from published literature and the postmarketing databases regarding the spontaneous reports of seizures in patients taking viloxazine are insufficient to determine whether seizure events were related to drug effects. The findings from the nonclinical studies should be described in the labeling. Healthcare professionals should be aware that viloxazine has not been studied in patients at high risk of seizure. Reports of seizures should continue to be monitored in the postmarketing period given the nonclinical findings.

7.6.2. Risk of Suicidal Ideation and Behavior

Issue

Patients who received viloxazine ER were more likely than patients who received placebo to experience suicidal ideation and behavior.

Background

Children and adolescents with ADHD may be more likely to experience suicidal ideation and behavior than the general pediatric population. Any increased risk of suicidal ideation and behavior associated with viloxazine ER should be characterized and described in the labeling to allow healthcare professionals to assess the benefit-risk profile. The review team evaluated the data related to suicidal ideation and behavior from the controlled clinical studies and the open-label long-term safety extension.

Assessment

In Studies 812P202, 812P301, 812P302, 812P303, and 812P304, six viloxazine ER-treated patients and two placebo-treated patients reported suicidal ideation as adverse events. All patients who experienced suicidal ideation recovered and all suicidal ideation events in the viloxazine ER group were categorized as mild. One patient (who received the 100 mg dose) was withdrawn from the study because of suicidal ideation. This patient (202-(b) (6)) had a history of a mood disorder. No other patients who reported suicidal ideation had a reported history of a mood disorder and none reported suicidal ideation or behavior on the C-SSRS at screening or at baseline. Most of these patients did not report any other psychiatric adverse events during the study. Patients did report suicidal ideation on postbaseline C-SSRS assessments. Of note, all of

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the viloxazine ER-exposed patients who experienced suicidal ideation were male and ≤10 years of age (Table 39).

Suicidal ideation in one patient (303-(b) (6)) was categorized as a serious adverse event. The patient was a 6-year-old male who was randomized to receive viloxazine ER 200 mg. He experienced suicidal ideation 10 days after starting the drug. His mother reported that he was hyperactive and defiant but that his mood appeared to be at baseline. He was reprimanded for talking back to his mother and said, "I want to die." He was easily distracted and calmed within 2 minutes. He did not attempt to harm himself. He did not have a history of suicidal ideation. Although suicidal ideation was categorized as a serious adverse event, the patient was not hospitalized, and no life-threatening complications were reported. The severity of the event was rated as mild.

Table 39. Patients Reporting Suicidal Ideation as an Adverse Event After Viloxazine ER Exposure–Phase 2 and Phase 3 Studies

Subject ID	Dose	Age	Gender	Severity	SAE?	Other Psychiatric Adverse Events	Disposition
202 (b) (6)	100 mg	9	M	Mild	No	None	Completed
202	100 mg	9	M	Mild	No	None	Withdrawn (AE)
202	200 mg	7	M	Mild	No	None	Withdrawn by patient
202	200 mg	7	M	Mild	No	None	Completed
303	200 mg	6	M	Mild	Yes	Tearfulness, insomnia	Completed
303	200 mg	10	M	Mild	No	None	Completed

Abbreviations: AE = adverse event; ER = extended release; SAE = severe adverse event

One patient in the placebo group and one patient in the viloxazine ER group (302-(b) (6)) reported suicidal ideation on the C-SSRS but did not report suicidal ideation as an adverse event.

- Patient 302-(b) (6): 15-year-old-female who was randomized to receive viloxazine ER 200 mg. She reported a wish to be dead on the C-SSRS on day 21. She did not experience any adverse events and completed the study. She had no psychiatric diagnoses other than ADHD and did not receive any concomitant medications.

Three patients who were treated with viloxazine ER reported suicidal behavior on the C-SSRS but did not report suicidal behavior as an adverse event. None of the patients had a reported history of psychiatric diagnoses other than ADHD.

- Patient 303-(b) (6): 9-year-old male who was randomized to receive the 200 mg dose of viloxazine ER. He reported suicidal behavior on the C-SSRS at the Week-6 visit. No suicidal behavior was reported at the EOS visit. He experienced adverse events of cough and fatigue but did not report psychiatric adverse events. He completed the study.

- Patient 303-(b) (6): 6-year-old male who was randomized to receive viloxazine ER 400 mg. He reported suicidal behavior at Weeks 4 and 5 but did not report any suicidal behavior by the end of the study. He experienced an adverse event of irritability as well as multiple nonpsychiatric adverse events (ear infection, pyrexia, nasal congestion, vomiting, headache, fatigue, seasonal allergy, and nasopharyngitis).

- Patient 303-(b) (6): 7-year-old male who was randomized to receive viloxazine ER 200 mg. He reported suicidal behavior at Week 2. He did not complete the study (was lost to

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follow up) but did not report suicidal behavior at his last study visit (Week 6). He experienced adverse events including irritability, insomnia, somnolence, and limb abscess.

Two patients receiving viloxazine ER reported suicidal behavior as adverse events in the placebo-controlled trials and their case narratives are summarized below.

- Patient 303 (b) (6): 10-year-old female with a history of depression and anxiety who reported frequent thoughts of killing herself with a knife 55 days after starting treatment with viloxazine ER (400 mg dose). She waited until her mother fell asleep and took a knife from kitchen with the intent of killing herself. Ultimately, she did not harm herself with the knife and went back to bed. She was subsequently seen at a crisis center and discharged. A similar event reportedly occurred 1 month after treatment initiation but was not disclosed until the second event. The patient also reported history of suicidal ideation prior to study enrollment that she had not disclosed. The patient completed the study. In addition to suicidal behavior, adverse events reported during treatment included somnolence, irritability, and abdominal discomfort. No concomitant medications or psychiatric conditions other than ADHD were reported. This patient did report suicidal ideation at screening on the C-SSRS and at the end of study visit.

- Patient 304- (b) (6): 15-year-old male with history of anger outbursts and emotional lability but no other psychiatric conditions besides ADHD reported on medical history. No concomitant medications were reported. He was admitted to a psychiatric unit approximately 7 weeks after starting treatment with viloxazine ER 400 mg for an unwitnessed suicide attempt. The patient had reportedly wrapped the wire of his headphones around his neck in an attempt to strangle himself. In addition to suicidal behavior, adverse events reported during treatment included affect lability, fatigue, and polydipsia. He was discontinued from the study because of the suicide attempt and reportedly recovered. Of note, the patient did not report suicidal ideation or behavior on the C-SSRS at baseline or during the study.

By the 120-day safety update (data cutoff July 31, 2019), 1116 patients had enrolled in the long-term safety extension study (812P310) and 1097 had received study medication during the open-label period. Of them, 18 patients reported suicidal ideation, 2 reported suicide attempts, 5 reported intentional self-injury, and 1 patient reported self-injurious ideation. In 11 patients, suicidal ideation or behavior was classified as an SAE. Nine patients were withdrawn from Study 812P310 because of suicidal ideation or behavior.

The clinical information of the two patients who reported suicide attempts in Study 812P310 is below:

- Patient 202- (b) (6): 8-year-old male with a medical history of eczema, enlarged tonsils, oppositional defiant disorder, stuttering, allergies, myringotomy, and constipation. His concomitant medications included cetirizine and melatonin. He received viloxazine ER 300 mg daily in the double-blind treatment period in Study 812P202. In the open-label extension, he was receiving viloxazine ER 200 mg when he made a suicide attempt. His mother reported that he attempted suicide by starving himself, stabbing himself with a pen, and falling on the floor. The patient stated that he was trying to commit suicide. Psychosocial stressors at the time of the event included teasing at school and parental divorce. He had been diagnosed with depression at some point after starting viloxazine ER treatment and was enrolled in psychotherapy. No change to the dose of viloxazine ER was made after the event

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but the patient ultimately was discontinued from the trial because of an adverse event of major depression.

- Patient 302-[redacted] (b) (6): 16-year-old female. No narrative was provided for this case, although the suicide attempt was categorized as a serious adverse event. From a review of the safety databases, this patient had a reported medical history of ADHD, acne, and tympanoplasty. Her only concomitant medication was an oral contraceptive pill. The patient received placebo in the double-blind treatment phase of Study 812P302. She entered the open-label extension in [redacted] (b) (6) and her dose was titrated from 200 mg to 600 mg. The patient reported suicide attempts on [redacted] (b) (6) and [redacted] (b) (6). The drug was withdrawn in [redacted] (b) (6) because of adverse events of major depressive disorder, suicidal ideation, and self-injurious behavior. She recovered from the suicide attempt and other adverse events.

Conclusion

In total, 12/1118 (1.2%) viloxazine ER-treated patients who participated in the placebo-controlled clinical trials experienced suicidal ideation or behavior, reported either as an adverse event or on the C-SSRS. In contrast 3/487 (0.6%) placebo-treated patients experienced suicidal ideation or behavior. Most of the viloxazine ER-treated patients who reported suicidal behaviors appeared to have a pre-enrollment history of mood problems or reported psychiatric adverse events during the study. Patients who reported suicidal ideation without suicidal behavior in general did not necessarily have a prior history of a mood disorder or report other psychiatric adverse events during treatment. Most patients who developed suicidal ideation recovered and were able to complete the study. Patients, caregivers, and healthcare professionals should be aware that suicidal ideation can arise in patients without a history thereof and without accompanying reports of mood disturbance. This serious and potentially unexpected risk can be communicated in the labeling by means of a boxed warning. Of note, atomoxetine, also a norepinephrine reuptake inhibitor, carries a boxed warning for risk of suicidal ideation.

7.6.3. Risk of Negative Effects on Weight and Growth

Issue

Patients receiving viloxazine ER more frequently reported diminished appetite, were less likely to gain weight, and were more likely to lose weight than patients receiving placebo.

Background

ADHD is a childhood-onset disorder and viloxazine ER is intended for chronic use in the pediatric population. Negative impacts on appetite and nutritional status could worsen concentration in pediatric patients with ADHD; increase the risk of general cognitive dysfunction, irritability, and fatigue; and affect immunologic, reproductive, and bone health. The review of this risk issue focused on the clinical significance of viloxazine ER's effects on appetite, weight, and growth.

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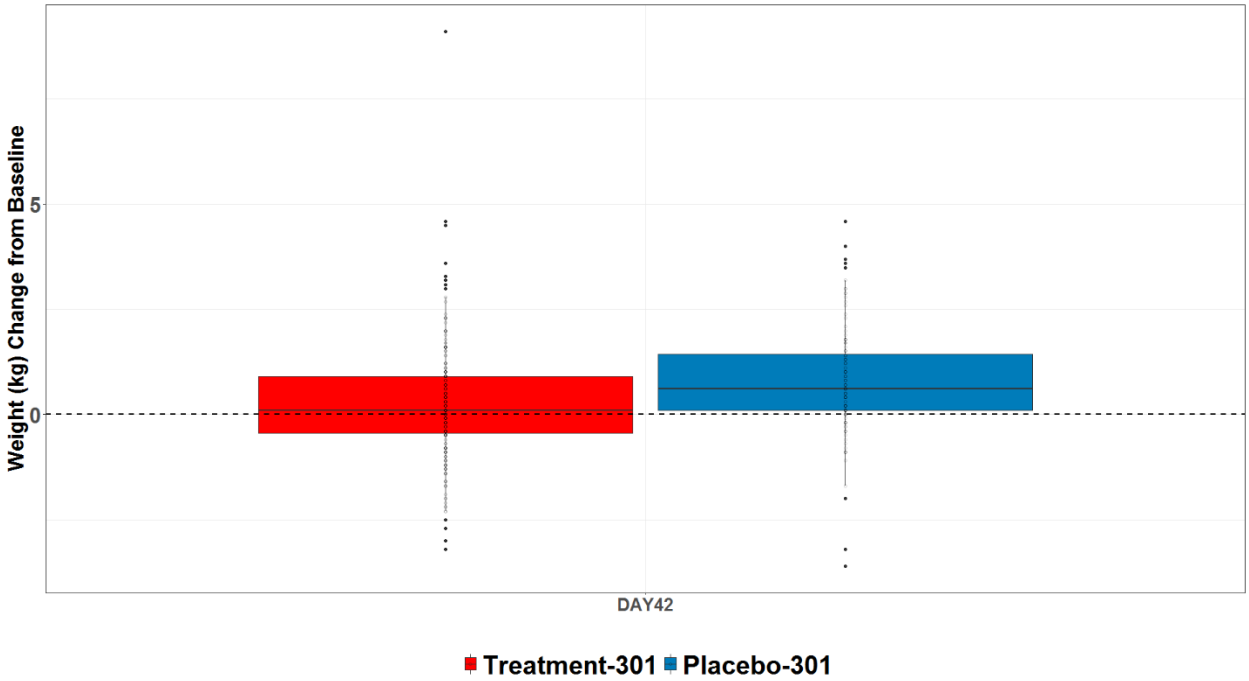
Assessment

In nonclinical studies, viloxazine treatment caused dose-dependent decreases in body weight, weight gain, and/or food consumption (by up to 15% to 20% at high doses, which were approximately 2- to 3-fold the MRHD based on mg/m^2 in children). The decreases occurred most often during the first few weeks after treatment initiation but were reversible. These effects are likely associated with the adrenergic pharmacology of the drug.

Patients treated with viloxazine ER were more likely to report decreased appetite as an adverse event than were patients receiving placebo (7.2% versus 0.4%). Decreased weight was not commonly reported as an adverse event in the viloxazine ER group or the placebo group (1.1% versus 0.4%). However, patients in the viloxazine ER group had minimal change in weight over the course of treatment while patients in the placebo group on average gained weight.

In Study 812P301, which included patients ages 6 to 11 years, the mean change from baseline weight was 0.4 kg in the viloxazine ER 100 mg group, 0.1 kg in the viloxazine ER 200 mg group, and 1.3 kg in the placebo group (Figure 20).

Figure 20. Mean Change in Weight from Baseline (Study 812P301)



Source: advs.xpt. Created by the Clinical Data Scientist.

In Study 812P303, which also included patients ages 6 to 11 years, the mean change from baseline was 0.3 kg in the viloxazine ER 200 mg group, -0.1 kg in the viloxazine ER 400 mg group, and 1.3 kg in the placebo group (Figure 21).

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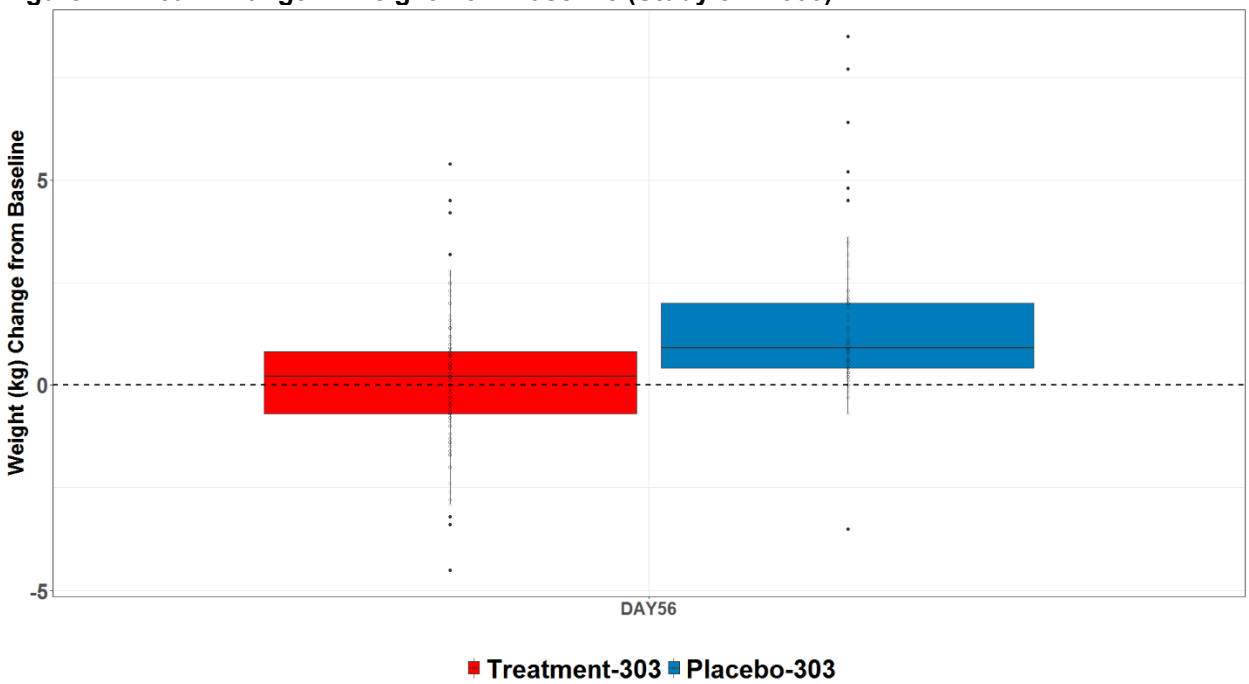
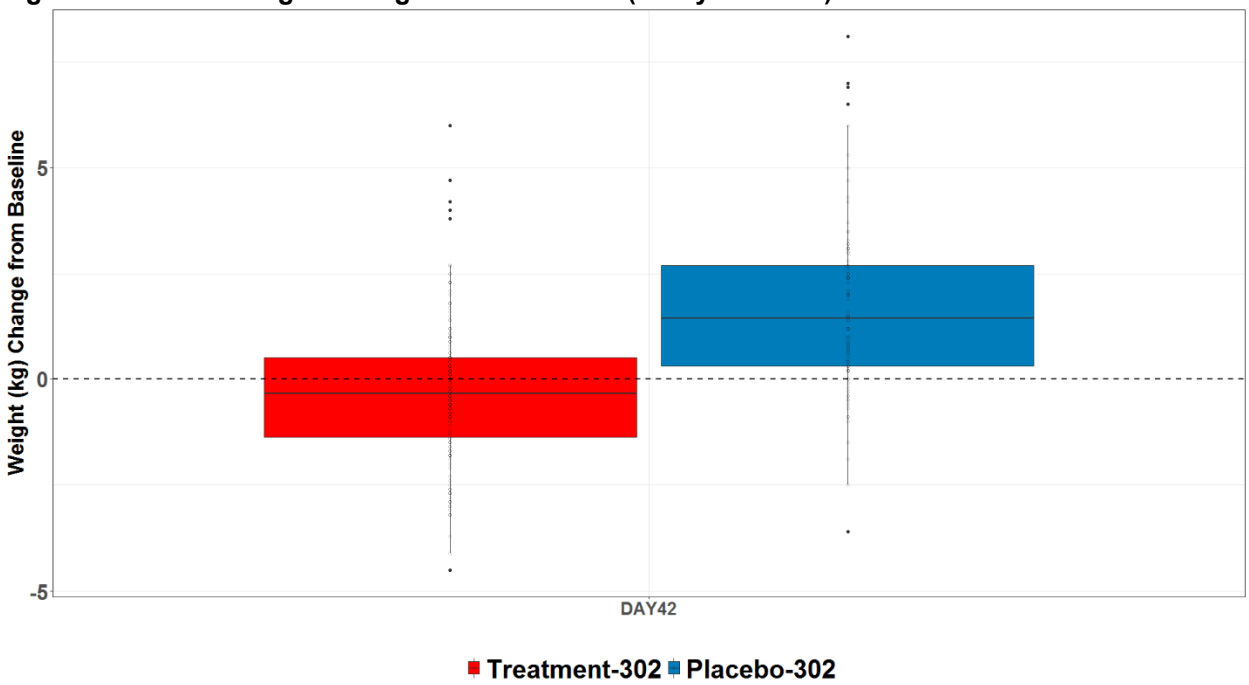
Figure 21. Mean Change in Weight from Baseline (Study 812P303)



Source: advs.xpt. Created by the Clinical Data Scientist.

In Study 812P302, which included patients ages 7 to 12 years, the mean change from baseline weight was 0 kg in the viloxazine ER 200 mg group, -0.4 kg in the viloxazine ER 400 mg group, and 1.6 kg in the placebo group (Figure 22).

Figure 22. Mean Change in Weight from Baseline (Study 812P302)



Source: advs.xpt. Created by the Clinical Data Scientist.

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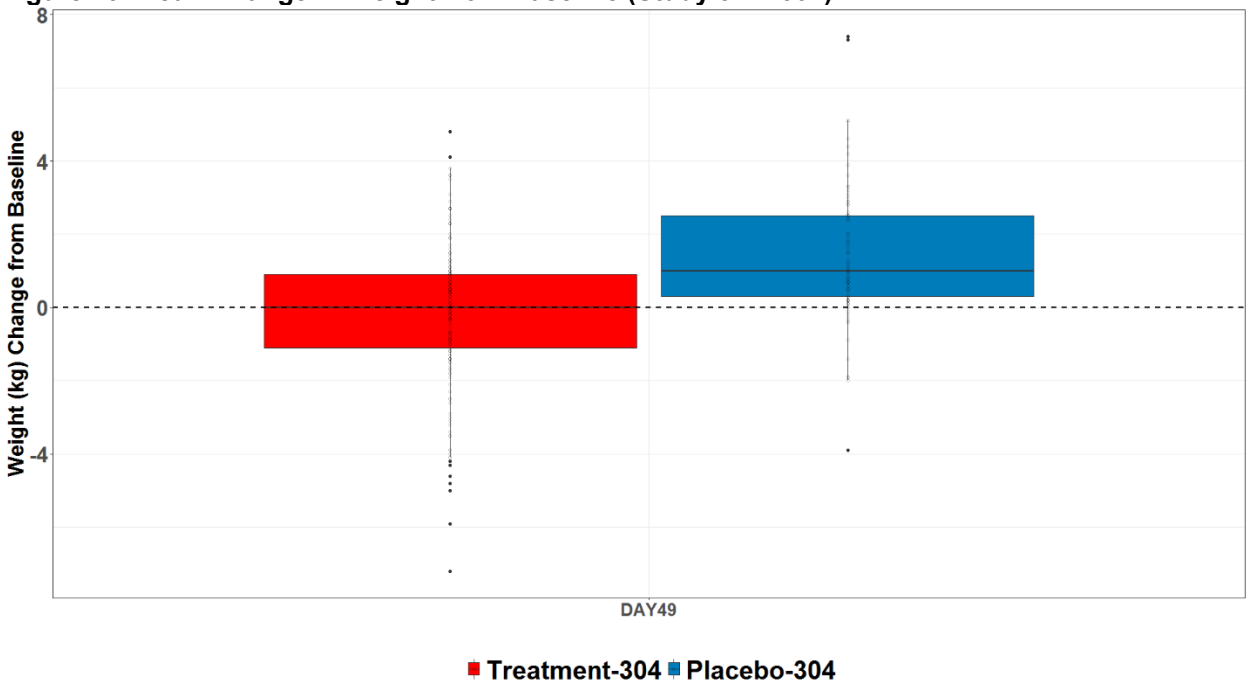
In Study 812P304, which also included patients ages 12 to 17 years, the mean change from baseline was 0 kg in the viloxazine ER 400 mg group, -0.2 kg in the viloxazine ER 600 mg group, and 1.3 kg in the placebo group (Figure 23).

Figure 23. Mean Change in Weight from Baseline (Study 812P304)



Source: advs.xpt. Created by the Clinical Data Scientist.

Overall, the mean change from baseline weight in patients treated with viloxazine ER in the phase 3 controlled studies was 0.2 kg in patients ages 6 to 11 years (compared to 1 kg in the placebo group). The mean change from baseline in patients ages 12 to 17 years treated with viloxazine ER was -0.17 kg (compared to 1.5 kg in the placebo group). As discussed in Section **Error! Reference source not found.**, the review team concluded that (b) (4) . The mean change in weight in adolescents receiving the 200 mg and 400 mg doses was -0.16 kg. The mean change from baseline weight in all patients receiving viloxazine ER was 0.04 kg (compared to 1.2 kg in patients receiving placebo).

In addition, patients on viloxazine ER were more likely to have a ≥7% decrease in body weight over the course of the short-term safety and efficacy studies (Table 40).

Table 40. Percentage of Patients With a ≥7% Decrease in Body Weight, Phase 3 Placebo-Controlled Trials

Viloxazine 100 mg (N=154) n (%)	Viloxazine 200 mg (N=367) n (%)	Viloxazine 400 mg (N=305) n (%)	Viloxazine 600 mg (N=99) n (%)	Total Viloxazine (N=925) n (%)	Total Placebo (N=463) n (%)
2 (1)	9 (3)	5 (2)	4 (4)	20 (2)	3 (1)

Data from the long-term study are limited by the number of dropouts and the lack of a control group but suggest that patients taking viloxazine have a decreased growth trajectory. Patients who were still enrolled in Study 812P310 at 12 months had on average gained 2.9 kg and grown

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4.4 cm over the course of the year. The mean increase in BMI was 0.3 kg/m^2 over 12 months. However, the BMI, weight, and height-for-age percentiles declined over time (Table 41).

Table 41. Growth Parameters from Baseline to Month 12 (Study 812P310)

Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
BMI-for-age percentile	Baseline	1096	58.6 (28.4)	63.6 (0, 99.5)	-	-
BMI-for-age percentile	Month 3	810	54.6 (29.1)	57.3 (0.1, 99)	-4.1 (11.7)	-2.2 (-53.8, 47.4)
BMI-for-age percentile	Month 6	624	53.6 (29.5)	57.3 (0, 99)	-5.2 (13.8)	-3.6 (-66.6, 35.2)
BMI-for-age percentile	Month 9	491	53.2 (29.6)	54.8 (0.2, 98.7)	-5.8 (14.7)	-4 (-65.4, 42.9)
BMI-for-age percentile	Month 12	339	52.9 (29.2)	56.3 (0, 99.9)	-5.1 (16.8)	-4.1 (-71.7, 85.4)
Body Mass Index (kg/m2)	Baseline	1096	18.7 (3.4)	17.9 (11.6, 36.8)		
Body Mass Index (kg/m2)	Month 3	810	18.5 (3.5)	17.8 (12.8, 32.3)	-0.2 (0.9)	-0.1 (-4.8, 4.9)
Body Mass Index (kg/m2)	Month 6	624	18.5 (3.6)	17.6 (12.4, 33.3)	-0.1 (1.2)	-0.1 (-4.5, 6.9)
Body Mass Index (kg/m2)	Month 9	491	18.6 (3.6)	17.6 (12.8, 33.3)	0 (1.3)	0 (-5.2, 5.9)
Body Mass Index (kg/m2)	Month 12	339	18.8 (4.5)	17.7 (12.7, 76.3)	0.3 (3.3)	0.1 (-5.2, 61.2)
Height-for-age percentile	Baseline	1096	53.8 (29)	55 (0, 100)	-	-
Height-for-age percentile	Month 3	810	52.3 (29.1)	52.2 (0, 100)	-1.2 (5.9)	-1.2 (-23, 68)
Height-for-age percentile	Month 6	624	51.2 (29)	50.3 (0, 100)	-2.3 (8.2)	-1.7 (-40.9, 60.7)
Height-for-age percentile	Month 9	491	50.5 (29.7)	50.1 (0, 100)	-2.7 (9.5)	-1.9 (-49.6, 32.2)
Height-for-age percentile	Month 12	339	49.2 (30.2)	46.6 (0, 99.4)	-3.9 (10.3)	-2.6 (-39.4, 36.8)
Height (cm)	Baseline	1096	145.3 (17.3)	143.9 (106.6, 191.8)		
Height (cm)	Month 3	810	146.1 (17.2)	144.5 (106.6, 190.5)	1 (1.4)	0.8 (-4, 13.6)
Height (cm)	Month 6	624	146.5 (17.2)	145.1 (106.8, 192)	2.1 (1.9)	2 (-5.9, 16.5)
Height (cm)	Month 9	491	147.1 (17)	145.6 (108.1, 192)	3.3 (2.4)	3 (-5.9, 12.7)
Height (cm)	Month 12	339	147.8 (16.4)	147.3 (108.1, 187.9)	4.4 (2.8)	4 (-2.6, 15.2)
Weight-for-age percentile	Baseline	1096	58.4 (27.5)	61.5 (0.1, 99.3)	-	-
Weight-for-age percentile	Month 3	810	55 (28.3)	57.8 (0.3, 99.2)	-3.3 (8)	-2.4 (-44.7, 34.6)

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Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
Weight-for-age percentile	Month 6	624	53.7 (28.6)	57.3 (0.1, 99.5)	-4.6 (9.8)	-3.6 (-47.6, 30)
Weight-for-age percentile	Month 9	491	53.2 (28.7)	55.4 (0.1, 98.9)	-5.2 (10.9)	-4 (-46.2, 51.6)
Weight-for-age percentile	Month 12	339	52 (28.7)	53.5 (0.5, 100)	-5.2 (13)	-5.1 (-46.5, 88.6)
Weight (kg)	Baseline	1096	41.1 (15.9)	37.6 (18.3, 96.2)		
Weight (kg)	Month 3	810	41.2 (16)	37.5 (18.4, 96.3)	0.2 (1.9)	0.2 (-9.2, 12.3)
Weight (kg)	Month 6	624	41.4 (16)	37.5 (19.3, 96.2)	0.8 (2.6)	0.7 (-8.6, 16.7)
Weight (kg)	Month 9	491	41.8 (16)	37.2 (19.7, 98.9)	1.7 (3.2)	1.3 (-9.1, 16)
Weight (kg)	Month 12	339	42.4 (16.3)	38 (20.2, 156)	2.9 (7.1)	2.1 (-8.2, 128)

Source: advs.xpt. Software, R. Created by the Clinical Data Scientist; modified by Clinical Review Team.
[1] Unscheduled visits are not included. Data cutoff July 31, 2019.
Abbreviations: BMI = body mass index

Conclusion

Pediatric patients, particularly prepubertal patients, are expected to demonstrate gains in weight and height. The available data raise the possibility that viloxazine ER slows the velocity of weight and height gains, although interpretation of the long-term data is hampered by the lack of a control group. Currently approved medications for ADHD—stimulants and atomoxetine—have also been associated with negative effects on growth parameters. Healthcare professionals who are considering viloxazine ER as a treatment option for ADHD in the pediatric population should be informed of the possibility that viloxazine ER will impact weight and growth. The review team has determined that including this risk in Section 5 (Warnings and Precautions) is appropriate. In addition, decreased appetite will be listed as a common adverse reaction in Section 6.

7.6.4. Risk of Heart Rate and Blood Pressure Changes

Issue

The review team assessed the potential risk of clinically significant heart rate and blood pressure changes associated with viloxazine ER because of the drug's known adrenergic effects.

Background

Viloxazine ER is a norepinephrine reuptake inhibitor. Other medications with adrenergic effects have been associated with increases in heart rate and blood pressure. Approved labeling for stimulant medications cautions that CNS stimulants cause an increase in blood pressure (mean

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increase of about 2 to 4 mm Hg) and heart rate (mean increase of about 3 to 6 bpm) and advises monitoring of all patients for potential tachycardia and hypertension. The labeling for atomoxetine, another norepinephrine reuptake inhibitor, cautions that use may be associated with heart rate and blood pressure increases, orthostasis, and syncope, and that Raynaud's phenomenon has been reported. Healthcare professionals are advised to exercise caution in patients with hypertension, tachycardia, cardiovascular disease, or cerebrovascular disease. Pulse and blood pressure should be measured at baseline, following dose increases, and periodically while on atomoxetine therapy.

In pediatric placebo-controlled trials of atomoxetine, atomoxetine-treated patients experienced a mean heart rate increase of 6 bpm. Also, 2.5% of patients had heart rate increases of at least 25 bpm and a heart rate of 110 bpm (compared with 0.2% of patients on placebo). Tachycardia was identified as an adverse event in 0.3% of atomoxetine-treated patients and no placebo patients. Pediatric patients treated with atomoxetine experienced mean increases of about 1.6 mmHg and 2.4 mmHg in systolic and diastolic blood pressures, respectively, as compared with placebo. At the EOS visit, 4.8% of atomoxetine-treated patients had an elevated systolic blood pressure (compared with 3.5% of placebo-treated patients) and 4% had an elevated diastolic blood pressure (compared with 1.1% of placebo-treated patients).

The mean increase in heart rate in adult patients treated with atomoxetine in placebo-controlled trials was 5 bpm. Adult patients taking atomoxetine had a mean systolic blood pressure increase of 2 mmHg and a mean diastolic blood pressure increase of 1 mg Hg. Also, 2.2% of adult patients treated with atomoxetine had a systolic blood pressure of ≥150 mmHg at the final study visit (compared with 1% of patients on placebo); 0.4% had a diastolic blood pressure of ≥100 mmHg (compared with 0.5% of patients on placebo).

The evaluation of this review issue focused on assessment of the clinical meaningfulness of the heart rate and blood pressure changes observed in the placebo-controlled phase 3 trials of viloxazine ER. The review also considered how the vital sign changes observed in the viloxazine ER development program compare to those associated with stimulants and atomoxetine. However, no study directly comparing the safety of viloxazine ER and these drug products was performed and so no definitive conclusion about relative safety can be reached.

Assessment

Heart Rate

In the phase 3 placebo-controlled studies, 1.7% of patients treated with viloxazine ER reported tachycardia or increased heart rate as a treatment-emergent adverse event, compared with no patient in the placebo group. Bradycardia was not reported as an adverse event. The mean change in heart rate from baseline to EOS ranged from 2.4 to 6.3 bpm in patients treated with viloxazine ER across the dose groups; the mean heart range change in patients receiving placebo ranged from 0 to 1 bpm. Higher doses of viloxazine ER were associated with greater mean increases in heart rate (Table 42, Table 43, Table 44, and Table 45). The mean change in heart rate from baseline to EOS in all patients receiving viloxazine ER was 4.2 bpm with an SD of 13 mmHg, compared with 0.4 bpm (SD 10.8 mmHg) in patients on placebo.

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Table 42. Mean Change in Heart Rate (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Heart Rate (beats/min)	Week 6 (EOS)	139	84.5 (11.5)	2.4 (12)	146	85.6 (13.6)	3.7 (13.9)	142	83.1 (10.6)	0 (10.4)

[1] Source: advs.xpt. Does not include unscheduled visits. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 70 to 120 beats per minute
Abbreviations: EOS = end of study; SPN = viloxazine

Table 43. Mean Change in Heart Rate (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Heart Rate (beats/min)	Week 6 (EOS)	89	81.2 (11.6)	2.7 (13.4)	97	80.2 (12.7)	4.5 (12.9)	102	77 (11.3)	0 (10.9)

Source: advs.xpt. Does not include unscheduled visits. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 60 to 100 beats per minute
Abbreviations: EOS = end of study; SPN = viloxazine

Table 44. Mean Change in Heart Rate (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Heart Rate (beats/min)	Week 8 (EOS)	99	84.4 (13.5)	5.7 (11.8)	84	86.8 (14.6)	5.2 (13.3)	93	83.2 (10.2)	1 (11)

Source: advs.xpt. Does not include unscheduled visits. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 70 to 120 beats per minute
Abbreviations: EOS = end of study; SPN = viloxazine

Table 45. Mean Change in Heart Rate (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Heart Rate (beats/min)	Week 7 (EOS)	91	81.4 (13.6)	4.9 (12.1)	90	82.8 (12.3)	6.3 (14.4)	89	75.6 (12.3)	0.5 (11)

Source: advs.xpt. Does not include unscheduled visits. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 60 to 100 beats per minute
Abbreviations: EOS = end of study; SPN = viloxazine

In Studies 812P301 and 812P303, which enrolled patients ages 6 to 11 years, the reference range for heart rate was 70 to 120 bpm. In Study 812P301, two patients receiving viloxazine ER 200 mg had a heart rate of >120 bpm at EOS. In Study 812P303, three patients (receiving viloxazine ER 200 or 400 mg) had a heart rate of >120 bpm at EOS. No patients in the placebo group in either study had elevated heart rates at the EOS visit. In Study 812P301, the percentage of patients with a heart rate of <70 bpm decreased by the EOS visit in both dosage groups, but there was no change in the placebo group. In Study 812P303, the percentage of patients with a heart rate of <70 bpm decreased in all treatment groups by EOS (Table 46 and Table 47).

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Table 46. Heart Rate Out-of-Range (Study 812P301)

		SPN-812 ER 100 mg (N=154)					SPN-812 ER 200 mg (N=161)					Placebo (N=159)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Heart Rate (beats/min)	Baseline	154	21	14	0	0	161	22	14	0	0	159	12	8	0	0
Heart Rate (beats/min)	Week 6 (EOS)	139	11	8	0	0	146	15	10	2	0	142	11	8	0	0

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 70 to 120 beats per minute
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 47. Heart Rate Out-of-Range (Study 812P303)

		SPN-812 ER 200 mg (N=107)					SPN-812 ER 400 mg (N=100)					Placebo (N=103)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Heart Rate (beats/min)	Baseline	107	19	18	0	0	100	18	18	0	0	103	13	13	0	0
Heart Rate (beats/min)	Week 8 (EOS)	99	13	13	2	2	84	9	11	1	1	93	7	8	0	0

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 70 to 120 beats per minute
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

In Studies 812P302 and 812P304, which enrolled patients ages 12 to 17 years, the reference range for heart rate was 60 to 100 bpm. In Study 812P302, 4.5% of patients in the viloxazine ER 200 mg group and 5.2% of patients in the 400 mg group had a heart rate of >100 bpm at the EOS visit, compared with 2.9% of patients in the placebo group. In Study 812P304, 7.7% of patients in the viloxazine ER 400 mg group and 10% of patients in the 600 mg group had a heart rate of >100 bpm at EOS, compared with 1.1% of patients in the placebo group. A higher proportion of patients on placebo in both studies had a heart rate of <60 bpm both at baseline and at EOS.

Table 48. Heart Rate Out-of-Range (Study 812P302)

		SPN-812 ER 200 mg (N=99)					SPN-812 ER 400 mg (N=105)					Placebo (N=104)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Heart Rate (beats/min)	Baseline	99	3	3	2	2	105	6	6	2	2	104	6	6	0	0
Heart Rate (beats/min)	Week 6 (EOS)	89	1	1	4	5	97	4	4	5	5	102	5	5	3	3

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 60 to 100 beats per minute
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 49. Heart Rate Out-of-Range (Study 812P304)

		SPN-812 ER 400 mg (N=100)					SPN-812 ER 600 mg (N=99)					Placebo (N=97)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Heart Rate (beats/min)	Baseline	100	5	5	3	3	99	8	8	1	1	97	10	10	1	1
Heart Rate (beats/min)	Week 7 (EOS)	91	2	2	7	8	90	1	1	9	10	89	6	7	1	1

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
Heart rate reference range, 60 to 100 beats per minute
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

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Patients treated with viloxazine ER were more likely than those treated with placebo to have potentially clinically meaningful increases in heart rate (i.e., increases in heart rate ≥15 bpm or 25 bpm) at the EOS visit. Of note, a change of ≥25 bpm was observed in ≥5% of patients in all viloxazine ER dosage groups and was most notable in the 600 mg group, in which 10% of patients had an increase in heart rate of that magnitude (Table 50 and Table 51).

Table 50. Patients in Phase 3 Controlled Studies with a ≥15 BPM Increase in Heart Rate at EOS

Treatment Group	Number of Patients n (%)
Placebo (N=426)	41 (10)
Viloxazine ER 100 mg (N=139)	20 (14)
Viloxazine ER 200 mg (N=334)	69 (21)
Viloxazine ER 400 mg (N=272)	62 (23)
SPN-812 ER 600 mg (N=90)	28 (31)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 51. Patients in Phase 3 Controlled Studies with a ≥25 BPM Increase in Heart Rate at EOS

Treatment Group	Number of Patients n (%)
Placebo (N=426)	6 (1)
Viloxazine ER 100 mg (N=139)	7 (5)
Viloxazine ER 200 mg (N=334)	20 (6)
Viloxazine ER 400 mg (N=272)	16 (6)
SPN-812 ER 600 mg (N=90)	9 (10)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Overall, viloxazine ER appeared to have a consistent and dose-related effect on heart rate across the phase 3 controlled studies. Based on the data available in the viloxazine ER studies, the mean increases in heart rate may be comparable to those with atomoxetine and stimulants. However, these studies did not directly compare viloxazine ER to other approved ADHD medications.

Systolic Blood Pressure

Hypertension or increased blood pressure was reported as an adverse event in 0.8% of patients receiving viloxazine ER in the phase 3 controlled trials and 0.2% of patients on placebo. Hypotension was reported in 0.3% of patients receiving viloxazine ER but was not reported in any patients who received placebo. The mean change in systolic blood pressure ranged from -0.6 mm Hg to 2.8 mmHg in the viloxazine ER groups and -0.3 mmHg to 1.5 mmHg in the placebo group (Table 52, Table 53, Table 54, and Table 55). The mean change from baseline to EOS in systolic blood pressure among all patients receiving viloxazine ER was 0.8 mmHg (SD 9.9 mmHg), which was comparable to that in patients on placebo (0.7 mmHg, SD 10.1 mmHg).

Reference ID: 4698714

Table 52. Mean Change from Baseline in Systolic Blood Pressure (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Systolic Blood Pressure (mmHg)	Week 6 (EOS)	139	106.8 (10.2)	0.4 (11)	146	105.4 (11)	0.5 (10.4)	142	106.3 (9)	1.3 (10.1)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
1 Does not include unscheduled visits.
Systolic blood pressure reference range, 90 to 120 mmHg
Abbreviations: EOS = end of study; SPN = viloxazine

Table 53. Mean Change from Baseline in Systolic Blood Pressure (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Systolic Blood Pressure (mmHg)	Week 6 (EOS)	89	114.2 (11)	-0.3 (9.9)	97	114.3 (9.7)	1.1 (9.2)	102	112 (9.7)	-0.3 (10.2)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Systolic blood pressure reference range, 90 to 135 mmHg
Abbreviations: EOS = end of study; SPN = viloxazine

Table 54. Mean Change from Baseline in Systolic Blood Pressure (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Systolic Blood Pressure (mmHg)	Week 8 (EOS)	99	103.6 (9.3)	-0.6 (9.8)	84	105.9 (9.3)	2.8 (8.9)	93	104 (9.4)	0.3 (10.3)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Systolic blood pressure reference range, 90 to 120 mmHg
Abbreviations: EOS = end of study; SPN = viloxazine

Table 55. Mean Change from Baseline in Systolic Blood Pressure (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Systolic Blood Pressure (mmHg)	Week 7 (EOS)	91	112.8 (9.3)	0.5 (9.5)	90	113.9 (9.5)	2.5 (9.8)	89	112.9 (9.2)	1.5 (9.9)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Systolic blood pressure reference range, 90 to 135 mmHg
Abbreviations: EOS = end of study; SPN = viloxazine

The reference range for systolic blood pressure was 90 mmHg to 120 mmHg for patients ages 6 to 11 years (Studies 812P301 and 812P303). The percentage of patients with an out-of-range systolic blood pressure was variable across the two trials, both in patients receiving viloxazine ER and placebo (Table 56 and Table 57).

Table 56. Systolic Blood Pressure Out-of-Range (Study 812P301)

		SPN-812 ER 100 mg (N=154)					SPN-812 ER 200 mg (N=161)					Placebo (N=159)				
Parameter	**Visit**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**
Systolic Blood Pressure (mmHg)	Baseline	154	6	4	14	9	161	16	10	10	0.1	159	11	7	13	8
Systolic Blood Pressure (mmHg)	Week 6 (EOS)	139	4	3	14	10	146	9	6	10	0.1	142	4	3	9	6

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Systolic blood pressure reference range, 90 to 120 mm Hg
Abbreviations: EOS = end of study; ER = extended release; Hi = high; SPN = viloxazine

Table 57. Systolic Blood Pressure Out-of-Range (Study 812P303)

		SPN-812 ER 200 mg (N=107)					SPN-812 ER 400 mg (N=100)					Placebo (N=103)				
Parameter	**Visit**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**
Systolic Blood Pressure (mmHg)	Baseline	107	3	3	7	7	100	2	2	2	2	103	4	4	5	5
Systolic Blood Pressure (mmHg)	Week 8 (EOS)	99	3	3	3	3	84	2	2	4	5	93	5	5	5	5

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Systolic blood pressure reference range, 90 to 120 mm Hg
Abbreviations: EOS = end of study; ER = extended release; Hi = high; SPN = viloxazine

The reference range for systolic blood pressure was 90 to 135 mmHg for patients ages 12 to 17 years (Studies 812P302 and 812P304). In those studies, a small number of patients in all groups had systolic blood pressures outside the reference range (Table 58 and Table 59).

Table 58. Systolic Blood Pressure Out-of-Range (Study 812P302)

		SPN-812 ER 200 mg (N=99)					SPN-812 ER 400 mg (N=105)					Placebo (N=104)				
Parameter	**Visit**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**
Systolic Blood Pressure (mmHg)	Baseline	99	0	0	2	2	105	1	1	1	1	104	1	1	0	0
Systolic Blood Pressure (mmHg)	Week 6 (EOS)	89	1	1	3	3	97	0	0	1	1	102	2	2	0	0

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Systolic blood pressure reference range, 90 to 135 mm Hg
Abbreviations: EOS = end of study; ER = extended release; Hi = high; SPN = viloxazine

Table 59. Systolic Blood Pressure Out-of-Range (Study 812P304)

		SPN-812 ER 400 mg (N=100)					SPN-812 ER 600 mg (N=99)					Placebo (N=97)				
Parameter	**Visit**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**	**N**	**Low**	**%**	**Hi**	**%**
Systolic Blood Pressure (mmHg)	Baseline	100	1	1	0	0	99	1	1	1	1	97	0	0	0	0
Systolic Blood Pressure (mmHg)	Week 7 (EOS)	91	0	0	0	0	90	1	1	0	0	89	0	0	1	1

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Systolic blood pressure reference range, 90 to 135 mm Hg
Abbreviations: EOS = end of study; ER = extended release; Hi = high; SPN = viloxazine

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Patients receiving viloxazine ER 600 mg were more likely to have an increase in systolic blood pressure of ≥10 mmHg at the EOS (Table 60). Otherwise, patients treated with viloxazine ER or placebo did not appreciably differ in terms of the proportion with potentially clinically significant increases in systolic blood pressure.

Table 60. Patients with a ≥10 mmHg Change in Systolic Blood Pressure at EOS

Treatment Group	Number of Patients n (%)
Placebo (N=426)	75 (18)
Viloxazine ER 100 mg (N=139)	23 (17)
Viloxazine ER 200 mg (N=334)	58 (17)
Viloxazine ER 400 mg (N=272)	50 (18)
SPN-812 ER 600 mg (N=90)	24 (27)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 61. Patients with a ≥20 mmHg Change in Systolic Blood Pressure at EOS

Treatment Group	Number of Patients n (%)
Placebo (N=426)	16 (4)
Viloxazine ER 100 mg (N=139)	7 (5)
Viloxazine ER 200 mg (N=334)	10 (3)
Viloxazine ER 400 mg (N=272)	9 (3)
SPN-812 ER 600 mg (N=90)	4 (4)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Overall, the mean changes in systolic blood pressure in the phase 3 controlled trials were small, not clearly clinically meaningful, and comparable to those in the placebo group. Most patients receiving viloxazine ER maintained a systolic blood pressure within the reference range for their age group.

Diastolic Blood Pressure

The mean changes in diastolic blood pressure in the phase 3 placebo-controlled studies ranged from 1.2 mmHg to 3.4 mmHg in patients receiving viloxazine ER and -0.5 mmHg to 1.2 mmHg in patients receiving placebo (Table 62, Table 63, Table 64, and Table 65). The mean change from baseline to EOS in diastolic blood pressure was 2.4 mmHg (SD 9.2) in all patients receiving viloxazine ER, compared with 0.4 mmHg (SD, 8.5) in patients receiving placebo.

Table 62. Mean Change from Baseline in Diastolic Blood Pressure (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Diastolic Blood Pressure (mmHg)	Week 6 (EOS)	139	67.4 (7.7)	1.9 (8.5)	146	68.1 (8.5)	3.2 (9.5)	142	66 (8.1)	1 (8.8)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Abbreviations: EOS = end of study; SPN = viloxazine

Reference ID: 4698714

Table 63. Mean Change from Baseline in Diastolic Blood Pressure (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Diastolic Blood Pressure (mmHg)	Week 6 (EOS)	89	71.2 (6.6)	1.2 (8.4)	97	72.4 (7.7)	3 (9.3)	102	69 (7.8)	-0.5 (8.5)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Abbreviations: EOS = end of study; SPN = viloxazine

Table 64. Mean Change from Baseline in Diastolic Blood Pressure (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Diastolic Blood Pressure (mmHg)	Week 8 (EOS)	99	66.3 (7.8)	2.3 (8.9)	84	67.1 (8.1)	1.2 (9.6)	93	65.3 (7.6)	-0.5 (8.6)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Abbreviations: EOS = end of study; SPN = viloxazine

Table 65. Mean Change from Baseline in Diastolic Blood Pressure (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Diastolic Blood Pressure (mmHg)	Week 7 (EOS)	91	71.8 (7.5)	2.9 (10.5)	90	72.2 (7.9)	3.4 (9.2)	89	69.3 (7.5)	1.2 (7.8)

Source: advs.xpt. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] Does not include unscheduled visits.
Abbreviations: EOS = end of study; SPN = viloxazine

The reference range for diastolic blood pressure for patients ages 6 to 11 was 50 to 80 mmHg (Studies 812P301 and 812P303). In Study 812P301, patients receiving viloxazine ER were not more likely than those receiving placebo to have an elevated diastolic blood pressure at EOS. In Study 812P303, patients in the placebo group were more likely to have an elevated diastolic blood pressure at baseline but less likely to have an elevated diastolic blood pressure at EOS than those receiving viloxazine ER 200 mg or 400 mg.

Reference ID: 4698714

Table 66. Diastolic Blood Pressure Out-of-Range (Study 812P301)

		SPN-812 ER 100 mg (N=154)					SPN-812 ER 200 mg (N=161)					Placebo (N=159)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Diastolic Blood Pressure (mmHg)	Baseline	154	2	1	4	3	161	2	1	7	0	159	1	1	1	1
Diastolic Blood Pressure (mmHg)	Week 6 (EOS)	139	1	1	4	3	146	2	1	13	0.1	142	0	0	7	5

Source: Table created by the Clinical Data Scientist and Clinical Reviewer.
Diastolic blood pressure reference range, 50 to 80 mmHg
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 67. Diastolic Blood Pressure Out-of-Range (Study 812P303)

		SPN-812 ER 200 mg (N=107)					SPN-812 ER 400 mg (N=100)					Placebo (N=103)				
-Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Diastolic Blood Pressure (mmHg)	Baseline	107	3	3	2	2	100	0	0	3	3	103	2	2	5	5
Diastolic Blood Pressure (mmHg)	Week 8 (EOS)	99	1	1	4	4	84	1	1	2	2	93	2	2	1	1

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Diastolic blood pressure reference range, 50 to 80 mmHg
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

The reference range for diastolic blood pressure for patients ages 12 to 17 was 64 to 83 mmHg (Studies 812P302 and 812P304). In both studies, a large number of patients had a diastolic blood pressure below the reference range cut-off (64 mmHg) at baseline and at EOS. However, only 4% of patients receiving viloxazine had a diastolic blood pressure of <60 mmHg at EOS (compared with 9.4% of patients receiving placebo) and no patients treated with viloxazine had a diastolic blood pressure of <50 mmHg at EOS. Patients in the viloxazine ER 400 mg and 600 mg groups were more likely to have a diastolic blood pressure of >83 mm Hg at EOS compared with those in the placebo group (Table 68 and Table 69).

Table 68. Diastolic Blood Pressure Out-of-Range (Study 812P302)

		SPN-812 ER 200 mg (N=99)					SPN-812 ER 400 mg (N=105)					Placebo (N=104)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Diastolic Blood Pressure (mmHg)	Baseline	99	20	20	6	6	105	21	20	4	4	104	23	22	2	2
Diastolic Blood Pressure (mmHg)	Week 6 (EOS)	89	10	11	3	3	97	13	13	9	9	102	25	25	6	6

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Diastolic blood pressure reference range, 64 to 83 mmHg
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

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Table 69. Diastolic Blood Pressure Out-of-Range (Study 812P304)

		SPN-812 ER 400 mg (N=100)					SPN-812 ER 600 mg (N=99)					Placebo (N=97)				
Parameter	Visit	N	Low	%	High	%	N	Low	%	High	%	N	Low	%	High	%
Diastolic Blood Pressure (mmHg)	Baseline	100	29	29	4	4	99	19	19	2	2	97	31	32	4	4
Diastolic Blood Pressure (mmHg)	Week 7 (EOS)	91	12	13	5	6	90	12	13	8	9	89	14	16	3	3

Source: Table created by the Clinical Data Scientist and Clinical Reviewer
Diastolic blood pressure reference range, 64 to 83 mmHg
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

In addition, patients receiving viloxazine ER were more likely to have a potentially clinically meaningful increase in diastolic blood pressure (i.e., increase of ≥10 mmHg or 20 mmHg) than those receiving placebo (Table 70 and Table 71).

Table 70. Patients with a ≥10 mmHg Change in Diastolic Blood Pressure at EOS

Treatment Group	Number of Patients	%
Placebo (N=426)	57	13%
Viloxazine ER 100 mg (N=139)	26	19%
Viloxazine ER 200 mg (N=334)	69	21%
Viloxazine ER 400 mg (N=272)	58	21%
SPN-812 ER 600 mg (N=90)	22	24%

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 71. Patients with a ≥20 mmHg Change in Diastolic Blood Pressure at EOS

Treatment Group	Number of Patients	%
Placebo (N=426)	5	1%
Viloxazine ER 100 mg (N=139)	3	2%
Viloxazine ER 200 mg (N=334)	13	3%
Viloxazine ER 400 mg (N=272)	10	4%
SPN-812 ER 600 mg (N=90)	4	4%

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

In summary, viloxazine ER was associated with greater increases in diastolic blood pressure in the phase 3 controlled trials compared to placebo. These increases may be dose related, although the mean changes in diastolic blood pressure and the proportion of patients with out-of-range diastolic blood pressure were not strikingly different among the viloxazine ER dose groups. More than 20% of patients treated with viloxazine ER had potentially clinically significant changes in diastolic blood pressure at the EOS visit.

Long-term Data on Heart Rate and Blood Pressure

The review team examined data from Study 812P310 to assess whether any persistent changes in heart rate and blood pressure were evident over time. Study 812P310 is ongoing, but data up to the Month 12 visit were analyzed given the considerable decrease in the number of patients for whom data at later time points are available. At Month 12, 339 patients were in the safety study population. On average, the mean changes from baseline at Month 12 in systolic and diastolic blood pressures were <1 mmHg. The mean change in heart rate at Month 12 was 1.2 bpm in the supine position and 2.9 bpm in the standing position (Table 72).

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Table 72. Vital Signs by Visit, Safety Population (Study 812P310)

Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
Diastolic Blood Pressure-Seated/Supine (mmHg)	Baseline	1094	68.3 (7.9)	69 (42, 97)		
Diastolic Blood Pressure-Seated/Supine (mmHg)	Month 3	809	68.8 (7.8)	69 (48, 104)	0.4 (8.4)	0 (-31, 39)
Diastolic Blood Pressure-Seated/Supine (mmHg)	Month 6	624	68.9 (7.8)	69 (40, 94)	0.5 (8.7)	0 (-30, 34)
Diastolic Blood Pressure-Seated/Supine (mmHg)	Month 9	491	69.6 (7.3)	70 (48, 90)	1.1 (8.3)	1 (-26, 37)
Diastolic Blood Pressure-Seated/Supine (mmHg)	Month 12	339	68.7 (7)	68 (50, 89)	0.1 (8.9)	0 (-23, 32)
Diastolic Blood Pressure-Standing (mmHg)	Baseline	922	70.1 (8.1)	71 (31, 109)		
Diastolic Blood Pressure-Standing (mmHg)	Month 3	809	70.8 (7.7)	71 (49, 99)	0.5 (8.1)	0 (-24, 45)
Diastolic Blood Pressure-Standing (mmHg)	Month 6	624	70.9 (7.7)	71 (48, 99)	0.3 (8.5)	0 (-22, 34)
Diastolic Blood Pressure-Standing (mmHg)	Month 9	491	71.9 (7.3)	72 (52, 96)	1.2 (8.5)	1 (-21, 34)
Diastolic Blood Pressure-Standing (mmHg)	Month 12	339	71.4 (7.3)	71 (49, 99)	0.8 (8.9)	0 (-22, 32)
Heart Rate-Seated/Supine (beats/min)	Baseline	1094	83.2 (12.7)	83 (50, 127)		
Heart Rate-Seated/Supine (beats/min)	Month 3	809	84.9 (14.1)	84 (51, 138)	1.5 (13.7)	2 (-48, 71)
Heart Rate-Seated/Supine (beats/min)	Month 6	624	85.3 (13)	85 (54, 134)	1.9 (12.2)	1 (-44, 42)
Heart Rate-Seated/Supine (beats/min)	Month 9	491	85.5 (13)	86 (50, 136)	1.8 (13.1)	2 (-37, 48)
Heart Rate-Seated/Supine (beats/min)	Month 12	339	85.1 (13.2)	84 (55, 132)	1.2 (12.5)	2 (-44, 40)
Heart Rate-Standing (beats/min)	Baseline	921	87.7 (13.9)	88 (50, 150)		
Heart Rate-Standing (beats/min)	Month 3	809	91.5 (15.4)	92 (52, 143)	2.4 (13.9)	2 (-46, 46)
Heart Rate-Standing (beats/min)	Month 6	624	91.9 (14)	92 (53, 132)	2.7 (13.2)	3 (-40, 49)
Heart Rate-Standing (beats/min)	Month 9	491	92.3 (14.2)	92 (53, 140)	3.4 (13.5)	3 (-59, 43)
Heart Rate-Standing (beats/min)	Month 12	339	92.3 (14.2)	91 (59, 137)	2.9 (14)	4 (-63, 37)
Systolic Blood Pressure-Seated/Supine (mmHg)	Baseline	1094	108.3 (10.3)	108 (70, 137)		
Systolic Blood Pressure-Seated/Supine (mmHg)	Month 3	809	108.4 (10.2)	108 (80, 138)	0.1 (10)	0 (-38, 44)
Systolic Blood Pressure-Seated/Supine (mmHg)	Month 6	624	108.9 (9.5)	108 (80, 136)	0.5 (10.4)	0 (-27, 36)
Systolic Blood Pressure-Seated/Supine (mmHg)	Month 9	491	109.4 (9.6)	108 (82, 139)	1.2 (9.9)	0 (-33, 33)

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Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
Systolic Blood Pressure-Seated/Supine (mmHg)	Month 12	339	108.5 (9.4)	109 (86, 136)	0.2 (10.2)	0 (-29, 26)
Systolic Blood Pressure-Standing (mmHg)	Baseline	922	109.1 (10.4)	109 (73, 147)		
Systolic Blood Pressure-Standing (mmHg)	Month 3	809	108.8 (9.7)	108 (80, 141)	-0.3 (9.8)	0 (-42, 31)
Systolic Blood Pressure-Standing (mmHg)	Month 6	624	109.2 (9.4)	109 (72, 140)	0 (10.6)	0 (-36, 36)
Systolic Blood Pressure-Standing (mmHg)	Month 9	491	109.8 (9.4)	110 (80, 146)	0.7 (10.9)	0 (-27, 35)
Systolic Blood Pressure-Standing (mmHg)	Month 12	339	109.2 (9.2)	110 (85, 135)	-0.4 (10.8)	-2 (-27, 31)

Source: advs.xpt; Software: R. Created by Clinical Data Scientist and Clinical Reviewer.
Data cutoff July 31, 2019 (120-day safety update)

At the Month 12 visit, 14.5% of patients had a ≥15 bpm change in baseline seated heart rate and 4% had a ≥25 bpm increase. Few patients ages 6 to 11 years had seated heart rates exceeding the upper limit of the reference range (120 bpm) compared to nearly 10% of patients ages 7 to 12 years. Standing heart rate was more likely to be elevated, with 8% of all patients experiencing a ≥25 bpm increase; 4% of patients ages 6 to 11 years and 20% of patients ages 12 to 17 years had a standing heart rate greater than the upper limit for age (Table 73).

Table 73. Change from Baseline to Month 12 in Heart Rate (Study 812P310)

	≥15 bpm CFB (All Patients)	≥25 bpm CFB (All Patients)	HR >120 bpm (Ages 6 to 11 Years)	HR >100 (Ages 12 to 17 Years)
Heart rate (seated)	49/339 (15%)	14/339 (4%)	1/225 (0.4%)	11/114 (10%)
Heart rate (standing)	47/339 (14%)	27/339 (8%)	9/225 (4%)	23/114 (20%)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: CFB = change from baseline; HR = heart rate

Few patients had a systolic blood pressure higher than the upper limit of the reference range or an increase in systolic blood pressure of ≥20 mmHg (Table 74).

Table 74. Change from Baseline to Month 12 in Systolic Blood Pressure (Study 812P310)

	≥20 mmHg CFB	SBP >120 mmHg (Ages 6 to 11 Years)	SBP >135 mmHg (Ages 12 to 17 Years)
SBP (seated)	13/339 (4%)	14/225 (6%)	1/114 (1%)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: CFB = change from baseline (increase); SBP = systolic blood pressure

Although <5% of patients had a diastolic blood pressure that exceeded the upper limit of the reference range at Month 12, 14% of patients had a diastolic blood pressure increase of ≥10 mmHg from baseline (Table 75).

Table 75. Change from Baseline to Month 12 in Diastolic Blood Pressure (Study 812P310)

	≥10 mmHg CFB	DBP >80 mmHg (Ages 6 to 11 Years)	DBP >83 mmHg (Ages 12 to 17 Years)
DBP (seated)	46/339 (14%)	11/225 (5%)	4/114 (4%)

Source: advs.xpt. Created by the Clinical Reviewer.
Abbreviations: CFB = change from baseline (increase); DBP = diastolic blood pressure

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Conclusion

Viloxazine ER was associated with a dose-dependent increase in heart rate of 2.4 to 6.3 bpm in the phase 3 controlled studies. Patients receiving viloxazine ER in the long-term, open-label safety extension also experienced increases in heart rate, although the change from baseline in heart rate at Month 12 was comparatively small (1.2 bpm seated and 2.9 bpm standing). Viloxazine ER was also associated with increases (1.2 mmHg to 3.4 mmHg) in diastolic blood pressure in the short-term phase 3 studies. In the long-term study, the mean change in diastolic blood pressure was less than 1 mmHg at Month 12, but 14% of patients had a potentially clinically meaningful increase in diastolic blood pressure (≥10 mmHg) from baseline. Viloxazine ER was not clearly linked to changes in systolic blood pressure. The labeling for viloxazine ER should inform healthcare professionals of the possibility of increased heart rate and diastolic blood pressure. Heart rate and blood pressure should be measured at baseline in patients receiving viloxazine ER and monitored during treatment.

7.6.5. Risk of Liver Injury

Issue

Reports of liver toxicity potentially related to the use of the immediate-release formulation of viloxazine have been found in postmarketing databases. Atomoxetine, another norepinephrine reuptake inhibitor, carries a warning regarding the risk of severe liver injury.

Background

The EudraVigilance, Vigibase, and FAERS databases contain reports of hepatobiliary disorders, including liver injury, that were possibly associated with immediate-release viloxazine exposure. Transaminase elevations were noted as a possible adverse reaction in the European labeling for viloxazine. However, case reports or other data regarding liver injury associated with viloxazine are not present in the published literature. No evidence of liver injury was detected in atomoxetine clinical trials, but rare cases of clinically significant liver injury that were considered probably or possibly related to atomoxetine have been reported in the postmarketing period. These reports included patients who presented with liver enzyme levels >20-fold the upper limit of normal (ULN) and jaundice with a bilirubin level >2-fold the ULN. The patients recovered upon atomoxetine discontinuation. Viloxazine ER has a similar mechanism of action to atomoxetine and the possibility of a class effect was considered. Nonclinical data and clinical data from the controlled clinical studies and the open-label extension study for viloxazine ER were examined for any signals of hepatoxicity. Also, postmarketing data from the immediate-release form of viloxazine were reviewed for cases of hepatobiliary disorders.

Assessment

<u>Nonclinical Findings</u>

In animal species (mouse, rat, and dog), repeat treatment of viloxazine caused hepatocellular hypertrophy and/or vacuolation in the liver. In addition, viloxazine caused small hepatocellular eosinophilic bodies or inclusion bodies in the liver in dog. These changes occurred at doses equal

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to or less than the MRHD (Table 76). Further staining and electron microscopy demonstrated that the vacuoles were primarily lipid droplet accumulation in hepatocytes and the inclusion bodies were likely due to hypertrophic endoplasmic reticulum. These changes did not correlate with any other histopathology lesions or significant changes in clinical chemistry indicative of liver injury and were reversible after drug free recovery period. Moreover, these changes did not lead to an increase in the incidence of liver tumors in the rodent carcinogenicity studies. Therefore, from a nonclinical perspective, these liver findings are likely adaptive in response to viloxazine administration and are not considered to be adverse.

Table 76. Viloxazine-Related Liver Findings in Nonclinical Species and Corresponding Exposure Multiples

Species	Dose (mg/kg/day)	Liver Findings	Exposure Multiples (mg/m^2)[1]
Mouse	≥130	↑ hepatocellular hypertrophy and vacuolation (lipid accumulation)	~1×
Rat	≥52	↑ hepatocellular vacuolation (lipid accumulation)	~ 0.5×
Dog	≥3.5	↑ hepatocellular hypertrophy, vacuolation (lipid accumulation), and inclusion bodies (hypertrophic endoplasmic reticulum)	~ 0.1×

Source: Modified/reformatted based on the data in the Applicant's study reports
[1] Safety margins are calculated using the average child body weight of 20 kg and conversion factor K_m of 25

Adverse Events

No adverse events in the Hepatobiliary SOC were reported in the phase 2 or phase 3 controlled trials. No adverse events related to liver transaminase or bilirubin elevations were reported in the phase 2 study (812P202). Among the 925 patients who were exposed to viloxazine ER in the phase 3 controlled studies, the following non-serious TEAEs related to liver transaminase investigations were reported:

- One patient (0.1%) reported increased hepatic enzyme levels
- Six patients (0.6%) reported an increased alanine aminotransferase (ALT) level
- Four patients (0.4%) reported an increased aspartate aminotransferase (AST) level

The open-label safety extension study (812P310) included 1097 patients in the safety population; of them, five patients reported nonserious elevations in hepatobiliary laboratory assessments:

- Two patients reported an increased ALT level
- One patient reported an increased AST level
- One patient reported an increased total bilirubin level
- One patient reported an increased alkaline phosphatase level

Laboratory Assessments

The mean changes in hepatobiliary laboratory assessments in the phase 3 clinical trials were small and unlikely to be clinically meaningful (Table 77,Table 78, Table 79, and Table 80).

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Table 77. Hepatobiliary Assessments (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	153	15.3 (6.5)		161	15 (5.2)		158	15.2 (6.9)	
Alanine Aminotransferase (U/L)	Week 6 (EOS)	136	15.8 (8.3)	0.4 (7.6)	138	16.9 (14.1)	2 (13.8)	139	15.3 (5.8)	0.1 (7)
Alkaline Phosphatase (U/L)	Baseline	153	251.9 (74)		161	250.6 (71)		158	249.1 (61.4)	
Alkaline Phosphatase (U/L)	Week 6 (EOS)	136	250.5 (69.5)	1.3 (35.7)	137	249.5 (68)	3.2 (57.9)	137	253.4 (63.1)	5.9 (39.4)
Aspartate Aminotransferase (U/L)	Baseline	153	26.4 (6.2)		161	25.7 (5.3)		158	25.8 (5.5)	
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	136	26 (6.8)	-0.3 (5.1)	138	26.5 (16.8)	1 (17.1)	139	26.1 (6.3)	0.3 (5.5)
Bilirubin (µmol/L)	Baseline	153	5.7 (3.6)		161	5.6 (3.3)		158	5.9 (4)	
Bilirubin (µmol/L)	Week 6 (EOS)	136	5.4 (2.8)	-0.3 (2.7)	138	5.3 (3)	-0.5 (2.5)	139	5.3 (2.8)	-0.6 (2.7)
Direct Bilirubin (µmol/L)	Baseline	153	3.1 (0.3)		159	3.1 (0.3)		158	3.1 (0.5)	
Direct Bilirubin (µmol/L)	Week 6 (EOS)	136	3 (0.3)	0 (0.3)	138	3.1 (0.3)	0 (0.3)	139	3 (0.3)	0 (0.4)

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included.
Reference ranges in patients ages 6 to 11 years: ALT, 5 to 30 U/L; AST, 0 to 47 U/L; a kaline phosphatase, 155 to 420; bilirubin, 2 to 21 µmol/L, direct bilirubin, 0 to 7 µmol/L
Abbreviations: EOS = end of study; SPN = viloxazine

Table 78. Hepatobiliary Assessments (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	98	14.8 (5)		104	16.1 (8.2)		104	14.8 (8.9)	
Alanine Aminotransferase (U/L)	Week 6 (EOS)	86	15.6 (7.4)	0.8 (6.6)	96	18.1 (12.4)	1.9 (11.1)	102	14.6 (7.8)	-0.2 (6.4)
Alkaline Phosphatase (U/L)	Baseline	98	210.5 (112.9)		103	207.7 (104.9)		104	206.2 (113)	
Alkaline Phosphatase (U/L)	Week 6 (EOS)	86	207 (106.8)	-4.5 (34.3)	95	197.7 (104)	-5.6 (31.9)	101	201.1 (109.6)	-2.1 (41.6)

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		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Bilirubin (µmol/L)	Baseline	98	8.7 (6)		104	7.2 (5.7)		104	8.1 (6.4)	
Bilirubin (µmol/L)	Week 6 (EOS)	86	8.1 (7.4)	-0.7 (6.3)	96	6.2 (5)	-1.2 (3.6)	102	7.9 (6.9)	-0.3 (4.1)
Aspartate Aminotransferase (U/L)	Baseline	98	21.3 (5.8)		104	21.5 (6.2)		104	20.4 (6.2)	
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	86	21.3 (6.4)	-0.3 (4.8)	96	21.5 (7.3)	0.2 (7.5)	102	20 (5.8)	-0.4 (4.7)
Direct Bilirubin (µmol/L)	Baseline	98	3.3 (0.7)		104	3.2 (0.6)		104	3.2 (0.7)	
Direct Bilirubin (µmol/L)	Week 6 (EOS)	86	3.2 (0.6)	-0.1 (0.7)	95	3.1 (0.4)	-0.1 (0.6)	102	3.2 (0.6)	0 (0.7)

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 12 to 17 years: ALT, 5 to 20 U/L; AST, 0 to 41 U/L; alkaline phosphatase, 110 to 630 U/L; bilirubin 2 to 21 µmol/L, direct bilirubin, 0 to 7 µmol/L
Abbreviations: EOS = end of study; SPN = viloxazine

Table 79. Hepatobiliary Assessments (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Alanine Aminotransferase (U/L)	Baseline	107	14.4 (4.9)		100	15 (6.1)		103	15.7 (6.3)	
Alanine Aminotransferase (U/L)	Week 8 (EOS)	97	15.1 (6)	0.7 (6.1)	81	16.2 (10.5)	1.1 (8.4)	92	15.6 (6.6)	-0.3 (7.1)
Alkaline Phosphatase (U/L)	Baseline	107	240.2 (63.5)		100	253.6 (76.8)		103	238 (55.2)	
Alkaline Phosphatase (U/L)	Week 8 (EOS)	97	240.7 (65.8)	5.5 (42.9)	81	247 (67.3)	-1.8 (52.7)	92	246.5 (60.5)	11.5 (39.6)
Aspartate Aminotransferase (U/L)	Baseline	107	25.8 (5.4)		100	26 (5.2)		103	26.8 (6)	
Aspartate Aminotransferase (U/L)	Week 8 (EOS)	97	26.5 (8.6)	0.8 (7.7)	81	25.8 (6.4)	-0.2 (5.4)	92	26.3 (6.5)	-0.4 (5.5)
Bilirubin (µmol/L)	Baseline	107	5.5 (3.2)		100	6.1 (3.5)		103	5.8 (3.2)	

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		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Bilirubin (µmol/L)	Week 8 (EOS)	97	4.8 (2.4)	-0.7 (2.8)	81	5.7 (3.7)	-0.8 (2.9)	92	5.9 (3.6)	0.5 (2.5)
Direct Bilirubin (µmol/L)	Baseline	107	3 (0.2)		100	3.1 (0.3)		103	3.1 (0.4)	
Direct Bilirubin (µmol/L)	Week 8 (EOS)	97	3 (0.1)	0 (0.2)	81	3.1 (0.4)	0 (0.4)	92	3.1 (0.4)	0 (0.4)

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1]Unscheduled visits are not included
Reference ranges in patients ages 6 to 11 years: ALT, 5 to 30 U/L; AST, 0 to 47 U/L; a kaline phosphatase, 155 to 420 U/L; bilirubin, 2 to 21 µmol/L; direct bilirubin, 0 to 7 µmol/L
Abbreviations: EOS = end of study; SPN = viloxazine

Table 80. Hepatobiliary Assessments (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	100	15.1 (8.1)		99	14.6 (5.6)		97	14.2 (7.9)	
Alanine Aminotransferase (U/L)	Week 7 (EOS)	86	20.2 (16.5)	5 (16.2)	88	16.9 (9.6)	2.3 (9.6)	88	13.9 (6.6)	-0.5 (5.2)
Alkaline Phosphatase (U/L)	Baseline	100	206.8 (116.5)		99	223.3 (106.3)		97	204.1 (114.4)	
Alkaline Phosphatase (U/L)	Week 7 (EOS)	86	207.2 (118.3)	3.1 (36.6)	88	219.5 (109.1)	2.6 (28.8)	88	194.1 (108.6)	-8.6 (31.9)
Aspartate Aminotransferase (U/L)	Baseline	100	21.1 (6.2)		99	21.4 (5.4)		97	20.2 (5.5)	
Aspartate Aminotransferase (U/L)	Week 7 (EOS)	86	23.1 (8.8)	2.3 (9)	88	20.9 (6.5)	-0.1 (5.6)	88	19.5 (5.4)	-0.5 (4)
Bilirubin (µmol/L)	Baseline	100	7.6 (4.3)		99	8.3 (4.6)		97	8 (5.3)	
Bilirubin (µmol/L)	Week 7 (EOS)	86	6.2 (3.6)	-1.4 (3.4)	88	6.6 (3.7)	-1.8 (3.5)	88	7.7 (4.5)	-0.2 (3.8)
Direct Bilirubin (µmol/L)	Baseline	100	3.1 (0.6)		99	3.2 (0.6)		97	3.2 (0.6)	
Direct Bilirubin (µmol/L)	Week 7 (EOS)	86	3.8 (7.1)	0.7 (7)	88	3.1 (0.3)	-0.1 (0.4)	88	3.2 (0.6)	0 (0.5)

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 12 to 17 years: ALT, 5 to 20 U/L; AST, 0 to 41 U/L; alkaline phosphatase, 110 to 630 U/L; bilirubin 2 to 21 µmol/L; direct bilirubin, 0 to 7 µmol/L
Abbreviations: EOS = end of study; SPN = viloxazine

In Studies 812P301 and 812P302, no clear difference in the frequency of out of range hepatobiliary laboratory assessments between the viloxazine ER and placebo groups was

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observed. In Study 812P303, 4.9% of patients receiving viloxazine ER 400 mg had increased ALT values (compared to 2.2% of the placebo group). In Study 812P304, patients receiving viloxazine ER were more likely that patients in the placebo group to have hepatic enzyme values that were higher than the upper limit of the reference range. ALT elevations were seen in 14% of patients receiving viloxazine ER 400 mg and 11.4% of patients receiving viloxazine ER 600 mg. AST elevations were seen in 7% of patients receiving viloxazine ER 400 mg and 2.3% of patients receiving viloxazine ER 600 mg (Table 81, Table 82, Table 83, and Table 84).

Table 81. Out-of-Range Hepatobiliary Assessments (Study 812P301)

		SPN-812 ER 100 mg (N=154)					SPN-812 ER 200 mg (N=161)					Placebo (N=159)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Alanine Aminotransferase (U/L)	Baseline	153	0	0	5	3	161	0	0	3	2	158	0	0	5	3
Alanine Aminotransferase (U/L)	Week 6 (EOS)	136	0	0	7	5	138	0	0	8	6	139	0	0	5	4
Alkaline Phosphatase (U/L)	Baseline	153	8	5	4	3	161	3	2	2	1	158	3	2	3	2
Alkaline Phosphatase (U/L)	Week 6 (EOS)	136	8	6	2	2	137	4	3	1	1	137	5	4	2	2
Aspartate Aminotransferase (U/L)	Baseline	153	0	0	4	3	161	0	0	1	1	158	0	0	2	1
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	136	0	0	5	4	138	0	0	3	2	139	0	0	3	2
Bilirubin (µmol/L)	Baseline	153	0	0	1	1	161	0	0	0	0	158	0	0	2	1
Bilirubin (µmol/L)	Week 6 (EOS)	136	0	0	0	0	138	0	0	1	1	139	0	0	1	1

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 6 to 11 years: ALT, 5 to 30 U/L; AST, 0 to 47 U/L; a kaline phosphatase, 155 to 420 U/L; bilirubin, 2 to 21 µmol/L
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 82. Out-of-Range Hepatobiliary Assessments (Study 812P302)

		SPN-812 ER 200 mg (N=99)					SPN-812 ER 400 mg (N=105)					Placebo (N=104)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Alanine Aminotransferase (U/L)	Baseline	98	0	0	1	1	104	0	0	7	7	104	0	0	9	9
Alanine Aminotransferase (U/L)	Week 6 (EOS)	86	0	0	3	4	96	0	0	13	14	102	0	0	8	8
Alkaline Phosphatase (U/L)	Baseline	98	23	24	0	0	103	18	18	0	0	104	18	17	0	0
Alkaline Phosphatase (U/L)	Week 6 (EOS)	86	17	20	0	0	95	15	16	0	0	101	17	17	1	1

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		SPN-812 ER 200 mg (N=99)					SPN-812 ER 400 mg (N=105)					Placebo (N=104)				
Aspartate Aminotransferase (U/L)	Baseline	98	0	0	1	1	104	0	0	1	1	104	0	0	2	2
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	86	0	0	1	1	96	0	0	2	2	102	0	0	0	0
Bilirubin (µmol/L)	Baseline	98	0	0	5	5	104	0	0	1	1	104	0	0	5	5
Bilirubin (µmol/L)	Week 6 (EOS)	86	0	0	3	4	96	0	0	1	1	102	0	0	5	5

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 12 to 17 years: ALT, 5 to 20 U/L; AST, 0 to 41 U/L; alkaline phosphatase, 110 to 630 U/L; bilirubin, 2 to 21 µmol/L
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 83. Out-of-Range Hepatobiliary Assessments (Study 812P303)

		SPN-812 ER 200 mg (N=107)					SPN-812 ER 400 mg (N=100)					Placebo (N=103)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Alanine Aminotransferase (U/L)	Baseline	107	0	0	2	2	100	0	0	4	4	103	0	0	2	2
Alanine Aminotransferase (U/L)	Week 8 (EOS)	97	0	0	1	1	81	0	0	4	5	92	0	0	2	2
Alkaline Phosphatase (U/L)	Baseline	107	5	5	2	2	100	4	4	2	2	103	4	4	0	0
Alkaline Phosphatase (U/L)	Week 8 (EOS)	97	6	6	2	2	81	2	3	1	1	92	4	4	0	0
Aspartate Aminotransferase (U/L)	Baseline	107	0	0	1	1	100	0	0	1	1	103	0	0	1	1
Aspartate Aminotransferase (U/L)	Week 8 (EOS)	97	0	0	3	3	81	0	0	2	3	92	0	0	1	1
Bilirubin (µmol/L)	Baseline	107	0	0	0	0	100	0	0	0	0	103	0	0	0	0
Bilirubin (µmol/L)	Week 8 (EOS)	97	0	0	0	0	81	0	0	1	1	92	0	0	1	1

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 6 to 11 years: ALT, 5 to 30 U/L; AST, 0 to 47 U/L; a kaline phosphatase, 155 to 420 U/L; bilirubin, 2 to 21 µmol/L
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

Table 84. Out-of-Range Hepatobiliary Assessments (Study 812P304)

		SPN-812 ER 400 mg (N=100)					SPN-812 ER 600 mg (N=99)					Placebo (N=97)				
Parameter	**Visit**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**	**N**	**Low**	**%**	**High**	**%**
Alanine Aminotransferase (U/L)	Baseline	100	0	0	8	8	99	0	0	4	4	97	0	0	6	6
Alanine Aminotransferase (U/L)	Week 7 (EOS)	86	0	0	12	14	88	0	0	10	11	88	0	0	4	5

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		SPN-812 ER 400 mg (N=100)					SPN-812 ER 600 mg (N=99)					Placebo (N=97)				
Alkaline Phosphatase (U/L)	Baseline	100	18	18	0	0	99	16	16	0	0	97	21	22	1	1
Alkaline Phosphatase (U/L)	Week 7 (EOS)	86	16	19	1	1	88	15	17	0	0	88	19	22	0	0
Aspartate Aminotransferase (U/L)	Baseline	100	0	0	1	1	99	0	0	0	0	97	0	0	0	0
Aspartate Aminotransferase (U/L)	Week 7 (EOS)	86	0	0	6	7	88	0	0	2	2	88	0	0	0	0
Bilirubin (µmol/L)	Baseline	100	0	0	2	2	99	0	0	3	3	97	0	0	1	1
Bilirubin (µmol/L)	Week 7 (EOS)	86	0	0	0	0	88	0	0	1	1	88	0	0	3	3

Source: ad b.xpt; Software, R. Created by the Clinical Data Scientist.
[1] Unscheduled visits are not included
Reference ranges in patients ages 12 to 17 years: ALT, 5 to 20 U/L; AST 0 to 41 U/L; alkaline phosphatase, 110 to 630 U/L; bilirubin, 2 to 21 µmol/L.
Abbreviations: EOS = end of study; ER = extended release; SPN = viloxazine

No patients receiving viloxazine ER in the development program met the criteria for drug-induced liver injury (increases >3-fold the ULN for AST or ALT with a total bilirubin level of >2-fold the ULN and an alkaline phosphatase level of <2-fold the ULN). Patients receiving viloxazine ER in the controlled phase 3 clinical studies were more likely to experience a shift in liver transaminases from within the reference range to greater than the upper limit of the reference range (Table 37). However, elevation of liver transaminases ≥3-fold the ULN occurred rarely in the phase 3 clinical trials. An 8-year-old male patient (301-18-1001) in Study 812P301 had baseline ALT and AST levels within the reference range but an ALT of >3-fold the ULN and an AST of >5-fold the ULN at the EOS visit. However, the EOS visit was conducted 118 days after the last intake of study medication (the patient was lost to follow up during this period) and the investigator assessed the liver transaminase elevations to be unlikely related to viloxazine ER.

Table 85 (provided by the Applicant) provides an overview of patients who had marked elevations in liver transaminase, bilirubin, and alkaline phosphatase levels in the phase 2 and phase 3 controlled studies. Overall, these elevations were uncommon and did not appear to be dose-related.

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Table 85. Number of Subjects with Abnormal Liver Enzymes and Liver Function Tests (Studies 812P202, 812P301, 812P302, 812P303, and 812P304)

Parameter	Placebo N=487 n (%)	100mg N=202 n (%)	200mg N=415 n (%)	300mg N=48 n (%)	400mg N=354 n (%)	600mg N=99 n (%)	All SPN-812 N=1117 n (%)
ALT[a]							
>3× ULN	0	0	1 (0.3)	0	2 (0.6)	0	3 (0.3)
>5× ULN	0	0	0	0	0	0	0
>10× ULN	0	0	0	0	0	0	0
AST[a]							
>3× ULN	0	0	1 (0.3)	0	0	0	1 (0.1)
>5× ULN	0	0	1 (0.3)	0	0	0	1 (0.1)
>10× ULN	0	0	0	0	0	0	0
ALT or AST[a]							
>3× ULN	0	0	1 (0.3)	0	2 (0.6)	0	3 (0.3)
>5× ULN	0	0	1 (0.3)	0	0	0	1 (0.1)
>10× ULN	0	0	0	0	0	0	0
Total bilirubin[a]							
>1.5× ULN	1 (0.2)	0	2 (0.5)	0	1 (0.3)	0	3 (0.3)
>2× ULN	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	2 (0.2)
ALP[b]							
>1.5× ULN	0	0	0	0	0	0	0
>2× ULN	0	0	0	0	0	0	0
ALT or AST >3× ULN and:[a, c]							
Total bilirubin >2× ULN	0	0	0	0	0	0	0
Total bilirubin >2× ULN and ALP <2× ULN	0	0	0	0	0	0	0

ADHD=Attention-Deficit/Hyperactivity Disorder; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; ULN=upper limit of normal.

Source: Applicant's Integrated Summary of Safety, Table 45, pages 100–101

Postmarketing Data

A review of the FAERS database conducted by the Division of Pharmacovigilance identified 4 reports of liver injury possibly associated with the previously marketed, immediate-release formulation of viloxazine.

- 3680944: 76-year-old male with a medical history of prostate cancer who was hospitalized for stroke. He had been prescribed clopidogrel for one month, carbamazepine for one year and one month, viloxazine for one year and two months, gonadorelin for two years, and bicalutamide for two years. On admission, laboratory tests showed hepatocellular damage. Abdominal ultrasound was unremarkable and HIV and cytomegalovirus (CMV) serologies were negative. All drugs were discontinued, and laboratory tests normalized within one week. All prescribed medications were considered possible causes of liver injury.

- 3805941: Female patient (age unknown) hospitalized for hepatitis. The patient was prescribed irbesartan, viloxazine, zolpidem, fluoxetine, atorvastatin, and paracetamol.

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Hepatic ultrasound was within normal limits and hepatitis A, B, C, and HIV serologies were negative. The event was assessed as possibly related to irbesartan.

- 3916193: 82-year-old female patient who developed fulminant hepatitis. The patient had a medical history of Horton's disease, hypertension, cardiac insufficiency, depression, and atrial fibrillation. The patient received viloxazine ER from (b) (6) . Citalopram was started on (b) (6). Other concomitant medications included fluindione, prednisone, metoprolol, acenocoumarol, alprazolam, and amiodarone. The hepatitis event occurred on (b) (6). The patient presented to the hospital with tachycardia and atrial fibrillation. Laboratory investigations revealed elevated AST, ALT, and prothrombin levels. Abdominal ultrasound revealed a lithiastic gall bladder and moderate distention of the bile duct. The patient fully recovered. The possibility of hepatitis due to citalopram or viloxazine was considered, as was acute hepatic ischemia.

- 4078413: 80-year-old male with a medical history of hyperthyroidism who was hospitalized for a general physical health condition that was associated with a decrease in weight. The patient was prescribed flecainide, viloxazine, clopidogrel, spironolactone, and furosemide. On admission, the laboratory assessments were remarkable for increased levels of gamma glutamyltransferase, alkaline phosphatase, and liver transaminases. The prescribed medications were discontinued, and the patient recovered.

Although the possibility of liver injury associated with viloxazine ER in the FAERS cases cannot be ruled out, the cases are confounded by the presence of other medications and underlying medical conditions.

The EudraVigilance database also includes reports of Hepatobiliary Disorders, including cholestasis, hepatitis, hepatitis cholestatic, hepatitis toxic, hepatocellular injury, and hyperbilirubinemia. Two of the reported cases of hepatitis were fatal. Vigibase contains 53 reports of hepatobiliary adverse reactions. EudraVigilance and Vigibase may contain duplicate reports, so it is not clear how many unique cases are represented in these databases. Additional clinical information about the case reports, including concomitant medical conditions and concurrent medications, was not available.

The list of adverse reactions associated with immediate-release viloxazine ER in European labeling includes elevations of transaminases but no other references to liver injury.

Conclusion

Adverse events in the Hepatobiliary SOC were not reported in the controlled trials of viloxazine ER. The laboratory data from the controlled clinical trials indicate that patients receiving viloxazine ER may be more likely to experience clinically meaningful increases in liver transaminases. However, no case of drug-induced liver injury was identified, and most transaminase elevations were moderate (i.e., elevations <3-fold the ULN). Hepatic injury in the context of exposure to immediate-release viloxazine has been reported in postmarketing databases. In the cases for which clinical information is available, the reports are confounded by other medications and medical conditions that could have plausibly contributed to the liver injury. Of note, no case of severe liver injury was observed in the clinical trials for atomoxetine (which is mechanistically similar to viloxazine ER), but severe liver injury associated with

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atomoxetine has been reported in the postmarketing period. The currently available data do not establish that viloxazine ER is associated with hepatotoxicity. No labeling or other regulatory actions are indicated at this time. However, routine postmarketing surveillance for adverse reactions may provide additional information on a potential risk of liver injury with viloxazine exposure over time.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

The AUC of viloxazine increases by ~90% after administration to patients with severe renal impairment (estimated glomerular filtration rate [eGFR] ≤30 mL/min/1.73 m^2, MDRD) without dialysis. In severely renal-impaired patients, the dose is recommended to not exceed 200 mg. Dosage adjustment is not recommended for patients with mild or moderate renal impairment.

Hepatic Impairment

Viloxazine ER is not recommended to be administered to patients with hepatic impairment because the effect in these patients has not been studied.

Other Intrinsic Factors

The primary cytochrome P450 (CYP) enzyme responsible for metabolism of viloxazine is CYP2D6. There is no clinically relevant difference in exposure between CYP2D6 poor (PM) and extensive (EM) metabolizers. Dose adjustment is not recommended.

Based on the population pharmacokinetic (PK) analysis, gender and race do not exert a clinically significant effect. Therefore, dose adjustment according to gender or race is not recommended. Based on the population PK analysis, a decrease in weight results in an increase in exposure. Pediatric patients ages 6 to 11 years exhibited a 40% to 50% increase in exposure compared to those ages 12 to 17 years.

The effects of intrinsic factors on viloxazine are presented in Figure 24.

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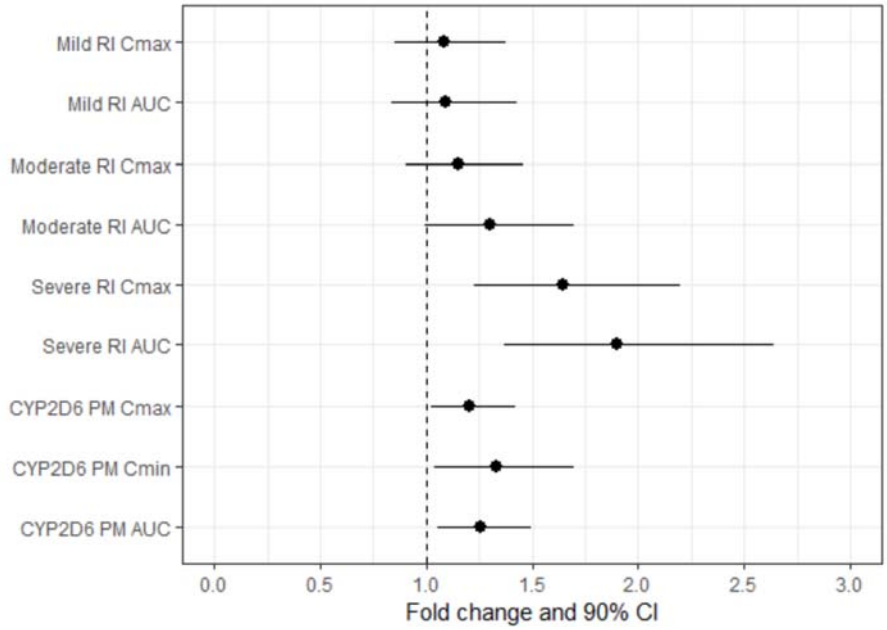
Figure 24. Effects of Intrinsic Factors on Viloxazine



Source: Reviewer's analysis
Abbreviations: AUC = area under the curve; RI = renal impairment

8.2. Drug Interactions

Viloxazine increases the AUC of caffeine (a sensitive CYP1A2 substrate) by up to 5-fold. Therefore, viloxazine ER should be contraindicated in patients taking sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (e.g., alosetron, caffeine, doluxetine, ramelteon, tasimelteon, tizanidine, theophylline). The effect of viloxazine on moderately sensitive CYP1A2 substrates has not to date been evaluated. Coadministration of viloxazine with moderately sensitive CYP1A2 substrates is not recommended; indeed, dose reduction may be warranted (e.g., clozapine, pirfenidone). Refer to the full prescribing information for details on concomitant use of these drugs with strong CYP1A2 inhibitors.

There is no clinically significant interaction between viloxazine and d-amphetamine or methylphenidate.

The effects of viloxazine on other drugs are presented in Figure 25. Additionally, the effects of d-amphetamine and methylphenidate on viloxazine are outlined in Figure 26.

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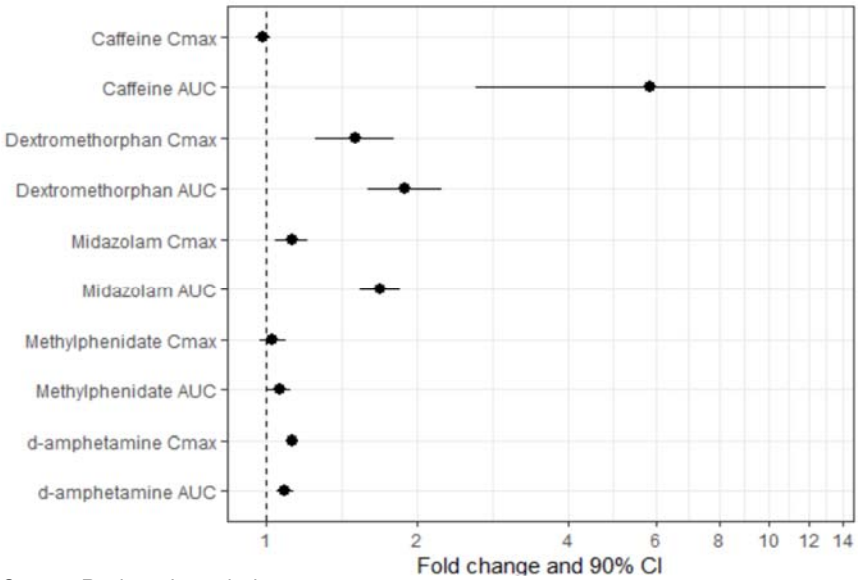
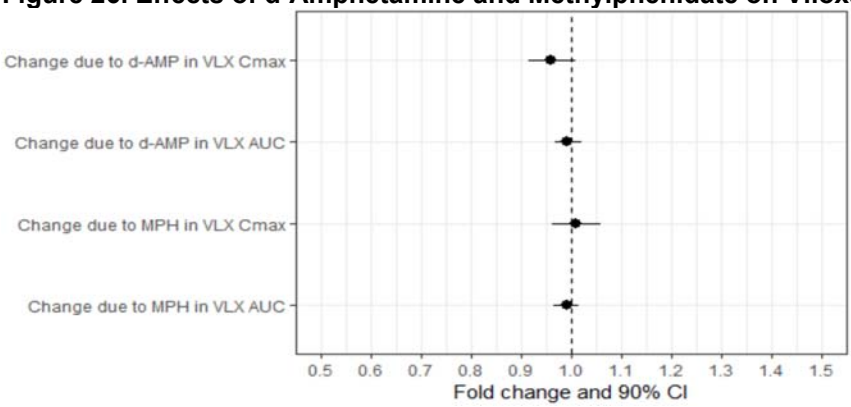
Figure 25. Effect of Viloxazine on Other Drugs



Source: Reviewer's analysis
Abbreviations: AUC = area under the curve

Figure 26. Effects of d-Amphetamine and Methylphenidate on Viloxazine



Source: Reviewer's analysis
Abbreviations: AUC = area under the curve; d-AMP = amphetamine; MPH = methylphenidate; VLX = viloxazine

8.3. Plans for Pediatric Drug Development

The viloxazine ER development program has evaluated safety and efficacy in pediatric patients 6 to 17 years of age. At the July 28, 2017 end-of-phase 2 meeting, the Agency agreed that pediatric patients ages 4 to 5 years could be studied in the postmarketing period. The agreed Initial Pediatric Study Plan includes a waiver of the requirement for studies in pediatric patients under age 4 years and a deferral of a safety and efficacy study in pediatric patients ages 4 to <6 years. The Applicant has also committed to a 6-month, open-label safety study in patients 4 to <6 years of age. The Applicant plans to conduct a phase 3 study to evaluate the safety and efficacy of viloxazine ER 100 mg in patients ages 4 to 5 years of age with ADHD (Study 812P401). The Applicant has submitted the draft protocol as IND 108864. Patients who complete this study will be eligible to enter the open-label safety extension (812P310). Use of medications approved for ADHD is anticipated in pediatric patients ages 4 to 5 years. The review team therefore recommends that the completion of a safety and efficacy study and a long-term safety study in

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patients 4 to <6 years of age should be a postmarketing safety requirement under the Pediatric Research Equity Act.

Juvenile Animal Studies

Viloxazine was administered orally to juvenile rats from postnatal day (PND) 23 to 79 at doses of 43, 130, and 217 mg/kg/day, which are approximately 1-, 2-, and 3-fold, respectively, the MRHD of 400 mg based on mg/m^2 in children. Viloxazine at 217 mg/kg/day decreased body weight, weight gain, and food consumption in both sexes. Sexual maturation, reproductive capacity, and learning and memory were not affected. The NOAEL for juvenile toxicity is 130 mg/kg/day, which is approximately 2-fold the MRHD based on mg/m^2 in children.

8.4. Pregnancy and Lactation

Embryofetal Developmental Toxicity

Viloxazine was administered orally to pregnant rats during the period of organogenesis at doses of 13, 33, and 82 mg/kg/day, which are less than, equal to, and 2-fold, respectively, the MRHD of 400 mg based on mg/m^2. Viloxazine did not cause maternal toxicity at doses up to 82 mg/kg/day. However, at a dose of 82 mg/kg/day, viloxazine increased early and late resorptions, delayed fetal development, and caused low incidences of fetal malformations or anomalies (craniorachischisis, missing cervical vertebrae, and morphological changes associated with hydranencephaly). The NOAEL for fetal toxicity and malformation is 33 mg/kg/day, which is approximately equal to the MRHD, based on mg/m^2.

Viloxazine was administered orally to pregnant rabbits during the period of organogenesis at doses of 43, 87, and 130 mg/kg/day, which are approximately 4-, 7-, and 11-fold, respectively, the MRHD of 400 mg based on mg/m^2. Viloxazine decreased maternal body weight, weight gain, and food consumption at doses ≥87 mg/kg/day but did not cause fetal toxicity at doses up to 130 mg/kg/day. The NOAELs for maternal and fetal toxicity are 43 and 130 mg/kg/day, respectively, which are approximately 4- and 11-fold, respectively. the MRHD based on mg/m^2.

Pre- and Postnatal Developmental Toxicity

Viloxazine was administered orally to pregnant rats during gestation and lactation at doses of 43, 87, and 217 mg/kg/day, which are approximately 1-, 2-, and 5-fold, respectively, the MRHD of 400 mg, based on mg/m^2. Viloxazine caused maternal toxicity of decreased body weight, weight gain, and food consumption at doses ≥87 mg/kg/day and maternal death at 217 mg/kg/day. At these maternally toxic doses, viloxazine reduced the rate of live birth, decreased viability, and delayed growth and sexual maturation without affecting learning and memory in the offspring. The NOAEL for maternal and developmental toxicity is 43 mg/kg/day, which is approximately equal to the MRHD, based on mg/m^2.

Viloxazine was administered orally to pregnant mice during gestation and lactation at doses of 13, 33, and 82 mg/kg/day, which are approximately less than, equal to, and 2-fold the MRHD of 400 mg, respectively, based on mg/m^2. Viloxazine at 82 mg/kg/day during the gestation period caused maternal death and decreased body weight in the offspring. The NOAEL for both

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maternal and developmental toxicity is 33 mg/kg/day, which is less than the MRHD, based on mg/m^2.

Although no direct measurement of viloxazine concentration in milk was conducted, circulating viloxazine was present in rat pups as early as PND 4; therefore, ***viloxazine is likely present in rat milk***.

It should be noted that in both rat and mouse, administration of viloxazine during the late gestation period caused maternal death at doses equal to or less than the MRHD based on mg/m^2 (mouse) or the AUC (rat). ***Therefore, dosing of viloxazine during pregnancy is not recommended from a nonclinical perspective.***

See the full review in DARRTS: Date 22 June 2020; Ref ID, 4629249 by Catherine Roca, MD and Miriam Dinatale DO of the Division of Pediatric and Maternal Health.

The clinical data are inadequate to fully characterize the risks from viloxazine during pregnancy and lactation. Therefore, postmarketing requirements (PMRs) for a single-arm pregnancy study and a milk-only lactation study for viloxazine will be issued to the Applicant. Labeling recommendations were made by the Division of Pediatrics and Maternal Health (DPMH).

Pregnancy

Despite several decades of use as an antidepressant in several European countries, clinical data related to viloxazine are limited to approximately 25 cases and are inadequate to establish a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There were no reports of maternal death in any of these cases. Given the unexplained maternal deaths in the nonclinical data and the availability of alternative treatments for ADHD, DPMH recommends that viloxazine be discontinued when pregnancy is recognized unless the benefits of therapy outweigh the potential risk to the mother. The previous lack of use in pregnant populations and labeling recommendation that discourages use during pregnancy make recruitment of a sufficient number of exposed pregnancies for a pregnancy registry unlikely. Therefore, a single-arm pregnancy safety study is recommended to evaluate the effect of viloxazine on pregnancy outcomes.

Lactation

There are no data available on the presence of viloxazine in human milk or on its effect on the breastfed infant or on lactation. Because there is a possibility that viloxazine will be used in females of reproductive potential, DPMH recommends that a milk-only (no infant exposure) study be performed to determine if viloxazine is present in breast milk.

Females and Males of Reproductive Potential

There are no human data on the effect of viloxazine on fertility. Animal studies did not demonstrate an adverse effect on fertility; therefore, Subsection 8.3 will not be included in the labeling.

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9. Product Quality

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

No financial disclosure concerns with the potential to influence the interpretation of safety or efficacy were uncovered.

Inspections were requested of the study sites (which enrolled a large number of patients relative to other sites) listed in Table 86. The Office of Scientific Investigations (OSI) identified one study site (Dr. Lopez-Brignoni) where there were dosing irregularities. OSI recommended that the Division consider excluding the data from this site from the per-protocol analysis. The Division included these data (in keeping with the randomization principle), but conducted a sensitivity analysis that determined that the data from this site did not change the overall study results. Please see the OSI consultative review for full details of the inspection results.

Table 86. Clinical Site Inspections (Studies 812P301, 812P302, 812P303, and 812P304)

Site	Protocol ID	Number of Subjects	Study Title
Site 006 Robert Bond Molpus, MD	812P301	53	Evaluation of SPN-812 ER 100 and 200 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
	812P302	28	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
Site 108 James E. Cain, MD	812P302	23	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
Site 121 Evelyn Lopez-Brignoni, MD	812P302	14	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial

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Site	Protocol ID	Number of Subjects	Study Title
Site 9 Andrea Marraffino, PhD	812P303	33	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
	812P304	31	Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; SPN = viloxazine

11. Advisory Committee Summary

Not applicable.

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III. Appendices

12. Summary of Regulatory History

The Agency has had interactions with the Applicant since the pre-IND stage. The Applicant has participated in a pre-IND meeting, end-of-phase 2 meeting, and pre-NDA meeting. The Agency has also provided guidance regarding the pediatric study plan and the assessment of QT interval effects.

During the March 2010 pre-IND meeting, the Agency advised the Applicant about required carcinogenicity studies as well as pharmacokinetic and other clinical pharmacology studies. The Agency also provided guidance about the development of a modified release form. The Applicant submitted a 2009 consultation report that investigated the reasons for viloxazine's withdrawal from the European market and confirmed that the drug was not withdrawn because of concerns over safety (Contracted Research Results to Determine Regulatory Status of Viloxazine in Selected European Countries, Module 1.13.10).

A second pre-IND meeting was held in June 2013. The Applicant had been previously advised that a laboratory classroom study would be necessary; during this meeting, the Agency clarified that in-classroom testing would no longer be required. The Agency agreed that that the ADHD Rating Scale–IV (ADHD-RS-IV) would be acceptable as a primary endpoint in efficacy studies. The Applicant also indicated that that the Clinical Global Impression-Improvement (CGI-I) scale would serve as a secondary endpoint. However, the Agency did not offer an opinion about the appropriateness of the CGI-I as an endpoint at that time.

The Applicant submitted the IND on June 2015, under which the studies were allowed to proceed beginning in July 2015.

The Agency provided further guidance on the phase 3 development program during an end-of-phase 2 meeting held in July 2017. The Agency agreed that safety and efficacy in patients ages 4 to 6 years could be evaluated in the postmarketing setting. The Agency also agreed that an updated version of the ADHD Rating Scale, the ADHD-RS-5, would be an appropriate primary endpoint in the phase 3 efficacy and safety studies. Although the Agency had previously advised that evaluations for ophthalmologic changes and urinary retention would be required because of warnings contained in the French labeling for viloxazine, the Applicant pointed out that the warnings were based on theoretical concerns and not on human safety findings. The Agency subsequently agreed that ophthalmologic and urinary tract evaluations would not be needed. The Agency recommended CYP2D6 genotyping in the phase 3 clinical trials and a total QT study. The Applicant additionally agreed to conduct a study to assess the PK of viloxazine ER in patients with renal impairment. The Agency agreed that nonclinical and clinical abuse potential studies were not necessary but advised that the Applicant monitor for abuse-related events.

The Agency discussed the ICH E1 guideline for long-term exposure (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for the Long-Term Treatment of Non-Life-Threatening Conditions), which recommends a minimum total exposure of 1000 to 1500

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patients, with at least 300 patients exposed for 6 months and 100 patients exposed for 12 months at the relevant doses.

The Agency noted that convulsions had occurred in multiple species in nonclinical studies. The Agency expressed concern over the lack of a safety margin between the no observed adverse effect level (NOAEL) exposures for seizures in animals and the blood levels already attained in clinical trials. After the meeting the Applicant submitted published literature on the clinical safety of viloxazine. The information in the document was derived from a literature search for relevant clinical studies and case reports. One of the included studies reviewed 120 viloxazine clinical trials and calculated the incidence of seizures associated with viloxazine treatment to be 0.01% (Edwards and Glen-Bott 1984). The Agency agreed after review of the submitted data that there did not appear to be a clear seizure risk associated with viloxazine in humans.

A pre-NDA meeting was held in July 2019, during which the Agency agreed that the completed clinical and nonclinical studies could support NDA filing. The Agency also agreed that the completed reproductive studies and the analysis of the metabolic profile were acceptable for filing. The Applicant confirmed that the final to-be-marketed formulation was used in key efficacy and clinical pharmacology studies. The Agency advised that a phototoxicity study should be completed and that a drug-drug interaction study with a strong CYP2D6 inhibitor may be required. The Agency expressed concern about the lack of a hepatic impairment study but after the meeting agreed that this study could be deferred (b) (4). The Agency also expressed reservations about the use of the CGI-I as a key secondary endpoint in the phase 3 trials because of its susceptibility to recall bias.

The Agreed Pediatric Study Plan was submitted in January 2019 and includes a waiver for children under the age of 4 years and deferral of one safety and efficacy study in children ages 4 to <6 years.

In October 2019, the Agency advised that Applicant's completed assessments of QT interval effects were adequate for NDA submission.

The Applicant submitted the 505(b)(1) NDA on November 8, 2019.

13. Pharmacology Toxicology: Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

All nonclinical studies were reviewed under the NDA (see Section 13.2).

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13.2. Individual Reviews of Studies Submitted to the NDA

Overall Comments on the Legacy Studies

Many of the nonclinical legacy general toxicity and reproductive and developmental toxicity studies were completed in the 1970s, before the good laboratory practice (GLP) regulation was implemented; therefore, they are not in full compliance with GLP. These studies were conducted to support the original marketing application (for the indication of major depressive disorder) in Europe and were accepted by the Agency during the current IND development stage to support large-scale clinical trials. Nevertheless, after evaluating the study reports, I did not identify any significant issues that would compromise the quality of the studies or the interpretation of the data; therefore, these studies are considered adequate and acceptable for the NDA review. For equivocal or less clearly defined findings, a more conservative strategy was adopted to define NOAELs at the next lower doses at which there were clearly no drug-related findings.

In addition, toxicokinetic (TK) measurements were not conducted in many of the legacy studies; therefore, body surface area was used to calculate safety margins.

13.2.1. Drug Impurities and Excipients

13.2.1.1. Impurities

The Applicant evaluated a total of 19 viloxazine-related impurities for mutagenic potential by quantitative structure-activity relationship ((Q)SAR) using the Derek Nexus and Leadscope Model Applier systems (Study 812V-Tox2019-044). An independent (Q)SAR analysis was conducted by the FDA Computational Toxicology Analysis Group. The conclusions from the Applicant's and Agency's analyses are in agreement, and a total of 7 mutagenic impurities were identified.

Based on the (Q)SAR analysis, the Applicant proposed a specification limit of (b) (4) ppm for individual mutagenic impurities ((b) (4) , which corresponds to (b) (4) µg/day for a maximum daily dose of 800 mg viloxazine free base.[3] In addition, the sum of the seven mutagenic impurities is limited to (b) (4) ppm, corresponding to a limit of (b) (4) µg/day. The

[3] The proposed limits of (b) (4) ppm and (b) (4) ppm for individual and total amount mutagenic impurities are presented as relative to viloxazine hydrochloride salt. At the maximal daily dose of 800 mg viloxazine free base, which is equivalent to 923 mg of viloxazine hydrochloride salt, the corresponding limits are (b) (4) µg/day and (b) (4) µg/day for individual and total amounts of impurities, respectively. The maximum recommended daily dose for the current pediatric ADHD indication is 400 mg/day.

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proposed limits are consistent with the ICH M(7) guideline and are adequate from a nonclinical safety perspective. Other nonmutagenic impurities are controlled per ICH Q3(A)&(B) guidance.

13.2.1.2. Excipients

There are no novel excipients of safety concern in the drug product. The excipients are either compendial (USP or NF monograph), controlled at levels lower than those in the FDA inactive ingredient database, or generally recognized as safe.

13.2.2. Pharmacology

13.2.2.1. Primary Pharmacology

The Applicant conducted multiple in vitro screening assays (Studies 809V-Tox2007-001a and -001b, and 809V-Tox2007-019-101027606) to investigate the binding of viloxazine to various receptors, transporters, and enzymes. Racemic viloxazine[4] at concentrations up to 10 µM showed binding affinity for the adrenergic β_2, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors and the norepinephrine transporter (NET) with K_i values of 1.1, 4.5, 2.3, 3.9, 6.4, 1.2, and 0.63 µM [5], respectively. At 100µM, viloxazine showed weak binding to a large number of enzymes and receptors (Study 812V-Pharm2018-035); however, given that the expected maximum plasma concentration (C_{max}) at the maximum recommended human dose (MRHD) of 400 mg is about 3.9 µg/mL (~16µM) or 0.78 µg/mL (~ 3µM) when adjusted for 80% protein binding, the clinical relevance of binding at such a high concentration appears limited. In another in vitro assay (812V-Tox2016-027), 5-hydroxyviloxazine, a human metabolite of viloxazine, showed binding affinity for the MT3 (melatonin receptor 3), 5-HT_{2B}, 5-HT_{2c}, and 5-HT_3 receptors; the NET; and the COX2 enzyme (66.4%, 54%, 82.5%, 54.1%, 96.9%, and 50.9% binding at 10µM, respectively).

In assays to differentiate the binding affinity of viloxazine isomers (Studies 809V-Tox2007-043, -044, and -051), R(+)- and S(-)-viloxazine generally showed similar binding profiles. Specifically, at 10µM, both R(+)- and S(-)-viloxazine showed binding affinity for the β_2, 5-HT_{2B} receptors, CYP1A2, and NET, with S(-)-viloxazine showing higher affinity for NET (K_i 0.09µM) relative to R(+)-viloxazine (K_i 1.9µM). In addition, R(+)- and S(-)-viloxazine showed binding affinity for the β_1 and 5-HT_{2C} receptors, respectively. None (R(+)-, or S(-)-viloxazine, or the racemic mixture) showed significant binding affinity for the neuronal α4β2 or α7 nicotinic receptors (Study 809V-Tox2008-007).

In follow-up in vitro functional assays (Studies 809V-Tox2007-001c and 812V-Pharm2019-001), racemic viloxazine inhibited norepinephrine (NE) uptake with a half maximal inhibitory concentration (IC_{50}) of 0.2µM, suggesting that viloxazine is a norepinephrine reuptake inhibitor. However, when tested in vitro for serotonergic activity (Studies 812V-Tox2018-007 and 812V-Pharm2019-001), viloxazine showed both weak agonist and antagonist activity at the 5-HT_{2B} receptor. In addition, viloxazine showed weak agonist activity at the 5-HT_{2C} receptor and weak

[4] Unless specified, viloxazine, when used alone in this review, stands for a racemic viloxazine mixture, whereas the R and S racemates are presented as R(+)-viloxazine and S(-)-viloxazine, respectively.

[5] Individual K_i, IC_{50}, or EC_{50} values of the same receptor may vary in different assays; however, they were generally in the same range; therefore, representative values from one study are presented.

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antagonist activity at the 5-$HT_{1B,}$ and 5-HT_7 receptors (Table 87). The *in vitro* activities of R(+)-, S(-)-viloxazine, and the racemic mixture, were generally similar (Studies 809V-Tox2007-035, -050, and SUP-2007-001a). In an ex vivo assay in the rat stomach fundus (Study 1-1027933-0), viloxazine at concentrations up to 30µM did not show any significant agonist or antagonist activity at the 5-HT_{2B} receptor, relative to the reference compounds, α-methyl-5-HT (agonist) and SB206553 (antagonist). Given the inconsistent findings for the serotonin receptors, there is inadequate evidence to support a serotonergic mechanism of action for viloxazine.

In male Sprague–Dawley rats (Studies 812V-Pharm2019-023 and 018), after a single intraperitoneal administration of 50 mg/kg, viloxazine increased the norepinephrine (NE), dopamine (DA), and serotonin (5-HT) levels in interstitial fluid collected from the prefrontal cortex, nucleus accumbens, and amygdala. Glutamate and gamma-aminobutyric acid levels were largely unaffected. The peak increases in the NE, DA, and 5-HT levels generally correlated with the C_{max}/ time to maximum concentration (T_{max}) of viloxazine, which were 12.7 µg/mL and 60 minutes, respectively (higher than the clinical C_{max} of 3.9 µg/mL at the MRHD of 400 mg).

In summary (Table 87), pharmacology studies showed that viloxazine inhibits NE reuptake and increases the brain NE level by inhibiting NET; however, the evidence is inadequate to support a clear drug effect on serotonin receptors.

Table 87. Summary of the Pharmacological Activity of Viloxazine at Various Receptors and Transporters

Target Receptor	In Vitro Binding (K_i, µM)	In Vitro Functional Assay[1]		In Vivo
		Agonist	Antagonist	
NET	0.63	No activity	Antagonist, IC_{50}=0.2µM	↑NE, 5-HT, and DA levels in rat brain (pre-frontal cortex, nucleus accumbens, and amygdala)
5-HT_{1A}	4.5	No activity	Weak antagonist, IC_{50}=17.5µM	
5-HT_{1B}	2.3	No activity	weak antagonist, IC_{50}=18µM	
5-HT_{2B}	3.9	No activity or agonist EC_{50}=1 µM	No activity or weak antagonist, IC_{50}=27µM	
5-HT_{2C}	6.4	No activity or agonist EC_{50}=1.6 µM	No activity	
5-HT_7	1.2	No activity or weak agonist, EC_{50}=32 µM	Weak antagonist, IC_{50}=100µM	
β_2	1.1	No activity	antagonist, IC_{50}=10µM	
DAT[2]	>100	ND	ND	
SERT[2]	17. 30	ND	Negligible antagonist activity IC_{50}=257µM	

Source: Modified/reformatted based on the data in the Applicant's study reports
[1] Depending on the assay, viloxazine showed inconsistent activity at various 5-HT receptors in functional assays, ranging from no activity to agonist and antagonist activity
[2] Binding affinity data based on published literature (Tatsumi et al. 1997)
Abbreviations: 5-HT = serotonin; DA = dopamine; ND = not determined due to minimal binding affinity at the transporter; NE = norepinephrine

In addition to the studies described above, the Applicant also referred to several published studies (Greenwood 1975; Pinder et al. 1977) that discuss the in vivo pharmacologic effects of viloxazine. In animals, viloxazine, similar to tricyclic antidepressants and benzodiazepines, exhibited central nervous system (CNS) depressive effects, such as decreased body temperature and locomotor activity, and an elevated seizure threshold. However, in the nonclinical studies in the current NDA package, chronic administration of viloxazine was associated with an increased

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incidence of convulsions in multiple animal species. Therefore, the anticonvulsive activity of viloxazine is questionable.

13.2.2.2. Secondary Pharmacology

No dedicated secondary pharmacology studies were submitted in this NDA. The off-target binding of viloxazine was investigated as part of the primary pharmacology program.

Except for those discussed in the primary pharmacology section, viloxazine did not show significant binding to several receptors, transporters, and enzymes in in vitro screening assays. In addition, viloxazine, at concentrations up to 100µM, did not show significant activity on the voltage-gated calcium channel. However, viloxazine induced a dose-dependent increase in the inhibition of the sodium channel with an IC_{50} of 18µM (15.7%, 34.2%, and 82.9% inhibition at 1, 10, and 100µM, respectively) (Study 812V-Pharma2019-002). Viloxazine also weakly inhibited serotonin uptake with an IC_{50} of 257µM (Study 812V-Pharm2019-003). Because the clinical C_{max} is less than 20µM, viloxazine at clinically relevant levels exerts a negligible serotonergic effect via SERT inhibition.

13.2.2.3. Safety Pharmacology

13.2.2.3.1. Central Nervous System

In Sprague-Dawley rats, after a single oral dose at 0 (control vehicle, water), 25, 100, and 400 mg/kg (n=5/sex/group, Study 809V-2007-022, GLP), viloxazine-related CNS effects included mydriasis at ≥100 mg/kg; decreased body temperature at 400 mg/kg; and decreased approach response at 400 mg/kg. The pupillary and body temperature response is likely associated with the adrenergic pharmacology of the drug as an NE reuptake inhibitor (Simmonds and Iversen 1969), whereas the decreased approach response is likely due to mydriasis and decreased visual acuity, rather than a direct drug effect, because other tactile responses are not affected.

The NOEL for CNS safety pharmacology is 25 mg/kg in rat.

13.2.2.3.2. Cardiovascular System

In vitro hERG Inhibition Assay

In an in vitro hERG assay (Study 809V-Tox2007-028, GLP), viloxazine dose-dependently inhibited hERG potassium currents with an IC_{50} value of 67.7µM. The percent inhibition was 8.6%, 28.4%, 59.7%, and 87.2% at 10, 30, 100, and 300µM viloxazine, respectively.

In Vivo Cardiovascular Safety Pharmacology Study

In telemetry-instrumented male conscious dogs (Study 809V-Tox2007-031, GLP), after a single oral dose (capsule) of viloxazine at 0 (control, empty capsule), 5, 25, and 50 mg/kg (n=4, Latin square design) there were no drug-related changes in ECG (PR, QRS, QT, or QTcF) or blood pressure (diastolic, systolic, or mean arterial pressure) parameters relative to controls. Heart rate was slightly decreased at all doses without a clear dose-response (decreases of 4%, 9%, and 5%, respectively); therefore, these effects are not considered to be adverse.

The NOAEL for cardiovascular safety pharmacology is 50 mg/kg in dog.

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13.2.2.3.3. Respiratory System

In male Sprague-Dawley rats (Study 809V-Tox2007-021, GLP), after a single oral dose of viloxazine at 0 (vehicle control, water), 25, 100, and 400 mg/kg (n=8/group), there were no drug-related changes in respiratory functions relative to controls.

The NOEL for respiratory safety pharmacology is 400 mg/kg in rat.

13.2.3. Pharmacokinetics/ADME

The bioanalytical methods are validated for determination of viloxazine in the plasma of rat, dog, mouse, and rabbit with a lower limit of quantitation of 1 ng/mL and a linearity range of 1 to 1000 ng/mL. The bioanalytical methods are validated for determination of R(+)-viloxazine and S(-)-viloxazine concentrations in the plasma of dog and rat with a lower limit of quantitation of 10 ng and a linearity range of 10 to 10,000 ng/mL.

13.2.3.1. Absorption and Distribution

The pharmacokinetic profile after a single oral dose of [^{14}C]-viloxazine at 100 mg/kg (150 µCi/kg) was investigated in male and female Sprague Dawley (albino) rats and male Long–Evans (partially pigmented) rats (Study 809V-Tox2007-023, GLP).

After oral administration to Sprague-Dawley rats, viloxazine was rapidly absorbed in both sexes. The blood and plasma radioactivity concentrations peaked (T_{max}) at 1 or 2 hours postdose and was eliminated relatively rapidly from plasma with a terminal half-life ($T_{1/2}$) of ~3.5 hours. Radioactivity primarily partitioned in the plasma with a blood-to-plasma ratio of ~0.6, suggesting limited binding or partitioning into red blood cells. The majority of radioactivity (~89%) was excreted within 24 hours, with urine as the primary route of elimination, followed by feces (~6%).

After oral administration to partially pigmented Long–Evans rats, viloxazine was rapidly and widely distributed to various tissues. In general, the tissue concentrations of radioactivity peaked at 1 or 2 hours postdose and were mostly eliminated by 24 hours postdose. High concentrations of radioactivity were found in tissues/organs along the gastrointestinal (GI) and urinary tracts, whereas lower radioactivity was observed in the muscle, eye lens, bone, testis, and abdominal fat. CNS tissues had very low radioactivity, which was not detected by 8 hours postdose. In pigmented tissues, the radioactivity concentration was relatively high in the uveal tract, peaking at 2 hours postdose and rapidly declined thereafter. The radioactivity concentration in the skin was generally low. These data suggest that viloxazine or its metabolites do not preferentially distribute to or accumulate in the skin; viloxazine and its metabolites reversibly bind to melanin in the uveal tract but are rapidly dissociated or eliminated.

In an in vitro plasma protein-binding assay (Study 809V-Tox2007-026, GLP), viloxazine at concentrations up to 10 µg/mL showed moderate protein binding in plasma samples from human (75.7% to 82.2% bound), rat (50.2% to 56% bound), and dog (40.8% to 48.8% bound, Table 88). In all species, the percentage of viloxazine bound to plasma proteins decreased with increasing drug concentration, suggesting potential saturation at high concentrations.

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Table 88. In Vitro Plasma Protein Binding of Viloxazine in Human, Rat, and Dog

Species/Concentration (µg/mL)	Percent Bound			
	0.5	1	3	10
Human	82.2	81.4	79.5	75.7
Dog	48.8	48.0	46.1	40.8
Rat	56.0	55.4	54.0	50.2

Source: Modified/reformatted based on the data in the Applicant's study reports

When incubated with human blood samples (Study 812V-Tox2018-030, GLP), viloxazine at clinically relevant concentrations (approximately 0.1-, 1-, and 10-fold the clinical C_{max}) did not preferentially bind to or accumulate in blood cells (blood-to-plasma ratio 0.42 to 0.88). Therefore, plasma is an appropriate biological matrix for PK and TK measurements.

13.2.3.2. Metabolism and Excretion

In Vitro Metabolism

The in vitro metabolism of [^{14}C]-viloxazine was investigated in primary hepatocytes derived from rat (male), dog (male), and human (male) (Study 809V-Tox2007-027, non-GLP). ***There were significant species differences in the in vitro metabolic profile, which were confirmed by in vivo studies***. Viloxazine was extensively metabolized in rat hepatocytes (>90%) with 11 metabolites identified, moderately metabolized in dog hepatocytes (~50%) with 9 metabolites identified, and minimally metabolized in human hepatocytes (<10%) with 4 metabolites identified (Table 89). Two rat-specific metabolites (U1, unknown and M5, desethyl-viloxazine) and 1 dog-specific metabolite (M 10, methyl-viloxazine) were identified. However, despite the difference in metabolism, ***there were no unique human metabolites***.

Table 89. In Vitro Metabolites of [^{14}C]-Viloxazine Formed in Rat, Dog, and Human Hepatocytes after a 120-Minute Incubation

	Fraction of Detected Radioactivity				
Metabolite Identification	Rat	Dog	Human Donor A	Human Donor B	Human Donor C
[^{14}C]SPN-809V	1.54%	50.8%	90.7%	93.9%	91.7%
Unknown	4.43%	ND	ND	ND	ND
Hydroxy-SPN-809V glucuronide	12.5%	3.68%	ND	ND	ND
Hydroxy-SPN-809V glucuronide	7.77%	1.90%	2.79%	ND	1.71%
Desethyl SPN-809V glucuronide	8.50%	ND	ND	ND	ND
Desethyl SPN-809V sulfate	44.4%	ND	ND	ND	ND
Hydroxy-SPN-809V	ND	8.82%	ND	ND	0.87%
Desethyl SPN-809V	ND	1.39%	ND	ND	ND
Hydroxy-SPN-809V	ND	6.52%	2.59%	3.17%	ND
Morpholine ring-opened SPN-809V	ND	ND	ND	ND	ND
N-methyl SPN-809V	ND	ND	ND	ND	ND
Hydroxy-SPN-809V	2.16%	12.1%	2.37%	2.72%	ND
Oxo-SPN-809V	3.01%	ND	ND	ND	ND

ND= Not Detected
Source: Excerpted from the Applicant's study reports.
Abbreviations: SPN = viloxazine

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Similar to the results from human hepatocytes, limited metabolic conversion of [^{14}C]-viloxazine was observed in pooled human hepatic microsomes (Study 809V-Tox2007-032). In subsequent assays using CYP-specific inhibitory antibodies or selective inhibitors, it was shown that multiple CYP enzymes were involved in the in vitro metabolism of viloxazine in human hepatic microsomes or in supersomes expressing recombinant human CYP enzymes (CYP2D6, CYP1A2, CYP2B6, and CYP3A4).

In Vivo Metabolism and Excretion

In rat, after oral administration (Study 809V-Tox2007-023, GLP), viloxazine is extensively metabolized. The primary metabolic conversion is O-dealkylation followed by sulfation or glucuronidation. Other metabolic pathways include hydroxylation of the phenyl ring, and hydroxylation and oxidation of the morpholine ring (Figure 27). In plasma, the primary metabolite is desethyl viloxazine (M5); at 1 hour postdose, it accounted for 60.2% and 45.6% of the total radioactivity in males and females, respectively, whereas the parent drug accounted for only ~9.17% and 21.7%, respectively. Similarly, in urine, desethyl viloxazine is the primary metabolite, accounting for 67.7% and 51.1% of the radioactivity in males and females, respectively. In feces, hydroxylated metabolites of viloxazine were the most abundant metabolites, accounting for ~18% of the radioactivity; the unchanged parent drug accounted for ~13% of the radioactivity in both males and females.

Compared to rat, the in vitro and in vivo metabolism of viloxazine in human is limited. In human liver microsomes and in supersomes expressing human CYP2D6 (Study 812V-Tox2018-023), 5-hydroxyviloxazine was generated as the main metabolite, which was further conjugated into glucuronidated-5-hydroxyviloxazine in the presence of UGT1A9 and UGT2B15, but not UGT1A1, UGT1A3, UGT1A4, UGT1A6, or UGT2B7 (Study 812V-Tox2017-001). In human, the major circulating drug-related components in plasma are glucuronidated 5-hydroxy-viloxazine (P1, which corresponds to metabolites M1/M2 in rat) and unchanged viloxazine (P2). In addition, unconjugated 4 and 5-monohydroxylated viloxazine (U2), as well as glucuronidated N-carboxylated-viloxazine (U4) were detected as minor metabolites in plasma (Table 90). In urine, there were four major components: glucuronidated 5-hydroxy-viloxazine, 5-hydroxy-viloxazine, unchanged viloxazine, and glucuronidated N-carboxylated-viloxazine.

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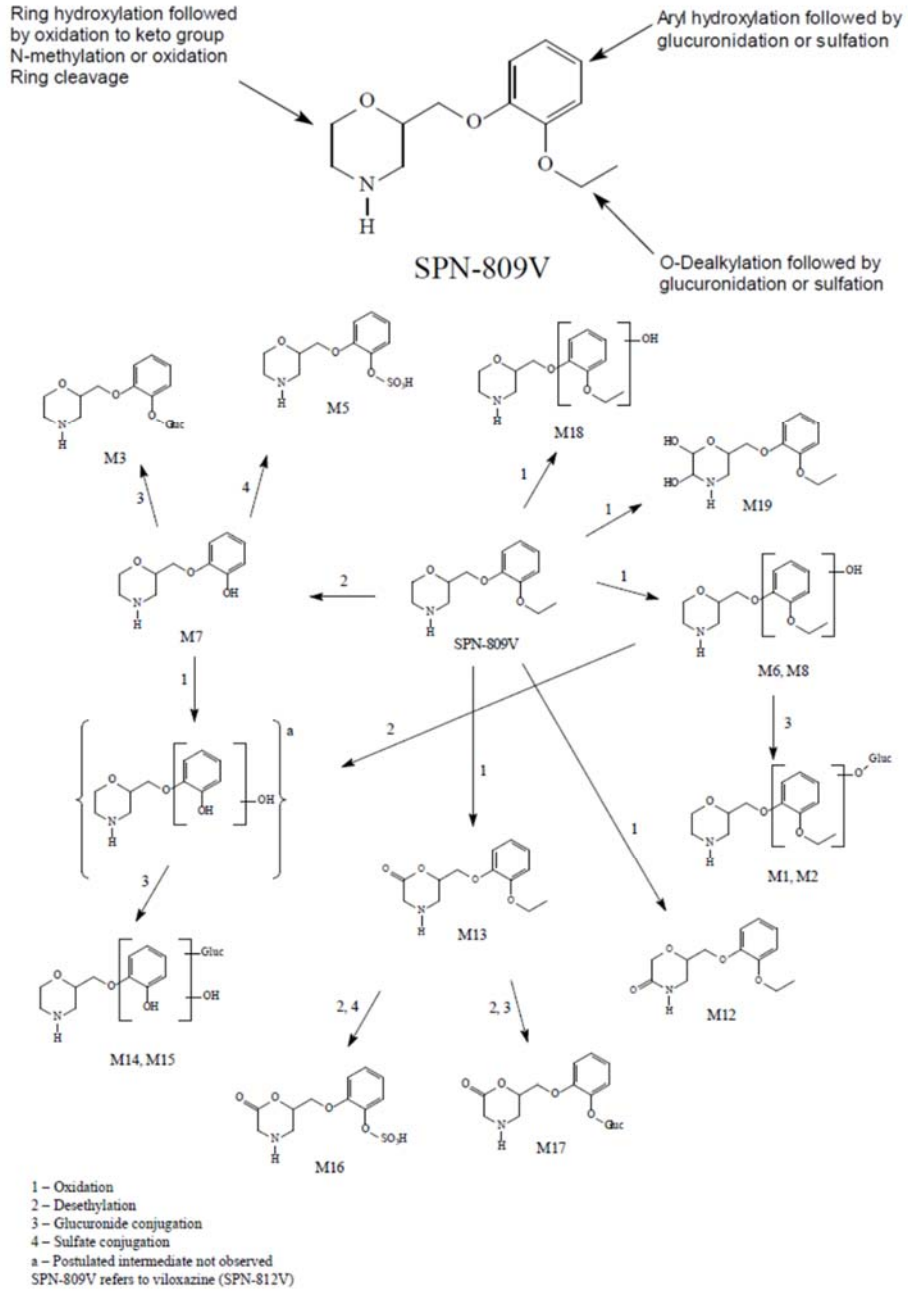
Figure 27. Metabolic Conversion of Viloxazine in Rat



Source: Excerpted from the Applicant's study reports
Abbreviations: SPN = viloxazine

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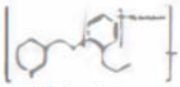
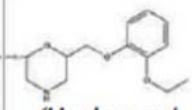
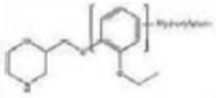
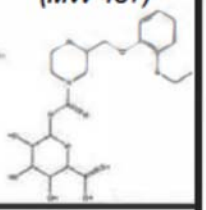
Table 90. Summary of Drug-Related Components in Human Plasma

	P1	P2	"U2"*	"U4"*
	$C_{19}H_{27}O_{10}N$ (MW 429)	$C_{13}H_{19}O_3N$ (MW 237)	$C_{13}H_{19}O_4N$ (MW 253)	$C_{20}H_{27}O_{11}N$ (MW 457)
	 (5-hydroxy-viloxazine glucuronide)	 (Unchanged SPN-812V)		
Sample Pool	**(% of total sample radioactivity)**			
Subject (b) (6) AUC pool	12.48	69.81	4.94	4.80
Subject AUC pool	10.11	71.72	2.46	5.79
Subject AUC pool	NO	71.38	3.48	6.34
Subject AUC pool	NO	63.40	4.16	7.24
Subject AUC pool	12.15	63.84	2.82	7.34
Subject AUC pool	16.20	57.32	3.31	6.79
Subject AUC pool	14.64	55.68	3.62	6.50
Subjects (b) (6) 1hr pool	NO	71.05	4.39	6.40
Subjects (b) (6) 8hr pool	10.57	53.05	2.78	4.42

NO Not observed above 10% of the total sample radioactivity

* The U2 (5-hydroxy-viloxazine) and U4 (formed by N-carboxylation followed by glucuronidation) components were initially only detected in the urine samples above 10% of the total sample radioactivity, however upon further evaluation they were also observed in all plasma samples but below 10% of the total radioactivity.

Source: Excerpted from the Applicant's study reports
Abbreviations: AUC = area under the curve; MW = molecular weight; SPN = viloxazine

It should be noted that the major human metabolite (glucuronidated-5-hydroxy-viloxazine, P1) is ***present at an adequate level in rat,*** despite being a minor metabolite (coded as M1 or M2) (Applicant Document 812V-Tox-2016-006). At 1, 4, and 8 hours postdose, the level of glucuronidated-5-hydroxy-viloxazine in rat was significantly higher (at least 5-fold) than in human (Table 91). Although AUC values were not provided, given the significantly higher level in rat at each time point, it can be reasonably concluded that the major human metabolite, glucuronidated-5-hydroxy-viloxazine, is adequately covered in rat.

The U4 metabolite, N-carbamoyl glucuronide conjugate, which accounts for ~6.4% and 4.4% of the total circulating drug-related material at 1 and 8 hours postdose in human plasma, is not detected in rat or dog plasma. However, no additional nonclinical study is needed for safety assessment of the U4 metabolite, because:

- It is a minor human metabolite (<10%)
- It is a nonreactive glucuronide conjugate (unlike the acyl glucuronides) and is generally considered to be low risk

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Table 91. Relative Levels of Glucuronidated 5-Hydroxy-Viloxazine in Human and Rat

	Human metabolite P1	Male Rat Metabolite M1	Male Rat Metabolite M2
	Mean concentration (µg equiv/ml)	Mean concentration (µg equiv/g)	Mean concentration (µg equiv/g)
1hour	<0.23	1.16	1.00
4 hours	No equivalent data	1.14	0.64
8 hours	0.118	0.786	0.632

Source: Excerpted from the Applicant's study reports
Rat exposure data were from Study 809V-Tox207-023; human exposure data were from the mass-balance Study 812p111

Both 5-hydroxyviloxazine and glucuronidated 5-hydroxyviloxazine were found to rapidly penetrate the mouse brain after a single IV viloxazine dose of 5 mg/kg, with T_{max} values of 1 and 0.5 hours, respectively (Study 812-Tox2018-020).

13.2.3.3. Drug-Drug Interactions

The inhibition or induction potential of viloxazine against CYP enzymes and transporters was investigated in multiple in vitro studies.

In pooled human liver microsomes (Study 809V-Tox2007-008), viloxazine at concentrations up to 100 µg/mL did not significantly inhibit CYP2B6, CYP2C8, CYP2C9, or CYP2C19. However, viloxazine competitively inhibited CYP1A2, CYP2D6, and CYP3A4 with IC_{50} values of 0.535, 54.6, and 65.2 µg/mL, respectively, and K_i values of 0.124, 12.7, and 26.8 µg/mL, respectively. The inhibition was not NADPH dependent. In another *in vitro* assay using pooled liver microsomes (Study 812V-Tox2018-024), viloxazine did not inhibit CYP2C8, CYP2C9, or CYP2C19. Viloxazine reversibly inhibited CYP1A2, CYP2B6, CYP2D6, and CYP3A4/5 with IC_{50} values of 0.269, 184, 141, and 221µM, respectively.

In primary human hepatocyte cultures (Study 809V-Tox2007-009), viloxazine at 2 µg/mL induced CYPA1A1/2 in 2 of 3 hepatocyte cultures. At 20 µg/mL, viloxazine induced CYP2C9, CYP1A2, and CYP2B6 in 1, 2, and 3 of 3 hepatocyte cultures, respectively. No enzyme induction was observed at 0.2 µg/mL. No CYP3A4/5 induction was observed at concentrations up to 20 µg/mL. In another set of assays using a different batch of human hepatocytes (Study 812V-Tox2017-002), viloxazine significantly induced mRNA expression of CYP1A2 and CYP2B6 with EC_{50} values of 16.7 and 15.4 µg/mL, respectively; no induction of CYP3A4 was observed.

In HEK293 cells expressing human OATP1B1*1a and OPAT1B3 transporters (Study 812V-Tox2018-025), viloxazine was not a substrate for OATP1B1*1a or OATP1B3. In cultures of MDCK and/or Caco-2 cells expressing human transporters of OAT1, OAT3, OCT2, OATPP1B1, OATP1B3, BCRP, and Pgp, viloxazine at 150µM did not inhibit OATP1B1, OATP1B3, or BCRP; but exerted a weak inhibitory effect on Pgp, OAT1, OAT3, and OCT2 (9.41%, 29.7%, 33.4%, and 43.9% inhibition, respectively). In a similar *in vitro* assay (Study 812V-Tox2018-026), viloxazine was a weak inhibitor of Pgp, BCRP, OATP1B1*1a, OATP1B3, and MATE1 with IC_{50} values of 1.5, 1.68, 1.84, 2.7, and 0.14mM, respectively. Viloxazine did not show any significant inhibition of MATE2-K at concentrations up to 3.3mM. Considering the clinical C_{max} of ~20µM, the risk for viloxazine-related inhibition of these transporters appears to be limited from a nonclinical perspective.

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13.2.4. General Toxicology

13.2.4.1. Single-dose Toxicity

In male Swiss–Webster mice (Study 723-0046, non-GLP), a single oral administration of viloxazine at ≥434 mg/kg caused ataxia, ***convulsions***, and/or deaths. Ataxia and/or convulsions generally occurred within 5 minutes postdose and their severity increased dose dependently. The median lethal dose (LD_{50}) and LD_2 were estimated to be 694 and 290 mg/kg[6], respectively.

In male and female Wistar rats (Study 723-0016, non-GLP), a single oral dose of viloxazine at ≥487 mg/kg caused CNS depression, ataxia, labored respiration, convulsions, and/or deaths. The toxicities generally occurred within 10 minutes postdose, and their severity increased dose dependently. The LD_{50} was estimated to be 1413 and 1821 mg/kg in males and females, respectively. Similar dose-dependent toxicities of CNS depression, ataxia, labored respiration, hunched posture, and/or deaths were also observed in Sprague-Dawley rats when orally administered the same doses, although convulsions were not observed at doses up to 971 mg/kg[7], suggesting strain-related differences in the convulsion threshold. The LD_{50} was estimated to be 1343 and 1179 mg/kg in males and females, respectively.

13.2.4.2. Repeat-dose Toxicity

13.2.4.2.1. Repeat-dose Toxicity Studies in Rat

Study Title.:	A 13-Week Oral Gavage Toxicity and Toxicokinetic Study of SPN-809V in Sprague Dawley Rats with a 4-Week Recovery Period
Study no.:	809V-Tox2009-006
Study report location:	EDR, SDN-1
Study initiation date:	August 21, 2009
Conducting laboratory and location:	(b) (4)
Duration:	13
Duration Units:	weeks
GLP compliance:	Y
Drug, lot #, and % purity:	Viloxazine; 080047 (CMLW-147/08-VL3); ~ 100% (100.2% based on HPLC)
Target Organ+:	LIVER

[6] LD_2 value was derived by extrapolation of the lower end of the LD_{50} curve.

[7] At doses higher than 971 mg/kg, deaths occurred without any observation of convulsions.

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Key Findings

- Viloxazine at 217 mg/kg/day caused, in both sexes, hepatocellular hypertrophy and vacuolation in the liver, with correlative increases in the liver weight and the serum alkaline phosphatase level. These changes were reversible after recovery.
- Females had higher drug exposure than males, which correlated with an increased incidence of histopathology findings in the liver.
- Based on liver findings, the NOEL is considered to be 87 mg/kg/day. The corresponding exposures after 13 weeks of repeat treatments were 10,600 and 15,300 ng*hour/mL for males and females, respectively.

Reviewer's note: Findings in the liver are likely an adaptive response to drug treatment and not necessarily adverse. Therefore, the NOAEL could arguably be set at 217 mg/kg/day for the current study. However, in a subsequent rat carcinogenicity study, viloxazine at 217 mg/kg/day caused convulsions in multiple animals. Therefore, given the overall evidence, it is appropriate to set the NOAEL at 87 mg/kg/day.

Table 92. Methods for A 13-Week Oral Gavage Toxicity and Toxicokinetic Study of SPN-809V in Sprague Dawley Rats with a 4-Week Recovery Period

Methods	Details
Doses:	0 (vehicle control), 22 (LD), 87 (MD), and 217 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=10/sex/group Recovery: additional n=5/sex in control and HD only TK: n=9/sex/group for LD, MD, and HD and n=3/sex for control
Dose volume:	10 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	RATRATRAT
Strain:	SPRAGUE-DAWLEY
Age/sexual maturity:	Approximately 7–8 weeks of age at treatment initiation
Comment on study design and conduct:	Dose selection was based on the 7-day and 4-week repeat dose studies. At 433 mg/kg/day, viloxazine induced severe CNS toxicity of convulsion and excessive decreases in body weight and weigh gain, indicating that the MTD was exceeded. At 217 mg/kg/day, viloxazine caused tolerable decreases in body weight (↓up to ~9%) and weight gain (↓up to 19%) and no severe CNS adverse effects. Therefore, 217 mg/kg/day was selected as the high dose in the current study.
Dosing solution analysis:	The stability and concentration of the dosing formulation were confirmed to be acceptable.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

There were no drug-related premature deaths in the study. One of 15 control males (No. 7758) was found dead on day 52 with no clear cause of death. One of 15 HDMs (No. 7705) was euthanized on day 13. The cause of death was hemorrhagic cystitis with inflammation in the urinary bladder. This single incidence in the HDM is not considered to be drug related because

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1) no similar finding was observed at this dose in the current study or at similar or higher doses in previous studies; and 2) existing knowledge of the pharmacology or toxicology of the drug does not provide a plausible mechanism for the hemorrhagic cystitis in the urinary bladder.

Clinical Signs

During the treatment period, compared to controls, HDM&Fs had an increased incidence of chromodachryorrhea (red material around the mouth); and males at all doses and HDFs had an increased incidence of chromorhinorrhea (red material around the nose). These observations generally occurred 2 to 4 hours postdose but were reversible during the recovery period. The overall health of the animals was not affected. Given the transient and reversible nature of these findings, they are not considered to be adverse.

Body Weights and Food Consumption

During the treatment period, compared to controls, there were slight decreases in weight gain at all doses in both sexes (~4%) without a clear dose-response relationship or correlative changes in food consumption. The decreases in weight gain were reversible during the recovery period. Because the decreases were of small magnitude and fully reversible, they are not considered to be adverse.

Ophthalmoscopy

Compared to controls, there were no drug-related ophthalmic changes.

Clinical Pathology (Hematology, Coagulation, Clinical Chemistry, and Urinalysis)

There were no drug-related adverse changes in clinical pathology parameters compared to the control group. Mild changes in some parameters were observed in the high dose (HD) group but were reversible (see below), and not considered to be adverse. The low dose (LD) and mid dose (MD) groups were not affected.

Hematology and Coagulation

During the treatment period, compared to controls, HDFs had higher absolute and relative reticulocyte counts (~45%) and a slightly higher hemoglobin distribution width (7.1%). These changes were reversible during recovery. Increased reticulocyte count and hemoglobin distribution width typically suggest a regenerative response to anemic condition. However, there were no correlative findings indicative of bleeding or anemia, and the values were within the historical control ranges at the test facility; therefore, they are not considered to be adverse.

Clinical Chemistry

During the treatment period, compared to controls, HDMs had slightly higher serum levels of albumin (7%) and alkaline phosphatase (32%); HDFs had higher levels of alkaline phosphatase (65%) and cholesterol (60%). These changes correlated with microscopic changes of centrilobular hepatocellular hypertrophy and midzonal vacuolation in the liver. However, the values, despite being higher than concurrent controls, were within the historical control range at

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the test facility and were reversible after recovery. Therefore, the toxicological relevance of these changes appears to be limited.

Urinalysis

Compared to controls, there were no drug-related changes in urinalysis.

Gross Pathology

At the terminal and recovery necropsies, compared to controls, there were no drug-related findings in gross pathology.

Organ Weights

The weight of an adequate number of tissues and organs was measured.

At the terminal necropsy, compared to controls, liver weight was slightly increased in HDMs (13.1%) and HDFs (17.1%), which correlated with histopathology findings of hepatocellular hypertrophy and vacuolation and an increased serum alkaline phosphatase level.

HDMs also had slightly increased kidney weights (11.5%); however, there were no correlative findings from histopathology, clinical chemistry, or urinalysis. Therefore, the toxicological relevance appears to be limited.

Histopathology

At the terminal and recovery necropsy, an adequate number of tissues/organs from the control and HD groups were evaluated for histopathology. In addition, the liver and pancreas from the animals in the LD and MD groups were evaluated for histopathology. Peer review was conducted.

At the terminal necropsy, compared to controls, HDM&Fs had increased incidences of centrilobular hepatocellular hypertrophy and midzonal vacuolation in the liver (Table 93). The vacuolation consisted of small to large clear vacuoles, predominantly in the midzonal region of the lobule but also involving the centrilobular regions. The incidence and severity were slightly higher in HDFs than HDMs, likely due to higher drug exposure in females at the same doses. These changes correlated with increased liver weight and increased albumin, alkaline phosphate, and/or cholesterol levels. These changes were reversible after recovery.

One of 11 HDMs (No. 7699) also had mild multifocal liver necrosis and one of 10 LDMs (No 7754) had minimal focal liver necrosis (Table 93). The necrotic foci were well-delineated, randomly distributed, and characterized by liquefactive necrosis and mild infiltration of lymphocytes. Because liver necrosis may occur spontaneously in rats (Greaves 2012), and because it occurred in only a single animal without correlative changes indicative of liver injury (such as inflammation or elevation of liver enzymes), this finding is likely to be incidental.

In addition, glandular atrophy in the pancreas was observed in 3/11 control males, 1/10 LDMs, and 3/10 HDFs. Because the incidences were similar between controls and treated animals and because pancreatic atrophy can occur spontaneously in rats (Greaves 2012), it is considered to be incidental.

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Table 93. Histopathology Findings in the Liver at the Terminal Necropsy from the 13-Week Rat Study

	Males				Females			
Dosage (mg/kg/day):	**0**	**25**	**100**	**250**	**0**	**25**	**100**	**250**
Liver	**11**	**10**	**10**	**11**	**10**	**10**	**10**	**10**
Hypertrophy, Hepatocellular, Centrilobular	0	0	0	8	0	0	0	6
Minimal	-	-	-	4	-	-	-	2
Mild	-	-	-	4	-	-	-	2
Moderate	-	-	-	0	-	-	-	2
Vacuolation, Hepatocellular, Midzonal	0	0	0	7	0	0	0	3
Minimal	-	-	-	5	-	-	-	0
Mild	-	-	-	1	-	-	-	3
Moderate	-	-	-	1	-	-	-	0
Necrosis	0	1	0	1	0	0	0	0
Minimal	-	1	-	0	-	-	-	-
Mild	-	0	-	1	-	-	-	-

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 22, 87, and 217 mg/kg/day

Toxicokinetics

On days 0 and 85, blood samples were collected from satellite TK animals at 0 (predose), 0.5, 1, 2, 4, 8, and 24 hours postdose[8]. The TK parameters of viloxazine were determined.

On both sampling days, after oral administration, viloxazine was rapidly absorbed and eliminated with a T_{max} of 0.5 to 2 hours and a half-life ($T_{1/2}$) of 0.6 to 3.6 hours. The C_{max} increased slightly less than dose proportionally whereas the $AUC_{0\text{-}24h}$ increased greater than dose proportionally. Compared to males, females had slightly higher drug exposure; the female-to-male exposure ratio ranged from 1.5 to 1.9. Repeat administrations did not significantly alter drug exposure, and there was no accumulation (Table 94).

Table 94. Toxicokinetic Parameters of Viloxazine in the 13-Week Rat Study

Daily Dose (mg/kg)	0 (Control)		25		100		250	
Sex:Number of Animals	M:15	F:15	M:10	F:10	M:10	F:10	M:15	F:15
Toxicokinetics:								
C_{max} (ng/mL)								
Study Day 0	NA	NA	1300	1500	1310	3910	5340	9040
Study Day 85	NA	NA	1170	1840	2890	4550	6840	8270
$AUC_{0\text{-}24hr}$ (ng•hr/mL)								
Study Day 0	NA	NA	1180	1800	7920	11100	28200	40800
Study Day 85	NA	NA	1490	2780	10600	15300	33800	56300

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 22, 87, and 217 mg/kg/day
Abbreviations: AUC = area under the curve; NA = not applicable

[8] For controls, blood samples were only collected at 1 hour postdose.

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Study title:	An 18-Month Chronic Oral Toxicity in Rats
Study no.:	723-0078
Study report location:	EDR, SDN-1
Study initiation date:	November 21, 1974
Conducting laboratory and location:	(b) (4)
Duration:	18
Duration units:	months
GLP compliance:	N
Drug, lot #, and % purity:	Viloxazine; ADM18420/72 PDRM W0058 and ADM 16009/73, PDRMW0091; 99.3% and 99.2%
Target organ+:	LIVER

Key Findings

- Excessive decreases in weight gain and food consumption in HD, leading to dose reduction from 156 to 104 mg/kg/day during Week 46. The decreased weight gain and food consumption correlated with decreased glucose and triglyceride levels in plasma.
- Increased incidence of hepatocellular vacuolation due to lipid accumulation in the liver in MD and HD at both the 6-month interim analysis and the 18-month terminal necropsy. These changes were reversible after recovery.
- Based on the decreases in weight gain and food consumption, the NOAEL in this study is 52 mg/kg/day. No TK analysis was conducted. It should be noted that viloxazine was administered via dietary intake in this study; therefore, the exposure profile is expected to be different from oral gavage studies in that dietary administration would result in a lower peak level but more continuous exposure to viloxazine.

Table 95. An 18-Month Chronic Oral Toxicity in Rats Methods

Methods	Details
Doses:	0 (control), 17 (LD), 52 (MD), and 156/104 (HD) mg/kg/day[9]
Frequency of dosing:	Daily (diet)
Number/sex/group:	6-month interim analysis sub-study: n=20/sex/group; 18-month main study: n=22/sex/group, from which n=5/sex in the control and HD groups were evaluated after a 6-week recovery
Dose volume:	Not applicable
Formulation/vehicle:	Purina Lab Chow
Route of administration:	DIETARY
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age/sexual maturity:	Approximately 7 weeks at treatment initiation

[9] Dose in HD was reduced from 156 to 104 mg/kg/day during week 46 due to excessive decreases in weight gain and food consumption.

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Methods	Details
Comment on study design and conduct:	This study is a dietary study that includes a 6-month interim analysis for all groups[10] and a 6-week recovery period for the control and HD groups after 18 months of treatment. A 2-week dosing titration was implemented at the beginning: all viloxazine treatment groups received 17 mg/kg/day in week 1, which increased to 52 mg/kg/day for the MD and HD groups in Week 2, and to 156 mg/kg/day for the HD group in Week 3. During the study (Week 46), due to excessive decreases in weight gain and food consumption, the dose in the HD group was reduced from 156 to 104 mg/kg/day.
Dosing solution analysis:	The viloxazine-containing diet was prepared weekly. The viloxazine concentration in the diet was confirmed to be within the acceptable range (10% of the proposed dose levels).

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

In the interim sub-study, 1/20 HDMs had a broken mandible (jaw bone), which led to inability to eat, subsequent body-weight loss, and early termination. This premature death is not considered to be drug related.

Compared to controls, there was no clear trend of drug-related deaths in the study. During the study, 2, 4, 5, and 4 male rats, and 3, 6, 1, and 4 female rats in the control, LD, MD, and HD groups, respectively, (n=42/sex/group) died prematurely (weeks 16 to 78). No causes of death were determined. However, the mortality rate (~6% to 12%, sex combined) is generally within the expected range for spontaneous death in an 18-month rat study. Moreover, the incidence and the time of deaths were comparable across all groups. Therefore, it is unlikely that the deaths are drug related.

Clinical Signs

In the main study, 1 MDM (No. 3136) had convulsions during weeks 73 and 74, which led to early termination in Week 75. Two LDFs (Nos. 2217 and 2216) were ataxic and circling in the cage with head tilt in weeks 68 and 70, respectively, which led to early termination in weeks 69 and 74, respectively. One HDM (No. 4117) was found recumbent in the cage and was euthanized in Week 69. One control female (No. 1236) had several vaginal bleedings throughout the study and was euthanized in Week 78. One control male (No. 1124) was ataxic with head tilt during Week 4 of the recovery phase but survived to the end of the recovery period.

Reviewer's note: The incidence of convulsion and convulsion-related clinical signs (ataxia) was relatively low in this study, and there was no clear dose relationship. However, it should be noted that convulsions and tremors were observed in the 2-year carcinogenicity study after approximately 4 months of dosing at 217 mg/kg/day, and two additional incidences occurred

[10] For the 6-month interim analysis substudy, findings for clinical signs, body weight, weight gain, food consumption, clinical pathology were generally similar to those in the main study; therefore, they are not discussed separately. For pathology parameters (gross pathology and histopathology), the results are discussed separately to provide a temporal relationship in terms of the drug-related histopathology changes.

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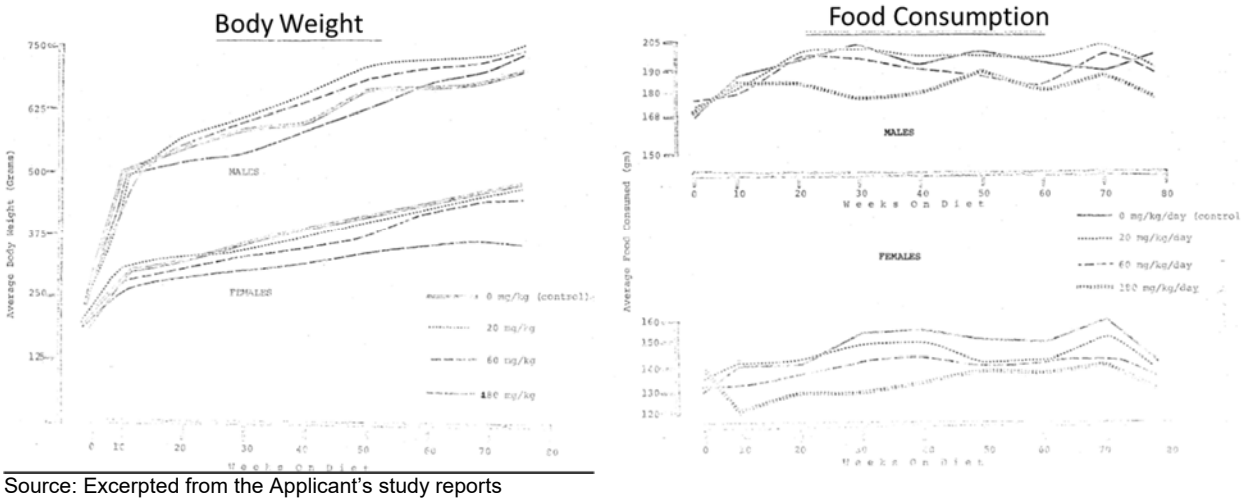
after the dose was reduced to 130 mg/kg/day. In comparison, in the 13-week study, viloxazine at the same dose of 217 mg/kg/day did not cause any clinical signs indicative of convulsions. It is possible that prolonged repeat drug treatment lowers the convulsion threshold (kindling effect).

Body Weights and Food Consumption

During the treatment period, compared to controls, weight gain and food consumption were decreased in HDM&Fs starting in Week 3 (Figure 28). The decreases in HDMs were generally less than 5%; however, the decreases in HDFs increased with increasing treatment duration from 13% at Week 3 to 17% at Week 46 in food consumption and from 4% at Week 3 to 18% at Week 46 in weight gain. Water intake was also decreased in HDMs (up to ~14%) and HDFs (up to ~27%). Due to the excessive decreases in weight gain and food consumption, the dose was reduced from 156 to 104 mg/kg/day in the HD group. After this dose reduction, no further decreases in food consumption and weight gain were observed.

Figure 28. Drug-Related Decreases in Weight Gain and Food Consumption in the 18-Month Rat Study



Source: Excerpted from the Applicant's study reports

Ophthalmoscopy

Compared to controls, there were no drug-related ophthalmic changes.

Hematology

Blood samples were collected during weeks 14, 27, 38, 53, 77, and 79. An adequate battery of hematology parameters was evaluated.

Compared to controls, there were no drug-related adverse changes in hematology parameters. Occasional changes in monocyte counts were observed in individual animals on some but not all sampling days. These are considered to be incidental or non-adverse based on their small magnitude and/or lack of a clear dose relationship.

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Clinical Chemistry

Serum samples were collected at the scheduled interim (month 6, n=10/sex/group) and terminal (month 18, n=14/sex/group) necropsies. An adequate battery of clinical chemistry parameters was evaluated.

At the interim necropsy, compared to controls, MDMs and HDMs had slight decreases in glucose (14% to 18%) and triglyceride (42% to 65%) levels. Similarly, at the terminal necropsy, slight decreases in triglyceride levels were observed in MDMs and HDMs (25% to 36%). These decreases are likely secondary to decreased food consumption and weight gain. Given their small magnitude, they are not considered to be adverse. Females were not affected.

Urinalysis

Urine samples were collected during weeks 14, 26, 37, 52, and 77. An adequate battery of urinalysis parameters was evaluated. In addition, urinary ascorbic acid levels were measured in the control and HD groups at the terminal (n=8/sex/group) and recovery (n=5/sex/group) necropsies.

Compared to controls, urinary calcium excretion was decreased in the HD group on all sampling days (up to ~55%). The Applicant proposed that the decreases in urinary calcium were secondary to decreased food consumption. This is a reasonable explanation. Because there were no correlative changes in histopathology, the toxicological relevance of these changes appears to be limited.

In addition, HDFs had increased urinary ascorbic acid excretion, particularly in Week 26 (~167%); however, at the terminal necropsy, the increase was only ~20%. The biological or toxicological relevance of such changes is likely to be limited[11].

Gross Pathology

At the scheduled interim, terminal, and recovery necropsies, animals were evaluated for gross pathology. In addition, their femur length was measured.

Compared to the controls, there were no drug-related gross pathology findings at the interim (6 months), terminal (18 months), or recovery necropsies. There were no drug-related changes in femur length.

Organ Weights

The weight of an adequate number of organs was measured.

At the 6-month interim necropsy, compared to controls, there were no drug-related changes in organ weights. The HD group had increased relative weights of the liver, brain, and testes, primarily due to a decreased body weight.

[11] Extremely high urinary ascorbic acid levels could interfere with the accuracy of some urinalysis parameters; however, at the terminal necropsy, HDFs exhibited an only ~20% increase in urinary ascorbate level; this is unlikely to have a noticeable impact on data collection and interpretation.

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Similarly, at the 18-month terminal necropsy, compared to controls, there were no drug-related changes in organ weights. The MD and HD groups showed dose-dependent increases in the relative weight (relative to body weight) of the liver, heart, kidney, and brain. These increases were mainly due to decreased body weight because the absolute weights of these organs did not change.

Histopathology

At the scheduled necropsy, an adequate number of organs/tissues was evaluated for histopathology. In addition, Oil Red O staining (for lipids) and electron microscopy were conducted to examine hepatic vacuolation.

At the 6-month interim necropsy, compared to controls, there were dose-dependent increases in the incidence and severity of hepatocellular vacuolation, which were due to lipid accumulation (Table 96).

Table 96. Drug-Related Centrilobular Vacuolation (Lipid Accumulation) at the 6-Month Interim Analysis in the 18-Month Rat Study

Centrilobular Fat Droplets	Control		LD		MD		HD	
	M	F	M	F	M	F	M	F
Minimal	9/20	1/20	15/20	4/20	11/20	2/20	1/19	11/20
Moderate	0/20	0/20	5/20	0/20	9/20	2/20	5/19	4/20
Marked	0/20	0/20	0/20	0/20	0/20	0/20	13/19	1/20

Source: Modified/reformatted based on the data in the Applicant's study reports
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

At the 18-month terminal necropsy, compared to controls, there were dose-dependent increases in the incidence and severity of hepatocellular vacuolation in MD and HD animals (Table 97). The vacuolated cells were typically enlarged and contained foamy cytoplasm with small, central nuclei or coalesced vacuoles with eccentric nuclei. The vacuolations were primarily due to dose-dependent increases in the amount of fat droplets in hepatocytes (Table 98). At the recovery necropsy, control and HD animals had comparable incidences and/or severities of hepatocellular vacuolation, suggesting recovery.

Table 97. Drug-Related Histopathology Changes at the Terminal and Recovery Necropsies in the 18-Month Rat Study

	18-Month Kill								Reversibility			
	Control		20 mg/kg/day		60 mg/kg/day		High Dose*		Control		High Dose*	
	M	F	M	F	M	F	M	F	M	F	M	F
No. Animals	(15)	(14)	(18)	(16)	(17)	(21)	(14)	(13)	(5)	(5)	(5)	(5)
No. Examined	15	14	18	16	17	21	14	13	5	5	5	5
Hepatocyte Vacuolations, Focal Areas, Centrilobular												
Minimal	0	4	8	8	7	13	0	8	0	4	1	2
Slight	0	0	5	3	5	1	3	5	0	0	1	1
Moderate	0	0	0	0	1	0	5	0	1	0	1	1
Marked	0	0	0	0	0	0	6	0	0	0	0	0
Hepatocyte Vacuolations, Focal												
Minimal	4	9	10	13	9	14	4	10	3	4	2	2
Slight	2	3	1	3	4	5	3	1	1	1	1	3
Moderate	0	0	1	0	0	1	0	0	0	0	0	0

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 17, 51, and 154/103 mg/kg/day, respectively

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Table 98. Incidence of Hepatocellular Fat Droplets at the Terminal and Recovery Necropsies in the 18-Month Rat Study

	18-Month Kill								Reversibility			
	Control		20 mg/kg/day		60 mg/kg/day		High Dose*		Control		High Dose*	
	M	F	M	F	M	F	M	F	M	F	M	F
No. of Animals	(15)	(14)	(18)	(16)	(17)	(21)	(14)	(13)	(5)	(5)	(5)	(5)
Centrilobular Fat Droplets Minimal (ORO)	15	14	13	15	11	19	0	9	4	5	4	4
Centrilobular Fat Droplets Moderate (ORO)	0	0	5	1	6	2	7	3	1	0	1	1
Centrilobular Fat Droplets Marked (ORO)	0	0	0	0	0	0	7	1	0	0	0	0

*180 mg/kg/day for 46 weeks and 120 mg/kg/day for 32 weeks.

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 17, 52, and 156/104 mg/kg/day, respectively
Abbreviations: ORO = Oil Red O

Toxicokinetics

Not conducted.

Other Repeat-Dose Toxicology Studies in the Rat

In a 4-week study (Study 809V-Tox-2007-017, GLP), Sprague-Dawley rats were orally treated with viloxazine at 0 (control), 22 (LD), 87 (MD), and 217(HD) mg/kg/day. Viloxazine at ≥87 mg/kg/day, caused dose-dependent decreases in body weight (up to 7.3%), weight gain (up to 19.2%), and food consumption (up to 14.4%). The decrease in body weight at 217 mg/kg/day persisted after recovery; therefore, it is considered to be adverse. In addition, a micronucleus assay of bone marrow was performed at the end of the treatment period. Compared to controls, viloxazine at doses up to 217 mg/kg/day was not cytotoxic to bone marrow, as demonstrated by the lack of a significant decrease in the polychromatic to normochromatic erythrocyte ratio. Viloxazine treatment at doses up to 217 mg/kg/day did not cause an increase in micronucleated polychromatic erythrocytes. Therefore, viloxazine is negative in the rat bone marrow micronucleus assay.

TK parameters were evaluated for both R(+)- and S(-)-viloxazine. In general, the TK profiles for R(+)- and S(-)-viloxazine were similar, and each accounted for approximately 50% of the total exposure of the racemic viloxazine mixture. Females had slightly higher viloxazine exposure than males. For metabolite profiling, a total of 18 metabolites was identified. These metabolites were formed from one or more phase I and phase II metabolic reactions, confirming that viloxazine is extensively metabolized in rat. In general, female rats had more glucuronide conjugates but fewer sulfate conjugates than male rats.

Based on the decreased body weight and weight gain, the NOAEL for general toxicity in the 4-week study is 87 mg/kg/day. The corresponding drug exposure levels (AUC) after 4 weeks of repeat treatments were 6834 and 12,523 ng*hour/mL for males and females, respectively.

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In a 7-day study (Study 809V-Tox2007-002, non-GLP) in Sprague-Dawley rats, viloxazine at ≥434 mg/kg/day was not tolerated and caused severe CNS toxicity (convulsions and tremors); excessive decreases in body weight, weight gain, and/or food consumption; and premature deaths. The drug exposures associated with premature deaths were C_{max} values of 6623 and 13,600 ng/mL and AUCs of 77,275 and 188,659 ng*hour/mL in males and females, respectively. Doses of up to 217 mg/kg/day were tolerated and the drug effects included hypoactivity, decreased body weight and food consumption. After 7 days of treatment at 217 mg/kg/day, the drug exposures were C_{max} values of 4040 and 5495 ng/mL and AUCs of 29159 and 66297 ng*hour/mL in males and females, respectively.

13.2.4.2.2. Repeat-dose Toxicity Studies in Mouse

Study title:	4-Week Oral Gavage Toxicity and Toxicokinetic Study with SPN-812V in rasH2 Transgenic Wild-Type mice with 2-Week Recovery
Study no.:	812V-Tox2011-007[12]
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
Duration:	4
Duration units:	weeks
GLP compliance:	Y
Drug, lot #, and % purity:	Viloxazine; L-8340-101-001; 99.9%
Target organ+:	CNS
Target organ+:	LIVER

Key Findings

- There was one potentially drug-related death at 173 mg/kg/day.
- Viloxazine caused dose-dependent CNS signs, including hypoactivity and impaired gait at 130 mg/kg/day and convulsions at 173 mg/kg/day.
- Viloxazine caused dose-dependent increases in hepatocellular vacuolation (lipid accumulation) and hypertrophy, which correlated with increased liver weight and increased alanine aminotransferase (ALT) level. These changes were reversible after recovery.
- Based on the clinical signs and liver findings at ≥130 mg/kg/day, the NOAEL is considered to be 43 mg/kg/day. The corresponding exposure levels after 28 days of repeat treatments are C_{max} values of 2618 and 2672 ng/mL in males and females, respectively; and AUCs of 11,593 and 11,809 ng*hour/mL in males and females, respectively.

[12] This study also served as the DRF study for the 6-month carcinogenicity study in Tg.rasH2 mice.

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Table 99. A 4-Week Oral Gavage Toxicity and Toxicokinetic Study with Viloxazine in rasH2 Transgenic Wild-Type Mice with 2-Week Recovery Methods

Methods	Details
Doses:	0 (vehicle control), 43 (LD),130 (MD) and 173 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=10/sex/group Recovery: n=5/sex for control and HD groups only TK: n=18/sex for viloxazine treated groups and n=3/sex for controls
Dose volume:	10 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2) Wild Type
Age/sexual maturity:	Approximately 9-10 weeks at treatment initiation
Comment on study design and conduct:	Dose selection was based on a 5-day DRF study (Study 812V-Tox2011-006). In this study, viloxazine, caused dose-dependent CNS toxicities, including hypoactivity at doses ≥43 mg/kg/day; impaired gait and a single incidence of convulsion at 130 mg/kg/day; convulsions and lateral recumbency in multiple animals at 217 mg/kg/day; and premature deaths at 433 mg/kg/day. The convulsion and premature death findings at ≥217 mg/kg/day indicate that the MTD was exceeded. Based on the findings, doses of 43, 130, and 173 mg/kg/day were selected.
Dosing solution analysis:	The concentration of the dosing formulation was confirmed to be within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

One of 5 HDF died on day 8. The cause of death could not be determined. However, because at the same dose viloxazine caused convulsions in multiple animals, which could lead to premature death, it is possible that this death was drug related.

Clinical Signs

During the treatment period, compared to controls, viloxazine caused dose-dependent CNS effects, including hypoactivity and impaired gait in the MD group and convulsions in the HD group (Table 100). Most of the clinical signs were observed within 1 to 2 hours postdose and were reversible within 4 to 5 hours. All affected animals appeared normal prior to the next dose. The LD group was not affected.

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Table 100. Drug-Related Clinical Signs in the 4-Week Mouse Study

Dose (mg/kg/day)	Group and Sex	Clinical signs (no. of animals)
150	G3M & G3F	Hypoactive (10/10 in each sex), wobbling (10/10 in each sex) and slightly impaired gait (10/10 males and 9/10 females).
200	G4M	Hypoactive (15/15), convulsions (8/15), lateral recumbency (8/15), walks on tip-toes (3/15), wobbling (15/15) and slightly impaired gait (15/15).
	G4F	Hypoactive (15/15), wobbling (15/15) and slightly impaired gait (14/15).
Slightly impaired gait = slightly abnormal placement of hind feet (slight abduction) while walking		

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 130 and 173 mg/kg/day, respectively

Body Weights and Food Consumption

During the treatment period, compared to controls, there were no significant or adverse changes in body weight or weight gain. MDFs and HDFs had slightly lower body weight and weight gain; however, their magnitude was small (<5%) and they are not considered to be adverse.

During the first week of treatment, food consumption was decreased in the MD and HD groups (up to 18%); however, it rapidly recovered and did not lead to adverse decreases in body weight or weight gain. Therefore, the initial decrease in food consumption is not considered to be adverse.

Ophthalmoscopy

There were no drug-related ophthalmic changes.

Hematology

At the terminal necropsy, compared to controls, HDFs had decreased absolute and relative lymphocyte counts (69% and 15%, respectively), which led to a non-significant decrease in the total white blood cell count. There were no correlative histopathology findings indicative of changes in the hematopoietic or lymphoid organs; and the changes were reversible after recovery. Therefore, the toxicological meaning appears to be limited.

Clinical Chemistry

At the terminal necropsy, compared to controls, the alkaline phosphatase level was slightly increased in males at all doses and in MD and HD females (23% to 47%) and the cholesterol level was slightly decreased in MD and HD males and females (28% to 62%). These changes are possibly associated with histopathology findings of hepatocellular vacuolation (lipid accumulation) and hypertrophy in the MD and HD groups. In addition, the glucose level was slightly decreased in MD and HD females (30% to 35%). The hypoglycemic effect is likely

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drug-related but nonadverse, given the small magnitude. These changes were reversible at the end of the recovery period.

Gross Pathology

At the terminal necropsy, pale discoloration (diffuse) in the liver was observed in 1/10 HDMs, 1/10 MDFs, and 5/11 HDFs. In addition, liver enlargement was observed in 1/10 HDMs. These changes are possibly correlative with increased liver weight and the histopathologic findings of hepatocellular vacuolation and hypertrophy.

Organ Weights

At the terminal necropsy, compared to controls, HDFs had slightly increased liver weight (↑11%), which correlated with histopathology of hepatocellular vacuolation and hypertrophy. Spleen weight was slightly decreased in MDFs and HDFs (↓19% in both groups). However, there was no correlative histopathology changes in the spleen; therefore, the toxicological relevance appears limited.

Histopathology

An adequate number of tissues/organs from animals in the control and HD groups was subjected to histopathology examination. In addition, the liver samples and any gross lesions in any group were examined. Peer review was conducted.

At the terminal necropsy, compared to controls, there were dose-dependent increases in the incidence and severity of hepatocellular vacuolation and hypertrophy in the MD and HD groups (Table 101). Subsequent Oil Red O staining showed that the vacuolation was due to lipid accumulation (presence of lipid droplets) in the liver. These changes were reversible after recovery.

Table 101. Drug-Related Histopathology Changes in the Liver in the 4-Week Mouse Study

Sex	MALES						FEMALES					
	Day 29				Day 43		Day 29				Day 43	
Groups Dose (mg/kg/day)	G1 0	G2 50	G3 150	G4 200	G1 0	G4 200	G1 0	G2 50	G3 150	G4 200	G1 0	G4 200
No. of mice	**10**	**10**	**10**	**10**	**5**	**5**	**10**	**10**	**10**	**11**	**5**	**4**
Liver No. examined	10	10	10	10	5	5	10	10	10	11	5	4
Hepatocyte vacuolation (confirmed as fatty change)	2	2	10	10	2	0	0	0	10	11	0	0
Minimal	2	2	4	3	1	—	—	—	3	1	—	—
Mild	0	0	6	5	1	—	—	—	7	10	—	—
Moderate	0	0	0	2	0	—	—	—	0	0	—	—
Hepatocellular enlargement	0	0	8	10	0	0	0	0	10	10	0	0
Minimal	—	—	3	3	—	—	—	—	7	0	—	—
Mild	—	—	5	6	—	—	—	—	3	5	—	—
Moderate	—	—	0	1	—	—	—	—	0	5	—	—

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 43, 130, and 173 mg/kg/day, respectively

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Toxicokinetics

On day 28, blood samples were collected from TK animals at 0.25, 0.5, 1, 4, 8, and 24 hours postdose. A TK analysis of viloxazine was conducted.

After oral administration, viloxazine was rapidly absorbed and eliminated, with a T_{max} generally of 0.25 to 1 hour (except for MDM) and a $T_{1/2}$ of ~2 hours. The exposure (AUC) increased in proportion to the dose. There was no significant different in exposure between males and females (Table 102).

Table 102. Toxicokinetic Parameters of Viloxazine in the 4-Week Mouse Study

Gender	Dose (mg/kg/day)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
Male	50	0.50	2618.46	15593.40	15599.28	2.08
	150	4.00	5852.85	48165.72	48182.48	1.99
	200	1.00	8255.63	58081.53	58140.32	2.38
Female	50	0.25	2672.35	11808.99	11820.62	2.43
	150	0.25	5154.41	30588.12	30605.81	2.22
	200	0.25	6946.29	40437.26	40500.18	2.58

$AUC_{0-last} = AUC_{0-24h}$
Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 43, 130, and 173 mg/kg/day, respectively
Abbreviations: AUC = area under the curve

13.2.4.2.3. Repeat-dose Toxicity Studies in the Dog

Study title:	A 13-Week Oral (Capsule) Toxicity and Toxicokinetics Study of SPN-809V in Beagle Dogs with a 4-Week Recovery Period
Study no.:	809V-Tox2009-005
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
Duration:	13
Duration units:	weeks
GLP compliance:	YYY
Drug, lot #, and % purity:	Viloxazine; CMLW-147/08-VL3; 100%
Target organ+:	CNS

Key Findings

- Viloxazine at 39 mg/kg/day caused continuous convulsions, intermittent tremors, altered respiration, and/or impaired muscle coordination, which led to early termination of the animals.
- Viloxazine at all doses decreased body weight, weight gain, and food consumption; the decreases were most profound and considered to be adverse at doses ≥22 mg/kg/day. These effects were reversible after recovery.
- Based on the findings, the NOAEL is considered to be 8.7 mg/kg/day in this study. The corresponding exposure levels after 85 days of repeat treatments are C_{max} values of 2660 and 2730 ng/mL in males and females, respectively; and AUCs of 13,200 and 14,700 ng*hour/mL in males and females, respectively.

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Table 103. A 13-Week Oral (Capsule) Toxicity and Toxicokinetics Study of SPN-809V in Beagle Dogs with a 4-Week Recovery Period Methods

Methods	Details
Doses:	0 (control), 8.7 (LD), 22 (MD), and 39 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=4/sex/group Recovery: n=2/sex for the control and HD groups only
Dose volume:	NA; viloxazine powder was administered in gelatin capsules (not liquid form)
Formulation/vehicle:	Gelatin capsules
Route of administration:	ORAL
Species:	DOG
Strain:	BEAGLE
Age/sexual maturity:	5-6 months of age at treatment initiation
Comment on study design and conduct:	Dose selection was based on previous 7-day and 4-week studies (Studies 809V-Tox2007-003 and 809V-Tox2007-018, respectively). In the 7-day study, viloxazine at 87 mg/kg/day exceeded the MTD and caused convulsions, body weight loss, ataxia, and lateral recumbency, which led to early termination. In the 4-week study, no toxicity was observed at 4 mg/kg/day. At 22 mg/kg/day, viloxazine caused mild and reversible toxicities of decreased body weight, weight gain and food consumption. At 52 mg/kg/day, viloxazine also caused poor clinical condition and premature deaths. Based on these findings, 39, 22, and 8 mg/kg/day were selected as the high, middle, and low doses in the current study.
Dosing solution analysis:	The stability of viloxazine powder was confirmed to be acceptable for use in this study.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

There were 4 premature deaths in the study, all in the HD group (3/6 HDMs and 1/6 HDF), 3 of which were likely drug-related. Two HDMs (Nos. 6830 and 6833) were euthanized on day 83 and 86, respectively, due to drug-related severe toxicities (prolonged convulsions, intermittent tremors, altered respiration, and/or impaired muscle coordination). Animal 6830 had repeated convulsions that led to dose cessation; however, the convulsions continued and eventually led to early termination of the animal. A post mortem examination revealed degeneration of the heart and skeletal muscle and elevated aspartate aminotransferase (AST) and sorbitol dehydrogenase levels, likely secondary to prolonged muscle exertion during convulsions. Animal 6833 was euthanized on day 86 due to severe convulsions and poor clinical condition (inactivity, prostration, and rigid muscle tone). A post mortem examination did not identify any abnormal clinical pathology, necropsy, or histopathology findings in this animal. Nevertheless, given the similarity of findings in HD animals, it is considered to be drug related.

One additional HDM (no. 6836) was euthanized on day 18 due to poor physical condition, including impaired balance, inactivity, hunched posture, hyper-reactivity to touch, and fever (103.5°F). Clinical observations in this animal included intermittent tremors and hypoactivity on day 1, slight weight loss and decreased food consumption in Week 1, and repeated excessive salivation and emesis prior to day 18. A post mortem examination revealed bacterial plaque at

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the aorta and an increased neutrophil count, suggesting infection as a potential cause of death. However, given the CNS effects and the high incidence of mortality in the HD group, the contribution of viloxazine to the general poor condition of the dog cannot be excluded.

One HDF (no. 6864) was euthanized on day 1 due to poor condition, including inactivity and abnormal respiration. A post mortem examination revealed necrosis, hemorrhage, and acute inflammatory infiltrates in the alveolar tissue, with extension through the pleura and involving the pericardium. Based on these findings, the death was likely due to aspiration of fluid (vomitus), rather than a direct drug effect. Because the mortality occurred on day 1, this animal was replaced with another female.

Clinical Signs

During the treatment period, compared to controls, multiple adverse effects, including tremors, convulsions, hypoactivity, rigid muscle tone, hyperactivity to touch, twitching, and/or hunched posture, were observed in HDMs, including the 3 HDMs that died prematurely. In 1 HDM (No. 6849), twitching, intermittent convulsions, tremors, rigid muscle tone, and white frothy material around the mouth (emesis) were observed from days 77 to 82. This animal survived and the clinical signs were not noted during the recovery period; also, there were no histopathology findings in the CNS or muscle in this animal at the recovery necropsy.

Other drug-related clinical signs in surviving animals included an increased incidence of reddened ears in MDM&Fs and HDM&Fs; mucoid feces in MDMs; and emesis containing white, yellow, and/or capsule material in HDM&Fs. LD animals were generally unaffected.

Reviewer's note: Emesis in HD animals, particularly with capsule materials, may lead to inaccurate/reduced drug doses.

Body Weights and Food Consumption

During the treatment period, compared to controls, body weight and weight gain decreased dose dependently (Figure 29). At the terminal necropsy, compared to controls, the mean body weight was decreased by 3.1%, 19.7%, and 22.8% in LD, MD, and HD males, respectively; and by 7.3%, 13.5% and 12.5% in LD, MD, and HD females, respectively. At the end of the treatment period, cumulative weight gain was decreased by 0.1, 2.5, and 2.9 kg in LD, MD, and HD males, respectively; and by 0.7, 1.2, and 1.3 kg in LD, MD, and HD females, respectively.

The decreases in body weight and weight gain correlated with decreased food consumption during the first 3 weeks of treatment. From Week 3 until the end of the treatment period, dietary supplementation was provided to all MD and HD animals, which alleviated the decreases in food consumption. In the LD group, which did not receive dietary supplementation, food consumption remained slightly lower than in the controls throughout the treatment period.

During the recovery period, dietary supplementation continued to be provided to HD animals. The body weight, weight gain, and food consumption of the HD animals were generally comparable to controls, suggesting recovery.

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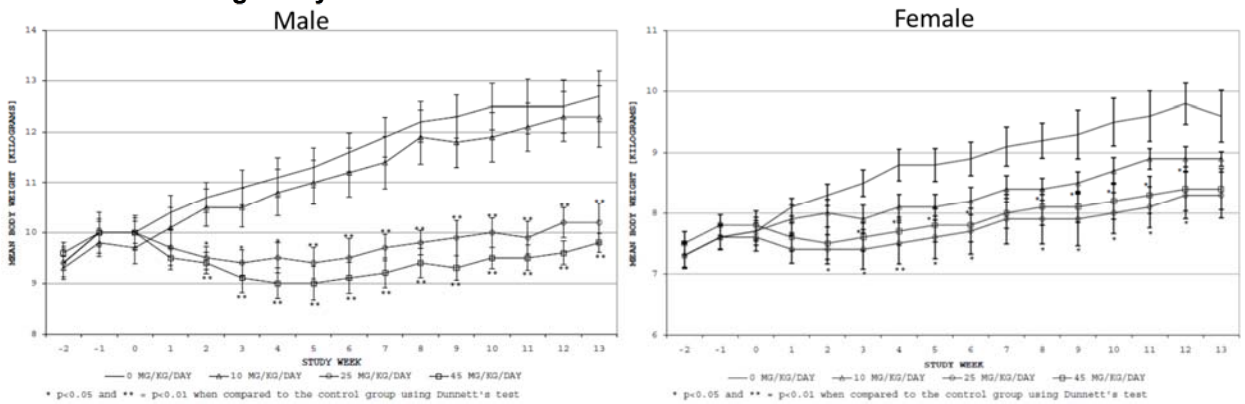
Figure 29. Drug-Related Decreases in Body Weight and Weight Gain during the Treatment Period in the 13-Week Dog Study



Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 8.7 (LD), 22 (MD), and 39 (HD) mg/kg/day, respectively
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Ophthalmoscopy

There were no drug-related ophthalmic findings.

ECG

Compared to controls, there were no drug-related adverse changes in ECG parameters. One of 4 MDMs (No. 6838) had infrequent arterial premature contraction in Week 12. Given the single incidence and lack of similar findings at higher doses, it is considered to be a normal variant. One of 2 HDFs (no. 6857) had infrequent second-degree atrioventricular block in the final week of recovery (Week 17), which is also considered an incidental finding because the animal has not been dosed for 4 weeks.

Compared to controls, HDFs had decreased heart rate in Week 12 (95 bpm compared to 134 bpm in controls, a decrease of 39 bpm*); however, the values were within the normal range; therefore, they are not considered to be adverse.

***Reviewer's note:** A similar finding of a decreased heart rate relative to concurrent controls was also observed in the 4-week dog study at similar doses. These decreases may be related to desensitization of the adrenergic effects after repeated exposure to viloxazine. In both studies, the magnitude was small, and the values were within the normal range; therefore, they are not considered to be adverse.

At the end of the treatment period, compared to controls, the QTc interval was slightly longer in MDFs and slightly shorter in HDMs (Table 104). Because the magnitude of changes was small and their direction was inconsistent and lacked a clear dose relationship, these small changes in QTc are considered to be within normal variations and non-adverse.

Table 104. QTc Interval at the End of the Treatment Period in the 13-Week Dog Study

Dose/QTc (ms)	0 mg/kg/day	8 mg/kg/day	22 mg/kg/day	39 mg/kg/day
Males	236±4.8	233±8.7	225±6.2	223±5.6*
Females	184±4.2	182±7.0	180±8.4	198±11.2*

Source: Modified/reformatted based on the data in the Applicant's study reports
* p<0.05 compared to concurrent controls

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Hematology and Coagulation

At the terminal necropsy, compared to controls, HDMs had increased basophil and large unstained cell counts (by 100% and 125%, respectively); these values were also higher than the pretreatment baseline (by 30% and 50%, respectively). The basophil counts exceeded the historical control range at the test facility. Therefore, they are considered to be drug related. However, there were no correlative histopathology findings, and the changes were reversible after recovery; therefore, they are not considered to be adverse.

Clinical Chemistry

At the terminal necropsy, compared to controls, triglyceride levels were decreased in MD and HD groups (by 42.9%, 35.7%, 43.5%, and 21.7% in MDMs, HDMs, MDFs, and HDFs, respectively). These values were also lower than the pretreatment baseline values, and likely secondary to decreased body weight, weight gain, and/or food consumption. Also, the changes were reversible after recovery.

HDFs also had decreased creatinine (33%) relative to controls; however, this was mainly due to an increase in controls relative to pretreatment baseline values rather than a drug effect in the treatment group.

Urinalysis

There were no drug-related changes in urinalysis parameters.

Gross Pathology

At the scheduled terminal and recovery necropsies, there were no drug-related gross pathology findings.

Organ Weights

At the terminal necropsy, compared to controls, the absolute and relative (to body or brain) liver weights were increased in females at all doses without a clear dose-relationship (up to 14% and 34% in absolute and relative liver weights, respectively). Liver weight was also increased in the only surviving HDM (26% and 16% in absolute and relative liver weights, respectively). There were no correlative histopathology findings in the liver or changes in clinical chemistry indicative of liver damage; in addition, these changes were reversible after recovery; therefore, they are not considered to be adverse.

Other changes in organ weights included decreased absolute heart weight in MDMs, decreased absolute kidney weight in MDFs, and increased relative thymus weight in MDFs. These were primarily secondary to decreased body weight rather than a direct drug effect on the organs/tissues.

Histopathology

An adequate number of tissues/organs of the animals in the control and HD groups (including the 2/4 pre-mature death HDMs that were treated for 83 and 86 days, respectively*) was subjected to

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histopathology evaluation. In addition, gross lesions in animals in all groups were evaluated for histopathology. Peer review was conducted.

At the terminal and recovery necropsies, compared to controls, there were no drug-related abnormal histopathology findings.

***Reviewer's note:** Due to premature deaths, only 1/4 HDM was evaluated for histopathology at the scheduled terminal necropsy. The MD and LD groups were not subjected to a full histopathology evaluation (only gross lesions were evaluated), which could have resulted in an inadequate histopathology evaluation. However, 2/4 HDMs were euthanized and evaluated for detailed histopathology on days 83 and 86, respectively, near the end of the treatment period. Therefore, a total of 3 HDMs was treated for an adequately long period (≥83 days), and the histopathology evaluation in this study is considered to be acceptable.

Toxicokinetics

Blood samples were collected on days 0 and 85 at 0 (predose), 1, 2, 4, 8, 12, and 24 hours postdose. A TK analysis of viloxazine was conducted.

On both sampling days, after oral administration, viloxazine was relatively rapidly absorbed, with a T_{max} of 1 to 2.5 hours on day 0 and 2.5 to 2.5 hours on day 85. The mean half-life $T_{1/2}$ was 1.9 to 2.5 hours on day 0 and 1.7 to 2.7 hours on day 85. There was no sex difference in viloxazine exposure. On both sampling days, the exposure levels (C_{max} and AUC) increased dose proportionally. Repeat administrations did not lead to drug accumulation (Table 105).

Table 105. Toxicokinetic Parameters of Viloxazine in the 13-Week Dog Study

Doses	T_{max} (h)		$T_{1/2}$ (h)		C_{max} (ng/mL)		AUC (ng*hour/mL)	
(mg/kg/day)	M	F	M	F	M	F	M	F
Day 0								
8 (LD)	1.3	2.5	2.2	2.0	3530	2370	12100	10000
22 (MD)	2.3	1.8	1.9	2.5	9070	7530	44600	37600
39 (HD)	2.0	1.0	2.5	2.5	16900	14700	94100	63300
Day 85								
8 (LD)	2.8	2.5	2.1	1.7	2660	2730	13200	14700
22 (MD)	5.5	4	1.5	1.8	5720	6660	47600	36800
39 (HD)	3.3	3.2	2.7	1.8	9470	8960	64200	55500

Source: Modified/reformatted based on the data in the Applicant's study reports
Abbreviations: AUC = area under the curve; HD = high dose; LD = low dose; MD = mid dose; T = time

***Reviewer's note:** TK samples were collected from the HDM (No. 6849) that had convulsions. However, the drug exposure levels in this animal were comparable to the group mean values, suggesting that the convulsions were not due to abnormally high drug exposure.

Reference ID: 4698714

Study title:	Viloxazine Hydrochloride: A 12-Month Oral Toxicity Study in Dogs
Study no.:	725-0016
Study report location:	EDR, SDN-2
Conducting laboratory and location:	(b) (4)
Duration:	12
Duration units:	months
GLP compliance:	N
Drug, lot #, and % purity:	Viloxazine; PDRM W0058 and 0091; 99.3% and 99.2%[13]
Target organ+:	LIVER

Reviewer's note: This is a legacy study primarily focused on histopathology evaluation of viloxazine treated animals at 6 months (interim), 12 months (terminal), and after 4 and 8 weeks of recovery.

Key Findings

- Viloxazine caused hepatocellular enlargement, intracytoplasmic inclusions, and lipid droplet accumulation in the liver. These changes occurred prior to 6 months of repeat treatments and were reversible after 4 to 8 weeks of recovery.

Table 106. Viloxazine Hydrochloride: A 12-Month Oral Toxicity Study in Dogs Methods

Methods	Details
Doses:	0 (control), 3.5 (LD), 10 (MD), and 10/21/31/36/42 mg/kg/day Dose titration was conducted for the HD group: started at 10 mg/kg/day for 1 week and escalated to 21, 31, 36, and 42 mg/kg/day at weeks 2, 3, 17, and 19, respectively.
Frequency of dosing:	Once daily
Number/sex/group:	Main study (12-month treatment): n=4/sex for control; n=6/sex for LD; n=5/sex for MD; and n=4/sex for HD Interim analysis (6-month treatment): n=5/sex/group 4-Week recovery: n=1/sex for control; n=1/sex for MD; n=2/sex for HD 8-Week recovery special evaluation for liver: n=2/sex for control; n=3/sex for HD
Dose volume:	NA, animals were dosed in gelatin capsules
Formulation/vehicle:	Gelatin capsules
Route of administration:	ORAL
Species:	DOG
Strain:	BEAGLE
Age/sexual maturity:	6–7 months at treatment initiation
Comment on study design and conduct:	This study has a complicated design, with multiple groups primarily designated for evaluation of liver-related histopathology findings at different time points (see above). Clinical signs and body weights were not included as regular endpoints.
Dosing solution analysis:	Not included in the study report

Source: summarized from the Applicant's study reports

[13] This report did not include purity information on the viloxazine lots used in the study. However, the same lots were also used in the 18-month rat study; therefore, the purity information from the 18-month rat study was listed.

Reference ID: 4698714

Observations and Results

Mortality

One HDF (no. 76-987) died in Week 52. In the study report, it was stated that due to "CNS signs", this animal received multiple dosing holidays and/or dose adjustment, including "7/21 no dose; 7/29-8/5 no dose; 8/6-8/13 36 mg/kg; 8/14-8/16 no dose; 8/17-9/7 24 mg/kg; 9/8-9/12 36mg/kg; 9/13-9/16 48 mg/kg; 9/16 dead." Although no detailed description of the clinical signs or moribund conditions was provided, given the information on the CNS effects of viloxazine, it is reasonable to conclude that this premature death is drug related.

One HDM (no. 76-441) died in Week 34. There were no remarkable moribund findings in this animal. Post mortem necropsy findings did not indicate a clear relationship with viloxazine. However, given that a potentially drug-related death occurred at the same dose (No. 76-987), a role for viloxazine in this animal's death cannot be excluded.

One HDM (no. 76-360) was euthanized in Week 32 due to necrotizing gingivitis. Because there are no similar findings in any of the nonclinical studies and because there is no plausible mechanism for viloxazine to cause gingivitis, this death is considered to be incidental.

Gross Pathology

At the 6-month interim necropsy, compared to controls, there were dose-dependent increases in the incidence of liver color changes, from a dark tan to a pale tan. The incidence increased from 0/6 in the control group to 2/10, 6/10, and 7/10 in the LD, MD, and HD groups, respectively.

Similar to the interim analysis, at the terminal necropsy, compared to controls, the MD and HD groups exhibited dose-dependent increases in the incidence of liver color change, tan, mottling with distinct acinar patterns, or purple mottling (Table 107). These correlated with histopathology findings of hepatocellular enlargement (hypertrophy), intracytoplasmic inclusions, and lipid accumulation in the liver.

Table 107. Drug-Related Gross Pathology Changes in the Liver at the Terminal Necropsy in the 12-Month Dog Study

	Control		LD		MD		HD	
	M (3)	F (3)	M (6)	F (6)	M (5)	F (5)	M (4)	F (4)
LIVER								
Dark tan	1	0	0	0	1	0	0	1
Light tan	0	0	0	0	0	1	1	0
Tan	0	0	0	0	2	0	1	1
Tan, mottled, with acinar pattern	0	0	0	0	0	0	1	0
Tan with mottled purple areas	0	0	0	0	1	0	0	0

Source: Excerpted from the Applicant's study reports
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Clinical Pathology

At the 6-month interim necropsy, compared to controls, HDMs had higher white blood cell counts (~50%), with no correlative findings in histopathology or in bone marrow assessment. Therefore, these changes are not considered to be adverse.

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No other drug-related changes in clinical pathology parameters were observed.

Histopathology

At the scheduled necropsy (6-month interim, 12-month terminal, and 4-week recovery), control and HD animals were subjected to a full histopathology evaluation. LD and MD animals were evaluated for histopathology findings in the liver, lung, testis, and any gross lesions. For the 8-week recovery group, liver samples were evaluated for histopathology. In addition, liver samples from the right central hepatic lobe of all animals were processed and evaluated by electron microscopy.

At the terminal necropsy, compared to controls, there were dose-dependent histopathology findings in the liver—including hepatocellular hypertrophy, intracytoplasmic inclusions, and lipid droplet accumulation—at all doses (Table 108). When evaluated by electron microscopy, the inclusion bodies appeared to be heterogeneous dense bodies and myelin figures (myeloid bodies). The heterogeneous dense bodies are composed of whirls of endoplasmic reticulum without a limiting membrane, arranged in a lamellar pattern around mitochondria, lipid, or amorphous material, which subsequently became "myelin figures/myeloid bodies," a form of secondary lysosomes. Cytoplasmic glycogen in hepatocytes was not affected by viloxazine treatment. The Applicant proposed that such changes were most likely associated with hypertrophic endoplasmic reticulum (Ghadially 1982), which appears to be reasonable.

It should be noted that similar histopathology findings in the liver were also observed at the 6-month interim necropsy, including dose-dependent increases in intracytoplasmic inclusions and lipid droplet accumulation, which suggest that the gross pathology and histopathology changes in the liver occurred prior to 6 months of viloxazine treatment.

These histopathology changes in the liver were generally reversible. After 4 weeks of recovery, compared to controls, the histopathology findings in the liver were limited to minimal numbers of cytoplasmic inclusion bodies/myelin figures in HD animals, as opposed to moderate to marked numbers at the terminal necropsy. There were no findings of hepatocellular hypertrophy, heterogeneous dense bodies, or lipid droplet accumulation after 4 weeks of recovery. After 8 weeks of recovery, there were no liver histopathology findings in the 4 HD animals (1 M/3 Fs) evaluated, suggesting full recovery.

Special Evaluation

At both the 6-month interim necropsy and the 12-month terminal necropsy, bone marrow smear samples were collected and evaluated for bone marrow cellularity. There were no drug-related changes in the bone marrow.

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Table 108. Drug-Related Histopathology Changes in the Liver at the Terminal Necropsy in the 12-Month Dog Study

	Control		LD		MD		HD	
	M (3)	F (3)	M (6)	F (6)	M (5)	F (5)	M (4)	F (4)
Hepatocyte enlargement, centrilobular								
minimal	0	0	0	0	0	2	0	2
moderate	0	0	0	1	1	2	0	0
Inclusions, intracytoplasmic, ragged, small								
minimal	2	0	3	6	4	4	2	2
moderate	1	3	2	0	0	1	0	0
Inclusions, intracytoplasmic, ground-glass, round								
minimal	0	0	2	1	3	1	1	1
moderate	0	0	0	0	1	2	1	0
marked	0	0	0	0	1	0	1	2
Sparse droplets Type IV, V, VI								
minimal numbers	0	0	0	2	0	0	0	0
moderate numbers	0	0	0	0	0	1	0	1
marked numbers	3	3	6	5	5	4	2	1
Moderate droplets Types II, III								
minimal numbers	0	1	0	0	0	1	0	0
moderate numbers	0	1	2	1	0	0	0	0
marked numbers	0	0	0	0	0	0	0	2
Dense droplets Types I, VII								
moderate numbers	0	0	0	0	0	1	0	0
marked numbers	0	0	0	0	0	0	1	0
Periportal, moderate or dense droplets Types I, VII	0	0	0	1	5	2	3	1
moderate numbers	0	0	0	0	0	0	0	1
marked numbers								

Source: Excerpted from the Applicant's study reports
Type I, dense cytoplasmic tiny and small droplets; type II, moderate cytoplasmic tiny and small droplets; type III, moderate cytoplasmic tiny, small, and medium droplets; type IV, sparse cytoplasmic tiny droplets; type V, sparse cytoplasmic tiny and small droplets; type VI, sparse cytoplasmic small and medium droplets; type VII, dense cytoplasmic tiny, small, and medium droplets
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Other Repeat-Dose Toxicology Studies in Dog

Four-week Repeat-Dose Study in Dog (Study 809V-Tox2007-018, GLP)

In a 4-week study, beagle dogs were orally treated with viloxazine at doses of 0 (control), 4 (LD), 22 (MD), and 52 (HD) mg/kg/day. Viloxazine at 52 mg/kg/day resulted in a poor clinical condition and premature deaths. Other findings at this dose included lymphocyte depletion in the

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thymus with correlative decreased thymus weight in both sexes and arterial inflammation or degeneration in males. These findings were most likely secondary to the stress and poor condition of the animals, rather than a direct drug effect, and were reversible after recovery.

At ≥22 mg/kg/day, compared to controls, viloxazine caused dose-dependent decreases in body weight (7% to 13%), weight gain (0.5 to 1.1 kg), and food consumption (22 to 41%). The decreases were reversible after recovery. No drug-related neurological effects were observed at any dose.

A chiral-specific TK analysis and qualitative metabolic profiling revealed that after oral administration, viloxazine was extensively metabolized in dog; 22 metabolites were identified. The exposure level to R(+)-viloxazine was slightly higher than that to S(-)-viloxazine in dog, with an R-to-S ratio of approximately 7:3 (slightly different from the rat, in which R-and S-viloxazine had comparable exposure levels).

Based on the premature deaths and decreased body weights, the NOAEL in this study is 4 mg/kg/day. The corresponding exposure levels after 27 days of repeat treatments are C_{max} values of 1002 and 983 ng/mL in males and females, respectively; and AUCs of 3089 and 3446 ng*hour/mL in males and females, respectively.

Sixteen-Week Repeat-Dose Study in Dog (Study (b) (4)-205, non-GLP)

In a 16-week study of potential drug-related pathological changes, beagle dogs were orally dosed with placebo gelatin capsules as the control group (n=1/sex), or viloxazine (n=6/sex) at the maximal tolerated dose (MTD, ~60 to 70 mg/kg/day, defined by anorexia and clinical signs). Animals were initially dosed at 20 mg/kg/day, and gradually titrated down to the MTD at 10 mg/kg/day.

One of 6 males and 2/6 females died prematurely after 8, 41, and 102 days of treatment, respectively. Each death was preceded by convulsions. The deaths were mainly due to respiratory asphyxiation and cardiac arrest that occurred during prolonged periods of severe muscle contractions and convulsions. The post mortem histopathology findings included vascular congestion and neuronal vacuolation in numerous neurons of the cerebral cortex and deep nuclei. The vacuoles were tiny, clear, multiple, and occupied the peripheral cytoplasm and their contents were not stainable with several common staining methods. It is unclear whether these neuronal findings were directly due to drug-induced neurotoxicity or secondary to prolonged convulsion and asphyxiation or post mortem autolysis/degeneration.

In dogs that survived to the scheduled necropsy, drug-related toxicities included moderate-to-severe anorexia, decreased body weight and weight gain, decreased motor activity, straightened and stiff hindlegs, ataxia, and convulsions. These clinical signs generally occurred within 1 hour postdose and lasted for about 1 to 1.5 hours; no correlative histopathology findings were observed in the brain. At the scheduled necropsy, compared to controls, 2 male and 2 female dogs in the treated group had small hepatocellular eosinophilic bodies (hyaline bodies) and variable-sized lipid vacuoles in the liver. The nuclei were not affected. The hyaline bodies morphologically resembled some cytoplasmic inclusion bodies that were shown to be proliferated smooth endoplasmic reticulum, lipid droplets, and myelin figures in the previous 12-month dog study (Study 725-0016), which were reversible.

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Together, these data showed that viloxazine at 60 to 70 mg/kg/day caused severe convulsions that led to premature death in some dogs and histopathology findings of neuronal vacuolation. In animals that survived to the scheduled necropsy, viloxazine caused inclusion bodies in the liver that were likely reversible. No other histopathology findings were observed in other organs/tissues, including the brain, spinal cord, and kidney.

13.2.5. Genetic Toxicology

13.2.5.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title:	*Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay
Study no.:	809V-Tox2007-024
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	07/06/2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Viloxazine (SPN-809V); 1009-30-2; 98.61%

Key Study Findings

Viloxazine was negative in an adequate Ames assay.

Table 109. *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay Methods

Methods	Details
Strains:	TA98, TA100, TA1535, TA1537, WP2uvrA
Concentrations in definitive study:	0 (vehicle control), 29, 87, 289, 867, 2166, and 4333 µg/plate in the presence and absence of S9 metabolic activation
Basis of concentration selection:	Dose selection was based on a DRF study in TA100 and WP2uvrA, in which no cytotoxicity was observed at doses up to 5000 µg/plate viloxazine hydrochloride in the presence of S9. In the absence of S9, cytotoxicity was observed at ≥3330 µg in TA 100. No precipitation was observed at up to 5000 µg/plate. Therefore, 5000 µg/plate viloxazine hydrochloride, which is equivalent to 4333 µg/plate viloxazine free base, was selected as the high dose for the definitive study.
Negative control:	Reverse-osmosis water
Positive control:	

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	–	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

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Methods	Details
Formulation/vehicle:	Reverse osmosis water
Incubation & sampling time:	Plate incorporation method was used. One-hundred microliters of tester strain and 200 µL of viloxazine or positive/negative controls were mixed with molten selective top agar in the presence or absence of S9 metabolic activation mix and then overlaid on the minimal bottom agar. Plates were inverted and incubated for 52±4 hours at 37±2°C before they were scored. Each concentration was tested in triplicate.

Source: summarized from the Applicant's study reports

Study Validity

Based on the following evidence, I consider the study to be valid:

- Three independent GLP-compliant assays were conducted.
- An adequate number of plates was evaluated.
- Tester strain selection and top dose selection were adequate.
- Positive and negative control values were within the expected range of historical controls.
- S10 metabolic activation (10%) is adequate.

Results

In the initial assay (Trial 29073-B1), the values of the negative vehicle control in TA100 in the presence and absence of S9 were out of the historical control range (~370 revertants compared to ~110 revertants in the historical control range). Therefore, a second assay (Trial 29073-D1) was conducted in TA 100 only, which generated acceptable values. In addition, due to the unexpected values in the initial assay, a confirmatory assay (Trial 29073-C1) was performed.

Based on the overall data from the three assays, both the negative and positive control values were within the historical range.

Compared to vehicle controls, viloxazine at concentrations up to 4333 µg/plate (5000 µg/plate viloxazine hydrochloride) was not mutagenic in any of the test strains in the presence or absence of metabolic activation.

13.2.5.2. In Vitro Assays in Mammalian Cells

Study title:	Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes
Study no.:	809V-Tox2007-025
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	07/03/2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Viloxazine (SPN-809V); 1009-30-2; 98.61%

Key Study Findings

Viloxazine was not clastogenic in an adequate in vitro chromosomal aberration assay in cultured human lymphocytes.

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Table 110. Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes Methods

Methods	Details
Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	Experiment 1: +S9: 0 (vehicle control), 18, 25, 36, 51, 73, 105, 150, 2114, 306, 437, 624, 893, 1274, 1820, and 2560 µg/mL. Experiment 2: -S9 3-hour incubation: 217, 433, 867, 997, 1127, 1213, 1300, 1386, 1473, 1603, 1733, and 2166 µg/mL (1127, 1300, 1386, and 1473 µg/mL were scored because 1473 µg/mL caused a ~52% reduction in mitotic index)
Basis of concentration selection:	The high dose of 2560 µg/mL was selected to achieve >10mM[14]. At the high dose there was no precipitation or any significant change in osmolality.
Negative control:	Reverse osmosis water
Positive control:	-S9: mitomycin (MMC) +S9: cyclophosphamide (CP)
Formulation/vehicle:	Reverse Osmosis water
Incubation and sampling time:	+S9: ~3 hours -S9: ~3 hours and ~22 hours

Source: summarized from the Applicant's study reports

Study Validity

The study is valid. The negative and positive controls generated the expected responses. The high dose selection was adequate. The S9 concentration (1.5%) was within the acceptable range (1 to 10%)[15].

Results

In the presence of metabolic activation and after 3 hours of incubation, viloxazine at doses of 624, 893, 1274, and 1820 µg/mL did not induce chromosomal aberrations. Doses higher than 1820 µg/mL were cytotoxic.

In the absence of metabolic activation and after 3 hours of incubation, viloxazine at doses of 1127, 1300, 1386, and 1473 µg/mL did not induce chromosomal aberrations. Doses higher than 1473 µg/mL were cytotoxic. When incubated for 22 hours, viloxazine at concentrations of 150, 214, 306, and 437 µg/mL did not induce chromosomal aberrations. Concentrations higher than 437 µg/mL were cytotoxic.

[14] Current ICHS2(R1) recommends selection of a high dose at 1mM. However, the original ICHS2 1997 recommended selection of a high dose at 10mM; therefore, it is acceptable to use 10 mM as the high dose instead of 1mM.

[15] Although 1.5% S9 is at the lower end of the acceptable range, the study report stated that this concentration has consistently caused the positive control (CP) to be highly clastogenic for multiple lots at the test facility.

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13.2.5.3. In Vivo Clastogenicity Assay in Rodent (Bone Marrow Micronucleus Assay)

The in vivo micronucleus assay was incorporated into a 4-week repeat-dose general toxicology study in rat. Viloxazine at doses up to 217 mg/kg/day was negative in the rat bone marrow micronucleus assay (Study Supernus 809V-TOX2007-017, see Section III.13.2.4).

13.2.6. Carcinogenicity Study

13.2.6.1. Two-year Oral Gavage Carcinogenicity Study of Viloxazine in Wistar Rats

Study no.:	812V-Tox2014-002
Study report location:	EDR, SDN-1
Study initiation date:	March 7, 2014
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Viloxazine; 5002946/130032; 100.5%
Prior exec CAC dose concurrence:	Y
Basis for dose selection:	Dose selection was based on a 13-week study in Sprague-Dawley rats, in which severe CNS toxicity such as convulsions was observed at oral doses ≥433 mg/kg/day, whereas doses up to 217 mg/kg/day were tolerated. ECAC initially recommended doses of 30, 87, and 217 mg/kg/day for LD, MD, and HD, respectively, based on MTD. During the study, due to severe CNS toxicity and mortality, doses were reduced twice to the final doses of 22, 43, and 87 mg/kg/day for LD, MD, and HD, respectively.

Key Findings

- Viloxazine did not increase the incidence of tumors in rats treated for 2 years at oral doses of 30/22, 87/65/43, and 217/130/87 mg/kg/day. The final high dose of 87 mg/kg/day is approximately equal to the MRHD of 400 mg, based on mg/m^2 in children[16].
- Viloxazine at ≥130 mg/kg/day caused CNS toxicities (convulsions and tremors) and premature deaths in both sexes, which led to dose reductions. No further drug-related CNS toxicities were observed after doses were reduced to ≤87 mg/kg/day. Mortality was significantly increased in HD males.

Reviewer's note: Although a TK analysis was conducted in this study, the last TK samples were collected on day 180, prior to the final dose reduction on day 197. The exposure level on day 180 is not an accurate representation of the drug exposure for the majority of the treatment duration. Therefore, the exposure multiple is calculated based on mg/m^2 rather than AUC.

[16] Because the proposed indication is for the pediatric population only (patients with ADHD ages 6 to 17 years), mg/m^2-based safety margins are calculated using the average child body weight of 20 kg and conversion factor K_m of 25.

Reference ID: 4698714

Table 111. Methods for Study 812V-Tox2014-002

Methods	Details
Doses:	0 (control), 30/22 (LD), 87/65/43 (MD), 217/130/87 (HD) mg/kg/day [17]
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=65/sex/group TK: n=12/sex/group
Dose volume:	10 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR
Age:	Five to seven weeks at treatment initiation
Comment on study design and conduct:	See comments on dose selection and rat strain differences.
Dosing comments (dose adjustments or early termination):	Due to CNS toxicity (tremors and convulsions) and mortality in HD, doses were first reduced from 217 and 87 mg/kg/day to 130 and 65 mg/kg/day on day 130 in HD and MD, respectively. After the first dose reduction, some HD animals continued to show convulsions from day 187 and mortality from day 191. Consequently, doses were further reduced from 130, 65, and 30 mg/kg/day to 87, 43, and 22 mg/kg/day in HD, MD, and LD, respectively, on day 197. These dose reductions were implemented with ECAC agreement/recommendation.
Dosing solution analysis:	The concentration of the dosing formulation was within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

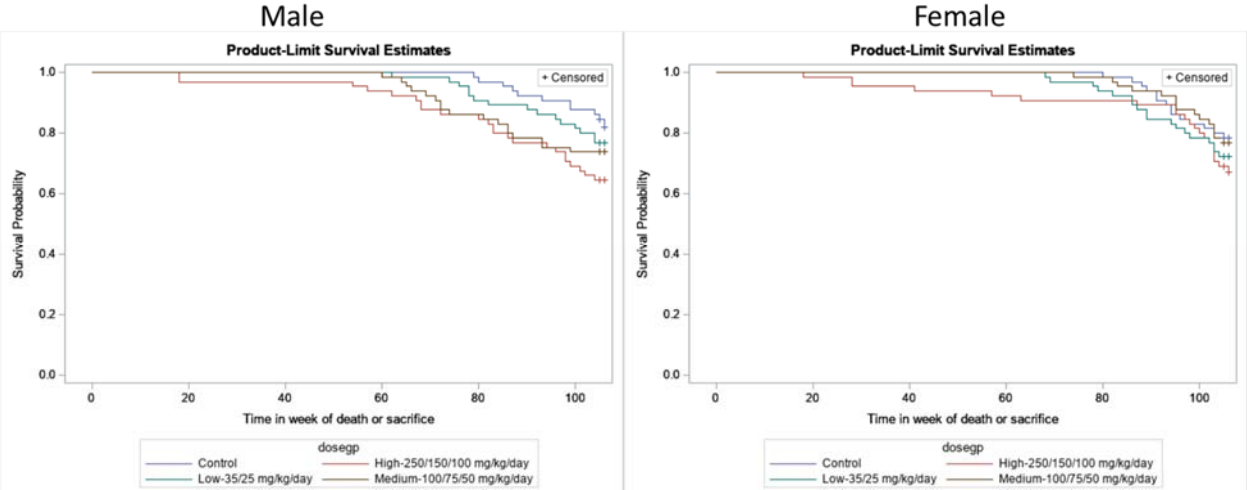
Five drug-related premature deaths occurred at the HD. Specifically, 2/65 HDMs (No. 4191 and 4228) and 1/65 HDF (No. 4452) died during days 123 to 126, which led to dose reductions from 217 and 87 mg/kg/day to 130 and 65 mg/kg/day in HD and MD, respectively, on day 130. After the initial dose reduction, two further HDFs died on days 191 and 193, which led to dose reductions from 130, 65, and 30 mg/kg/day to 87, 43, and 22 mg/kg/day in HD, MD, and LD, respectively, on day 197. No definitive cause of death was identified by the Applicant; however, prior to death, these animals had convulsions, which could have contributed to the deaths.

At the scheduled necropsy, there were 54 (83%), 50 (77%), 48 (74%), and 42 (65%) male rats and 51 (78%), 47 (72%), 50 (77%), and 44 (68%) female rats in the control, LD, MD, and HD groups, respectively (Figure 30). Based on Dr. Mbodj's statistical analysis, compared to controls, there is a statistically significant dose response in the mortality of male rats (p=0.0106) and the mortality rate was significantly increased in HDMs (p=0.011). The mortality rate in females was not affected by viloxazine.

[17] Doses are presented as free base-equivalent doses. The original doses of 0, 35/25, 100/75/50, and 250/150/100 mg/kg/day viloxazine hydrochloride are converted to free base-equivalent doses using a correction factor of 0.867.

Reference ID: 4698714

Figure 30. Kaplan–Meier Survival Curves in the 2-Year Rat Carcinogenicity Study



Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 30/22, 87/65/43, 217/130/87 mg/kg/day for LD, MD, and HD, respectively
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Clinical Signs

Compared to controls, HDM&Fs had CNS clinical signs of convulsions, tremors, salivation, and/or abnormal gait. In 2 HDMs and 3 HDFs, convulsions and/or tremors occurred prior to premature death, which led to dose reductions on day 130 and day 197, respectively (see mortality). After the dose was reduced to ≤87 mg/kg/day, no more clinical signs were observed.

Body Weights and Food Consumption

Compared to controls, viloxazine treatment caused dose-dependent decreases in body weight, weight gain, and/or food consumption in MDM&Fs and HDM&Fs. Body weight was decreased up to 7.7%, 8.4%, 12.5%, and 12.6% in MDMs, MDFs, HDMs, and HDFs, respectively (Figure 31). Cumulative weight gain was decreased by 5%, 7.3%, and 16.9% in HDMs, MDFs, and HDFs, respectively. Food consumption was decreased up to 11.0%, 18.3%, 9.4%, and 17.0% in MDMs, HDMs, MDFs, and HDFs, respectively. LD animals were not affected. It should be noted that the decreases were most apparent in the HD group early in the study when animals were treated at higher doses; after the second dose reduction, the decreases tended to resolve in HDM&Fs. Because the decreases in body weight were approximately in the range of the MTD (up to 12.6%), they are not considered to affect study quality or data interpretation.

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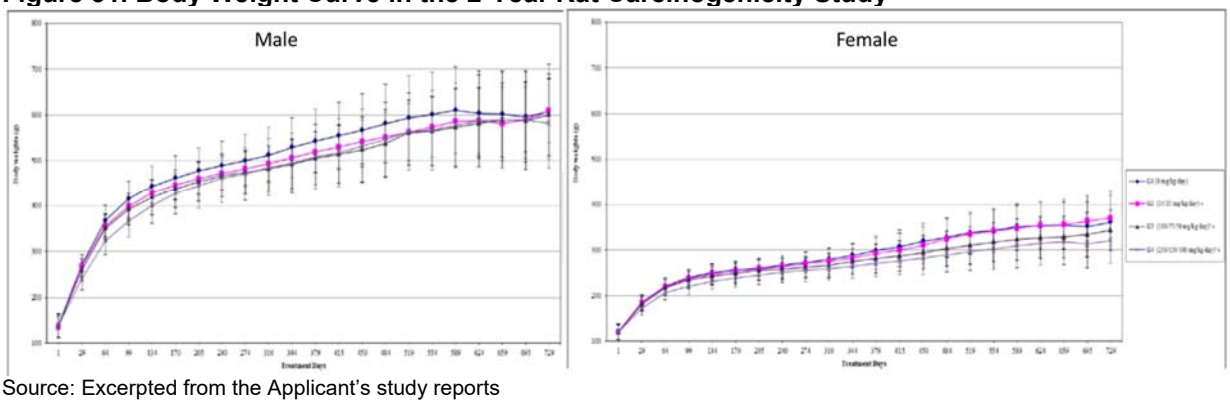
Figure 31. Body Weight Curve in the 2-Year Rat Carcinogenicity Study



Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 30/22, 87/65/43, and 217/130/87 mg/kg/day, respectively

Ophthalmology

Compared to controls, there were no drug-related ophthalmic findings.

Hematology

At the end of the treatment period, standard hematology parameters were evaluated in blood samples collected from the first 10 animals/sex/group. Compared to controls, there were no drug-related changes in hematology parameters.

Gross Pathology

There were no drug-related abnormal gross pathology findings in either animals that died prematurely or those surviving until the scheduled necropsy. The incidences of all observed findings, including palpable mass, were comparable across all of the groups.

Histopathology

Peer review conducted: Yes

Historical control provided for tumor incidence: Yes

Neoplastic

Compared to controls, there were no drug-related increases in the incidence of neoplastic tumors. Pairwise comparisons revealed a significant increase in the incidence of malignant cerebral glioma in MDMs relative to controls (4 of 65 [59] compared to 0 out of 65 [62] controls, Table 112). However, given the lack of significance in the trend analysis and the lack of similar findings in the HD group, this increase is not considered to be drug related.

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Table 112. Tumor Types with P-Values ≤0.05 for Pairwise Comparisons between the Treatment and Control Groups in the 2-Year Rat Carcinogenicity Study

sex	Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	24.15 mg Low (N=65) P - C vs. L	52.94 mg Med (N=65) P - C vs. M	114.47 mg High (N=65) P - C vs. H
Male	Brain, Cerebrum	Glioma, Malignant	0/65 (62) 0.3765	0/65 (59) NC	4/65 (57) 0.0497*	0/65 (53) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
*: Statistically significant at 0.05 for rare tumor in pairwise comparison.
Source: Excerpted from the statistical review of the Carcinogenicity Study
Doses are presented as adjusted doses due to dose reductions during the study

Dr. Malick Mbodj from the Division of Biometrics conducted the statistical review. The following is an excerpt from Dr. Mbodj's review:

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female rats. The pairwise comparisons test showed a statistically significant increases in the medium dose group for the incidences of malignant glioma, in the brain cerebrum, when compared to the vehicle control group in male rats with (p-value =0.0497).

Non-neoplastic

At the terminal necropsy, compared to controls, HDFs had an increased incidence of minimal to mild, focal, or multi-focal hepatocellular hypertrophy (10/44 compared to 3/51 controls). The Applicant considered this to be incidental. However, drug-induced hepatocellular hypertrophy and/or vacuolation were observed at comparable doses in previous 13-week and 18-month repeat-dose studies in rats of both sexes. In the general toxicology studies and carcinogenicity studies, females had higher drug exposure levels than males, which likely contributed to their increased incidence and/or severity of hepatocellular hypertrophy. Based on the similar findings of previous studies, it is considered to be drug related.

Toxicokinetics

On days 1 and 180, blood samples were collected from TK animals at 0.25, 0.5, 1, 3, 8, and 24 hours postdose[18]. TK parameters of viloxazine were analyzed. Two samples from control males on day 180 had quantifiable viloxazine concentrations. The values were very low and less than 0.3% of the C_{max} in the LD group; therefore, they do not affect data interpretation.

On both sampling days, after oral administration, viloxazine was rapidly absorbed and eliminated with T_{max} values of 0.25 to 1 hour postdose and $T_{1/2}$ values of 0.6 to 4.7 hours (Table 113). In general, the exposure levels were higher in females than males; however, the difference was generally less than 2-fold. In both sexes, the exposure (AUC) increased greater than dose proportionally. Due to dose reduction, the exposure levels were lower on day 180 relative to day

[18] For control animals, samples were collected only at 0.5 hours postdose.

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1. After adjustment for dose reduction, the exposure levels were comparable between days 1 and 180, and there was no accumulation.

Table 113. TK Parameters of Viloxazine in the 2-Year Rat Carcinogenicity Study

Sex	Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg)	$AUC_{0\text{-last}}$ (ng•hr/mL)	$AUC_{0\text{-24hr}}$ (ng•hr/mL)	DN $AUC_{0\text{-24hr}}$ (ng•hr/mL)/(mg/kg)	$t_{½}$ (hr)
Male	1	30 (LD)	0.50	1600	46	2200	2200	63	0.79
		87 (MD)	0.50	4500	45	9800	10000	100	0.95
		217 (HD)	0.25	9100	36	31000	37000	148	2.00
	180	30 (LD)	0.50	1400	40	2700	2700	77	4.70
		65 (MD)	0.25	4700	63	9700	9700	129	2.30
		130 (HD)	0.25	10000	67	17000	17000	113	2.80
Female	1	30 (LD)	0.50	1500	43	2800	2800	80	0.62
		87 (MD)	0.50	3300	33	15000	15000	150	0.99
		217 (HD)	1.00	9200	37	34000	48000	192	3.10
	180	30 (LD)	0.50	2000	57	4400	4400	126	2.70
		65 (MD)	0.50	4700	63	13000	13000	173	2.50
		130 (HD)	1.00	9400	63	35000	35000	233	3.90

Source: Excerpted from the Applicant's study reports
Doses were reduced on day 130 from 217 and 87 mg/kg/day to 130 and 65 mg/kg/day in the HD and MD groups, respectively
DN, dose-normalized C_{max} and AUC parameters
Abbreviations: AUC = area under the curve; HD = high dose; LD = low dose; MD = mid dose; T = time; TK = toxicokinetic

13.2.6.2. Twenty-six-Week Oral Gavage Carcinogenicity Study With Viloxazine in Transgenic rasH2 Mice

Study no.:	812V-Tox2016-002
Study report location:	EDR, SDN-1
Study initiation date:	February 2, 2016
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Viloxazine; 5003391/140016; 100.1%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Dose selection was based on a 5-day study at doses up to 434 mg/kg/day and a 4-week study at doses of 43, 130, and 173 mg/kg/day in Tg.rasH2 wild-type mice. CNS toxicity including convulsions were observed at doses ≥173 mg/kg/day and premature deaths occurred at 434 mg/kg/day, indicating that the MTD was exceeded at ≥173 mg/kg/day. No toxicities were observed at 43 mg/kg/day. Based on these findings, ECAC recommended doses of 0, 4.3, 13, and 43 mg/kg/day as the LD, MD, and HD, respectively.

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Key Findings

- Viloxazine did not increase the incidence of tumors in Tg.rasH2 mice treated for 26 weeks at oral doses of 4.3, 13, and 43 mg/kg/day. At the HD of 43 mg/kg/day, the exposure after 26 weeks of treatment is C_{max} values of 3930 and 3100 ng/mL and AUCs of 20,400 and 12,700 ng*hour/mL in males and females, respectively.
- Viloxazine at doses ≥4.3 mg/kg/day decreased body weight (up to 13%) and weight gain (up to 39%) in males. Females were generally not affected.

Reviewer's note: The Applicant conducted TK analysis in the wild-type mice on days 1 and 180. However, because the carcinogenicity study in the Tg.rasH2 mice is primarily used for hazard identification rather than risk assessment, the exposure multiples relative to the MRHD are not calculated.

Table 114. Methods for 812V-Tox2016-002

Methods	Details
Doses:	0 (control), 4.3 (LD), 13 (MD), and 43 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=25/sex/group in Tg.rasH2 mice TK study: n=18/sex/group in wild-type mice, of which 9/sex/group were evaluated for liver histopathology after 60 days of recovery Positive control: n=20/sex
Dose volume:	10 mL/kg
Formulation/Vehicle:	H_2O
Route of administration:	ORAL
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	Seven to eight weeks at treatment initiation
Comment on study design and conduct:	Positive control group was included, in which animals were treated intraperitoneally (IP) with urethane at 1000 mg/kg/day on days 1, 3, and 5. A TK analysis was conducted in wild-type mice.
Dosing comments (dose adjustments or early termination):	There was no dose adjustment or early termination.
Dosing solution analysis:	The concentrations of the dosing formulation were within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

Compared to controls, viloxazine did not affect survival in any of the treatment groups, when subjected to trend analysis or pairwise comparison. At the scheduled necropsy, there were 24 (96%), 23 (92%), 24 (96%), and 24 (96%) males and 24 (96%), 24 (96%), 25 (100%), and 24 (96%) females in the control, LD, MD, and HD groups, respectively.

In the positive control group, 10 (50%) males and 8 (40%) females died prematurely between days 57 and 133. Moribund clinical signs included hypoactivity, dehydration, abdominal respiration, swelling in the thoracic region, distended abdomen, and ventral recumbent. Post

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mortem necropsy identified gross lesions in the lungs and spleen, which correlated with microscopic findings of adenoma and carcinoma in the lung and hemangioma and hemangiosarcoma in the spleen. Given the clear evidence of tumor-related mortality, the remaining positive control animals were terminated on day 133.

Clinical Signs

Compared to controls, viloxazine did not cause any abnormal clinical signs. Animals in the positive control group showed ataxia immediately postdose on treatment days. These clinical signs are expected, based on the anesthetic effects of urethane (Hara and Harris 2002).

Ophthalmology

Compared to controls, there were no viloxazine-related ophthalmic findings.

Body Weights and Food Consumption

During the treatment period, compared to controls, body weight was decreased by up to 12.1%, 8.8%, and 13.5% in LD, MD, and HD males, respectively; weight gain was decreased by up to 30%, 22%, and 39% in LD, MD, and HD males, respectively. Females were generally not affected during the treatment period, except for a slight decrease in cumulative weight gain in HDFs (<5%).

At the end of the treatment period, compared to controls, body weight was significantly decreased in LDMs and HDMs; cumulative weight gain was decreased in LDMs, HDMs, and HDFs (Table 115). Food consumption was generally not affected by viloxazine.

Table 115. Summary of Body Weight and Cumulative Weight Gain at the End of the Treatment Period in the 26-Week Carcinogenicity Study in Tg.rasH2 Mice

Dose	Body Weight on Day 180 (g)		Cumulative Weight Gain (g)	
(mg/kg/day)	Male	Female	Male	Female
0 (Control)	34.37	23.92	12.18	6.23
4.3 (LD)	30.62*	23.37	8.6*	5.94
13 (MD)	31.40	23.41	9.48	5.99
43 (HD)	29.91*	22.90	7.4*	4.97[1]

Source: Excerpted from the Applicant's study reports
[1] p≤0.01
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Hematology

At the scheduled necropsy, blood samples were collected from all surviving main study animals.

Compared to the controls, slightly lower lymphocyte (4% to 17%) and higher neutrophil (33% to 39%) counts were observed in males at all doses. However, there was no clear dose relationship, and the values were within the historical control range at the test facility. Therefore, these changes are not considered to be drug related or adverse. Other hematology parameters were not affected.

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Gross Pathology

Compared to controls, the incidence of palpable mass was comparable across all groups. At the scheduled necropsy, HDFs had increased incidence of small thymus (9/25 compared to 1/25 controls) with correlative histopathology findings of thymus involution (7/25 HDFs relative to 1/25 control females). Thymus involution was also observed in other viloxazine-treated groups (see Histopathology). However, there was no clear dose relationship or other lesion in the thymus, and the thymus weight was not affected. Similar findings were not observed in the DRF study. Thymus involution is often associated with stress, particularly when the body weight was decreased in animals, rather than a direct drug effect on the thymus or immune system. Therefore, the toxicological significance of this finding appears to be limited.

Animals in the positive control group had a high incidence of lung (100% incidence) and spleen (~80% incidence) lesions, which correlated with histopathology of adenoma and/or carcinoma in the lung and hemangioma and hemangiosarcoma in the spleen.

Histopathology

Peer review conducted: Yes

Historical control provided for tumor incidence: Yes

Neoplastic

Compared to controls, there was no viloxazine-related increase in neoplastic findings at any dose. The positive control group had significant increases in the incidence of benign adenoma and malignant carcinoma in lung/bronchus and benign hemangioma and malignant hemangiosarcoma in the spleen in both sexes. Therefore, the Tg.rasH2 model used in this study is validated.

Dr. Malick Mbodj from the Division of Biometrics conducted the statistical review. The following is an excerpt from Dr. Mbodj's review:

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any non-positive control treated groups, when compare to the vehicle control group in both male and female mice.

Also the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of benign adenoma, malignant carcinoma in lungs/bronchus, benign hemangioma and malignant hemangiosarcoma in the spleen, when compared to the vehicle control group in both male and female mice (p-values <0.0001, 0.0004, <0.0001, <0.0001, and <0.0001, <0.0001, 0.0003, <0.0001, respectively).

Non-Neoplastic

Compared to controls, viloxazine at all doses increased the incidence of thymus involution in both sexes (Table 116). Involution of the thymus was characterized by reduced cortical and medullary cellularity, epithelia cysts, and increased prominence of epithelial cells. In the absence of other lesions in the thymus, these changes are likely due to aging and stress in the animals,

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rather than a direct drug effect on the thymus (Greaves 2012). No other nonneoplastic lesions were observed.

Table 116. Thymic Involution in the 26-Week Carcinogenicity Study in Tg.rasH2 Mice

	MALES					FEMALES				
Group No.:	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
Number of Animals on Study :	24	23	24	24	10	24	24	25	24	12
Number of Animals Completed:	(24)	(23)	(24)	(24)	(10)	(24)	(24)	(25)	(24)	(12)
THYMUS:										
Examined	(24)	(23)	(22)	(22)	(0)	(24)	(23)	(25)	(21)	(0)
Within Normal Limits	23	17	19	15	0	23	16	18	11	0
Not Examined: NOT PRESENT	0	0	1	1	0	0	0	0	2	0
Not Examined: UNSATISFACTORY SECTION, PRECLUDES EVALUATION	0	0	1	1	0	0	1	0	1	0
Involution	1	5	2	6	0	1	4	5	7	0
Cholesterol clefts	0	0	1	1	0	0	0	1	2	0
Epithelial hyperplasia	0	1	0	0	0	0	2	1	1	0
Lymphoid hyperplasia	0	0	0	0	0	0	1	0	0	0

Source: Excerpted from the Applicant's study reports
G1, control; G2, Low Dose; G3, Mid Dose; G4, High Dose

Special Histopathology Evaluation of the Liver

Wild-type TK animals were sacrificed at the end of the treatment (day 181) or after 2 months of recovery (day 240) (n=9/sex/group). The animals were examined for any gross lesions, and liver tissues were collected and evaluated for histopathology.

At the scheduled necropsy (days 181 and 240), compared to controls, there were no viloxazine-related gross pathology findings or histopathology changes in the liver. Hepatocellular vacuolation was observed at comparable incidences in male groups, including the controls; therefore, they are not considered to be drug related.

Toxicokinetics

On days 1 and 180, blood samples were collected from wild-type TK animals at 0.25, 0.5, 1, 3, 8, and 24 hours postdose[19]. The TK parameters of viloxazine were analyzed. A single sample from a control male had a quantifiable viloxazine concentration; however, the value was low (0.74% of the C_{max} in the LD group) and does not affect the data interpretation.

On both sampling days, after oral administration, viloxazine was rapidly absorbed and eliminated with a T_{max} of 0.25 hour postdose and a $T_{1/2}$ of 0.7 to 2.3 hours. The exposure levels were generally comparable between males and females and increased slightly greater than dose proportionally. Drug exposure did not change significantly with repeat administration, and there was no accumulation (Table 117).

[19] For the control TK group, blood samples were collected only at 0.25 hours postdose.

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Table 117. Summary of Viloxazine TK Parameters in the 26-Week Carcinogenicity Study in Tg.rasH2 Mice

Day	Gender	Group	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (ng•hr/mL)	AUC_{0-24hr} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	T_{last} (hr)	$t_{½}$ (hr)
1	Male	G2TK	5	0.25	720	789	1060	986	3	1.29
		G3TK	15	0.25	1260	3760	3780	3760	8	0.767
		G4TK	50	0.25	5400	19900	19900	19900	24	2.06
	Female	G2TK	5	0.25	510	767	1040	981	3	1.35
		G3TK	15	0.25	1350	2700	2770	2710	8	1.03
		G4TK	50	0.25	3030	15200	15200	15200	24	2.2
180	Male	G2TK	5	0.25	773	1120	1150	1120	8	1.08
		G3TK	15	0.25	1770	3310	3310	3310	24	2.32
		G4TK	50	0.25	3930	20400	20400	20400	24	2.08
	Female	G2TK	5	0.25	743	871	874	872	8	0.729
		G3TK	15	0.25	1490	2780	2840	2790	8	1.00
		G4TK	50	0.25	3100	12700	12700	12800	24	2.27

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 4.3, 13, and 43 mg/kg/day, respectively
Abbreviations: AUC = area under the curve; T = time; TK = toxicokinetic

13.2.7. Reproductive and Developmental Toxicology

13.2.7.1. Male and Female Fertility Study

Study title:	Viloxazine Hydrochloride: A Fertility and Reproductive Performance Study in Rat
Study no.:	723-0038
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
GLP compliance:	No (see overall comments)
Drug, lot #, and % purity:	Viloxazine; ADM 18420/72 and PDRM No. W0058; 99.3%

Key Findings

- Fertility parameters were not affected in male or female rats up to the maximum dose tested of 82 mg/kg/day.
- At 82 mg/kg/day, viloxazine slightly decreased body weight, weight gain, and/or food consumption in female rats.
- At 82 mg/kg/day, viloxazine decreased offspring viability with a correlative decrease in offspring weight.
- Viloxazine was present in offspring plasma when measured during early lactation days, most likely transported via milk.
- The NOAEL for male and female fertility is 82 mg/kg/day. The NOAEL for developmental toxicity in the offspring is 33 mg/kg/day.

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Table 118. Viloxazine Hydrochloride: A Fertility and Reproductive Performance Study in Rat Methods

Methods	Details
Doses:	0 (control), 13 (LD), 33 (MD), and 82 (HD) mg/kg/day
Frequency of dosing:	Daily (via diet)
Number/sex/group:	n=15/dose group for males; n=30/dose group for females
Dose volume:	Not applicable
Formulation/vehicle:	Purina laboratory chow
Route of administration:	DIETARY
Species:	Rat
Strain:	Sprague-Dawley
Comment on study design and conduct:	This study adopted a one-generation, two-litter design. Briefly, male and female rats were treated with viloxazine via dietary intake. Male rats (n=15/group) were treated for 8 weeks prior to the first mating period; see below) and continued to receive dietary viloxazine treatment until completion of the second littering (a total of 22 weeks). Female rats (n=30/group) were treated for 2 weeks prior to the first mating with treated males. Subsequently, 15 females per dose group were evaluated via cesarean section on gestation day (GD) 13. The remaining 15 females per dose group were allowed to deliver the first litter and mated again with the treated males 2 to 3 weeks after weaning of the first litter to produce a second litter. During this period, females continued to receive dietary viloxazine treatment until the last week of lactation of the second litter (a total of 13 weeks). At the terminal necropsy, all sires and dams were evaluated for gross pathology; in addition, 2 male and 2 female pups in each of the second litter were examined for gross pathology.
Dosing solution analysis:	The stability and concentration of viloxazine in the diet were confirmed to be within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

There were no drug-related premature deaths in the study.

Clinical Signs

There were no abnormal clinical signs in the study.

Body Weight and Food Consumption

Compared to controls, body weight and weight gain were slightly decreased in HDMs and sometimes in LDMs throughout the study. The decreases were generally mild (≤~5%) without clear correlative changes in food consumption; therefore, they are not considered to be adverse.

Compared to controls, HDFs had weight loss during the first two weeks (up to 2.2 g weight loss) after treatment initiation, which correlated with decreased food consumption (up to 20%). HDFs also had decreased weight gain during the last week of the second gestation period (~7%), which also correlated with decreased food consumption (~10%). After delivery of the second litter, the

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body weight gain was comparable across all groups during the lactation period. Given the transient nature and small magnitude, the slight decreases in body weight did not affect the overall health of the animal and are not considered to be adverse.

Reviewer's note: During the mating period, males received the same diet as females, in which the viloxazine concentration was adjusted based on female body weights. Because females generally weigh less than males, it is estimated that the actual viloxazine doses administered to the males were 10% to 30% lower than the designated values. However, because the mating period was only 2 weeks each, whereas males received adequate viloxazine doses during the rest of the 22-week treatment period, it is unlikely that the decreased viloxazine doses during the mating period would significantly affect the study outcome.

Similarly, for female rats, because body weights were not measured during the first lactational period, no dose adjustment was made for females when their body weights decreased due to parturition and their food consumption increased to support lactation. It is estimated that the viloxazine doses in females during the first lactation period increased by 50% to 75%. The increases in viloxazine doses do not impact study interpretation because they did not adversely affect maternal health during this period.

Fertility and Pregnancy Parameters

Compared to controls, male or female fertility was not affected by viloxazine; the fertility and gestation index were comparable across all groups, including the controls (Table 119). In addition, cesarean evaluation in females on gestation day (GD) 13 did not identify any drug-related effects. The number of viable embryos, resorption, implantation sites, corpora lutea, and pre- and postimplantation loss were comparable across all of the groups.

Table 119. Male and Female Fertility Index in the Rat Fertility Study

	mg Viloxazine HCl/kg/day	Male Fertility Index[a] # Sires/# Mated	%	Female Fertility Index[b] # Preg./	# with + evidence of mating	%	Gestation Index # Littering/# Preg.	%
First Mating	0	13/15	86.7	24/26[c]		92.3	12/12	100.0
	15	14/15	93.3	26/28[c]		92.8	12/12	100.0
	38	15/15	100.0	27/29[c]		93.1	13/13	100.0
	95	13/15	86.7	25/29[c]		86.2	11/12	91.7
Second Mating	0	12/15	80.0	12/14		85.7	12/12	100.0
	15	12/15	80.0	12/15		80.0	12/12	100.0
	38	13/15	86.7	13/15		86.7	13/13	100.0
	95	14/15	93.3	14/14		100.0	14/14	100.0

[a] Maximum mating interval of 7 days.
[b] Maximum mating interval of 14 days.
[c] Includes those rats killed at Day 13 of gestation.

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 13, 33, and 82 mg/kg/day, respectively

Viability of Offspring

Compared to controls, pup viability at birth and on lactation day (LacD) 4 was comparable across all groups; however, from LacD 4 (when all litters were culled to 10 pups per litter) to LD 21 (weaning), offspring viability (lactation index) was significantly decreased in the HD group

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(30%, Table 120) for the first littering period, which also correlated with decreased offspring body weight (up to 21%, Table 121).

The deaths of offspring primarily occurred between LacDs 8 and 14, during which 33 pups in 7 litters in the HD group died compared to 8 pups in 3 litters in the control group. The Applicant stated that the period of the greatest loss coincided with a 6.5-hour power outage, during which the temperature and humidity in the room gradually increased to over 80°F and 50%, respectively. However, given that the power outage affected all groups in the same room, the decreases in offspring viability in the HD group are most likely drug related, although the data could not distinguish between a direct drug effect on the offspring and an indirect drug effect due to deficits in maternal care.

Table 120. Drug-Related Decreases in Offspring Viability/Lactation Index in the Rat Fertility Study

	mg Viloxazine HCl/kg/day	Viable Pups/ Litter at Day 04	Viability Index at Day 04	Viable Pups/ Litter After Cull	Viable Pups/ Litter at Day 21	Lactation Index (Day 21)
	0	12.6	98.85	10.0	9.3	93.33
First	15	12.3	98.89	9.8	8.8	90.83
Litter	38	11.8	96.40	10.0	9.5	95.38
	95	10.8	97.78	9.2	5.9**	65.15**
	0	13.8	98.16	10.0	9.8	97.50
Second	15	12.6	95.90	9.8	9.3	95.00
Litter	38	12.3	94.81	9.9	9.6	96.84
	95	11.5	97.79	8.8*	8.5	96.92

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 13, 33, and 82 mg/kg/day, respectively
* p<0.05, ** p<0.01 compared to controls

Table 121. Drug-Related Decreases in Offspring Body Weight in the Rat Fertility Study

	mg Viloxazine HCl/kg/day	Average Weight (g) of Pups at Days 01 Obs.	01 Adj.[1]	04 Obs.	04 Adj.[1]	07 Obs.	07 Adj.[1]	14 Obs.	14 Adj.[1]
	0	6.99	7.06	9.28	9.43	13.42	13.42	25.49	24.80
First	15	6.86	6.89	9.15	9.23	12.99	12.99	27.46	27.13
Litter	38	6.88	6.89	9.56	9.55	13.95	13.95	27.35	26.05
	95	6.59	6.46**	8.33	8.09**	10.93**	10.94**	20.08**	22.12
	0	6.86	6.97	8.88	9.27	13.50	13.68	26.96	27.37
Second	15	6.78	6.79	8.97	8.99	13.05	13.10	26.01	25.99
Litter	38	6.73	6.73	9.01	8.94	13.66	13.84	27.58	27.87
	95	6.81	6.69	9.09	8.80	13.39	12.99	27.20	26.56

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 13, 33, and 82 mg/kg/day, respectively
Adj 1, adjusted for litter size; ** p<0.01 compared to controls

Necropsy

At the end of the second littering period, all F0 males and females as well as 2 male and 2 female pups from each litter were evaluated for gross pathology. Compared to controls, there were no drug-related gross pathology findings.

Reference ID: 4698714

Toxicokinetics

At the time of weaning (LacD21) of the first litters and culling (LacD4) of the second litters, blood samples were collected from male and female pups from several litters in each group. The plasma concentration of viloxazine was determined.

On LacD 4, viloxazine was present only in pooled plasma samples collected from pups in the HD group (Table 122). Although no direct measurement of the viloxazine level in milk was conducted, these data suggest that during early lactation days, pups were exposed to viloxazine likely via milk, because at that stage the viloxazine exposure via direct diet intake is expected to be minimal.

Table 122. Plasma Levels of Viloxazine in Pups on Lactation Day 4

Treatment (mg Viloxazine HCl/kg/day)	Number of Litters (2 to 3 culls)	Plasma Levels of Viloxazine Hydrochloride (Micrograms/ml)
Control (0)	4	None detected
Low (15)	4	None detected
Medium (38)	4	None detected
High (95)	1	None detected
	1	2.01
	1	1.88
	1	0.28

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 13, 33, and 82 mg/kg/day, respectively

On LacD21, viloxazine was also present in some but not all plasma samples collected from offspring in the HD group, and the levels were generally low (Table 123). At this stage, both lactational and dietary exposure to viloxazine could occur. The decrease in the plasma level of viloxazine in the offspring is likely due to increased metabolism in growing offspring.

Table 123. Plasma Levels of Viloxazine in Pups on Lactation Day 21

Treatment (mg Viloxazine HCl/kg/day)	Number of Samples	Plasma Levels of Viloxazine Hydrochloride Mean ± Standard Deviation (Micrograms/ml)
Control (0)	6 (3M, 3F)	None detected
Low (15)	6 (3M, 3F)	None detected
Medium (38)	10 (5M, 5F)	None detected
High (95)	10 (5M, 5F)	None detected
	5 (2M, 3F)	0.034 ± 0.010

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 13, 33, and 82 mg/kg/day, respectively

13.2.7.2. Embryofetal-Developmental Toxicity Study

Study title:	Viloxazine Hydrochloride: A Teratogenic Potential Study in Rats–Oral
Study no.:	723-0066
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
GLP compliance:	No (see overall comments)
Drug, lot #, and % purity:	Viloxazine; ADM 16009/73 and PRDM W0091; 99.2%

Reference ID: 4698714

Key Findings

- Viloxazine, at doses up to 82 mg/kg/day, did not cause maternal toxicity.
- At 82 mg/kg/day, viloxazine caused fetal toxicities, including increased early and late resorption and increased number of small fetuses with delayed development.
- At 82 mg/kg/day, possible drug-related fetal malformations or anomalies were observed at relatively low incidences, including a single fetus with craniorachischisis (severe neural tube defect), 2 fetuses from a single litter with darkening of the lining of the third ventricle (potentially associated with hydranencephaly), and 2 fetuses from a single litter with missing cervical vertebrae.
- The NOAEL for maternal toxicity is 82 mg/kg/day. The NOAEL for embryofetal toxicity and malformation is 33 mg/kg/day.

Reviewer's note: At 82 mg/kg/day, low incidences of fetal malformation or anomalies, such as craniorachischisis, internal hydrocephalus, and missing vertebrae, were observed in single dams in the HD group. These changes could be spontaneous. However, in the absence of historical control data, a drug effect could not be completely excluded. Because the study is a legacy study without full GLP compliance, considering the uncertainty of the overall evidence, The NOAEL for fetal malformation is conservatively set at 33 mg/kg/day.

Table 124. Viloxazine Hydrochloride: A Teratogenic Potential Study in Rats–Oral Methods

Methods	Details
Doses:	0 (control), 13 (LD), 33 (MD), and 82 (HD) mg/kg/day[20]
Frequency of dosing:	Once daily
Number/sex/group:	n=23/group
Dose volume:	5 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Not specified in the study report
Comment on study design and conduct:	Pregnant rats were orally treated with viloxazine at 0, 13, 33, and 82 mg/kg/day from GDs 6 to 15, which is slightly shorter than GDs 6 to 17, typically used in current studies. However, it is adequate to cover the period of organogenesis in rats. Cesarean evaluation was conducted on GD 20.
Dosing solution analysis:	The stability and concentration of viloxazine were confirmed to be acceptable for the study duration.

Source: summarized from the Applicant's study reports

Observations and Results

F_0 Dams

Mortality

There were no premature deaths in the study.

[20] Doses are presented as free base-equivalent doses. The original doses of 0, 15, 38, and 95 mg/kg/day viloxazine hydrochloride are converted to free base-equivalent doses using a correction factor of 0.867.

Reference ID: 4698714

Clinical Signs

There were no drug-related abnormal clinical signs. During the study, 3 dams were slightly injured due to repeated gavage procedure but recovered within 1 week.

Body Weight and Food Consumption

Compared to controls, there were no drug-related changes in body weight or weight gain. Food consumption was not measured; however, because there were no drug effects on body weight, weight gain, or any abnormal clinical signs, the animals appeared healthy throughout the study; and the lack of food consumption data did not affect data interpretation.

Cesarean Section Data

Two, two, four, and two females in the control, LD, MD, and HD groups were not pregnant. In addition, one dam each in the control (no. 1211) and MD (no. 3213) groups had no viable fetuses. Given the comparable incidences and lack of a clear dose relationship, these are not considered to be drug related. For comparison of group mean values, 20, 21, 18, and 21 dams were evaluated in the control, LD, MD, and HD groups, respectively.

Compared to controls, the HD group had increased mean number of corpora lutea, implantation sites, and early and late resorptions (Table 125). It should be noted that due to the increases in the absolute number of corpora lutea and implantation sites, the number of viable fetuses per dam was not decreased at the HD; however, after adjustment for the number of corpora lutea and implantation sites, the percentage of early and late resorption was increased at the HD, suggesting a potential drug-related embryotoxicity.

Table 125. Drug-Related Changes in Cesarean Parameters in the Rat Embryo-Fetal Developmental Toxicity Study

	Corpora Lutea	Implantation Sites	Viable Fetus	Early Resorption	Late Resorption
Control	14.7	261 (12.8)	12.4	13 (5 %)	0 (0%)
LD	15.9	287 (13.7)	13.1	14 (4.9%)	0 (0%)
MD	16.1	256 (14.1)	13.5	14 (5.5%)	0 (0%)
HD	17.9*	313 (14.8*)	13.1	33 (10.5%)*	5 (1.6%)*

Source: Modified/reformatted based on the data in the Applicant's study reports
Values are mean numbers per dam/litter
* p<0.05 compared to controls
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Necropsy/Histopathology

At the scheduled necropsy, there were no drug-related abnormal gross pathology findings. Histopathology evaluation in the dams was not conducted.

F_1 Offspring

Terminal Observations

Compared to controls, the HD group had an increased incidence of small fetuses (<3.2 g body weight and 0.5 g less in body weight than the rest of the same litter, mean fetal weight in the HD

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group was 3.86 g) when counted both by litter and by fetus (Table 126). These fetuses were slightly delayed in development, as evidenced by delayed ossification of the sternum. In addition, the crown-rump measurements (a measurement of fetal length and size) revealed a trend towards larger fetuses in the LD and MD groups and smaller fetuses in the HD group relative to the controls, although the difference did not reach statistical significance (Table 126). Other parameters, such as the fetal sex ratio, were not affected.

Table 126. Drug-Related External Fetal Observations in the Rat Embryo-Fetal Developmental Toxicity Study

	Litters with Small Fetuses	Number of Small Fetuses	Fetal Weight (g, Adjusted for Litter Size)	Crown-Rump Measurement (mm, Adjusted for Litter Size)
Control	5	5	3.95	37.12
LD	1	1	4.12	37.67
MD	2	2	4.18*	37.77
HD	7[a]	19[b,c]	3.86	36.59

Source: Modified/reformatted based on the data in the Applicant's study reports
[a] p<0.05 compared to controls
[b] Includes 1 litter of 11 fetuses (dam no. 4222), in which 8 were small. One of the small fetuses in this litter had craniorachischisis
[c] Includes 1 fetus with a placenta superimposed or fused with another placenta to a normal-size fetus
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Fetal Malformations/Variations (External, Visceral, Skeletal)

External

One HD dam (No. 4222) had 1 fetus (from a litter of 11) with craniorachischisis (a severe type of neural tube defect, in which both the brain and spinal cord remain open). No historical data were provided in the study report; based on current historical control data at the time of this review, craniorachischisis is a rare finding. The Applicant considered it to be incidental because there were no correlative malformations or anomalies (such as encephalocele, exencephaly, or spina bifida). Although this is a reasonable argument, given the visceral and skeletal findings in the HD group, a drug effect could not be completely excluded.

Visceral

Compared to the control group, the MD and HD groups had slight increases in the incidence of renal pelvic dilation. HD group had a single incidence of slightly distended bladder (Table 127). These are commonly observed fetal variations. Given the low incidence, they are not considered to be adverse.

Two fetuses from a single HD dam had darkening of the lining of the third ventricle (Table 127), a condition reported to be associated with internal hydrocephalus (Richardson and Hogan 1946). Therefore, a potential drug-related effect at the HD could not be excluded.

Skeletal

Compared to controls, 2 fetuses from a single HD litter (dam no. 4223) had only 6 cervical vertebrae (missing the seventh vertebra, a potential skeletal malformation). A potential drug-related effect could not be excluded. In addition, HD fetuses had an increased incidence of delayed ossification of the sternebrae, a nonadverse variation likely due to delayed fetal development.

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Table 127. Visceral Fetal Findings in the Rat Embryo-Fetal Developmental Toxicity Study

	Litters/Fetuses Examined	Renal Pelvic Dilation	Third Ventricle Discoloration	Urinary Bladder Slightly Distended
Control	20/84	2	0	0
LD	21/86	3	0	0
MD	19/79	6	0	0
HD	21/88[a]	5	2	1

Source: Modified/reformatted based on the data in the Applicant's study reports
[a] One additional fetus with craniorachischisis examined separately and not included in this table; this fetus also showed renal pelvic dilation
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

Study title:	Study of Effects of Orally Administered SPN-812V on Embryofetal Developmental Toxicity in New Zealand White Rabbits
Study no.:	812V-Tox2017-016
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Viloxazine; 5002946/130032; 100.5%

Key Findings

- Viloxazine, at doses ≥87 mg/kg/day, caused maternal weight loss or decreased weight gain, with correlative decreases in food consumption.
- Viloxazine, at doses up to 130 mg/kg/day, did not cause significant fetal toxicity and was not teratogenic.
- The NOAEL for maternal toxicity is 43 mg/kg/day. The corresponding exposure levels are C_{max} of 5460 ng/mL and AUC of 10,600 ng*hour/mL on GD 18.
- The NOAEL for fetal toxicity and teratogenicity is 130 mg/kg/day. The corresponding exposure levels are C_{max} of 19,100 ng/mL and AUC of 65,900 ng*hour/mL on GD 18.

Table 128. Study of Effects of Orally Administered Viloxazine on Embryofetal Developmental Toxicity in New Zealand White Rabbits Methods

Methods	Details
Doses:	0 (control), 43 (LD), 87 (MD), and 130 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/sex/group:	n=23/group for main study; additional n=3/group for TK
Dose volume:	3 mL/kg
Formulation/vehicle:	0.5% sodium carboxymethyl cellulose in water
Route of administration:	ORAL
Species:	Rabbit
Strain:	New Zealand White rabbit

Reference ID: 4698714

Methods	Details
Comment on study design and conduct:	The study also included a dose range-finding phase (part I), in which pregnant rabbits were orally treated with viloxazine at 0, 43, 87, 130, and 217 mg/kg/day (n=7/group) from GD 6 to 18. Cesarean evaluation was conducted on GD 29. Viloxazine did not cause any maternal or fetal toxicity at 43 mg/kg/day. At 87 and 130 mg/kg/day, viloxazine decreased maternal food consumption (up to 37%) with no fetal toxicity. At 217 mg/kg/day, viloxazine caused maternal weight loss (-0.12 kg compared to +0.12 kg in controls) and decreased food consumption (56.2%). At this maternally toxic dose, viloxazine also caused increased post-implantation loss (39%). These data suggest that MTD was exceeded at 217 mg/kg/day, whereas the maternal toxicities of decreased body weight and food consumption at 130 mg/kg/day were tolerated. Therefore, 130 mg/kg/day was selected as the high dose for the definitive phase (part II).
Dosing solution analysis:	The concentrations of the dosing formulation were within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

F_0 Dams

Mortality

There were no drug-related premature deaths in the study. One, two, zero, and one rabbit aborted in the control, LD, MD, and HD groups, respectively. One of the 2 LD animals (No. 3566) that aborted also died on GD 25; a post mortem evaluation did not identify any cause. Because there was no mortality observed at higher doses, this death is considered to be incidental.

Clinical Signs

During the treatment period, compared to controls, 1 HD animal showed clinical signs of hyperpnea and abduction of fore- and hind-limbs postdose on GDs 13 and 16 (treatment days 8 and 11). Considering the low incidence, transient nature, and no effect on the general health of the animal, this finding is not considered to be adverse. No other drug-related clinical signs were observed.

Body Weight and Food Consumption

During the treatment period (GD 6 to 18), compared to controls, body weight gain was dose-dependently decreased at all doses. The decreases were more profound in the MD (no weight gain) and HD (weight loss) groups, and correlated with decreased food consumption (up to ~45% in the MD and HD groups), and were reversible during the treatment-free period (GD 18 to 29, Table 129).

Reference ID: 4698714

Table 129. Drug-Related Decreased in Body Weight Gain in the Rabbit Embryo-Fetal Developmental Toxicity Study

Dose (mg/kg/day)	0 (Control)	43 (LD)	87 (MD)	130 (HD)
Body weight on GD 6 (kg)	3.2	3.18	3.14	3.16
Body weight on GD 18 (kg)	3.33	3.25	3.14	3.14
Body weight on GD 29 (kg)	3.41	3.37	3.30	3.27
Weight gain during treatment period (kg, GD 6-18)	0.13	0.07	0.0	-0.02
Weight gain during treatment free period (kg, GD 18-29)	0.08	0.12	0.16	0.13

Source: Modified/reformatted based on the data in the Applicant's study reports
Abbreviations: GD = gestation day; HD = high dose; LD = low dose; MD = mid dose

Cesarean Section Data

At the scheduled cesarean, compared to controls, there were no drug-related changes in maternal reproductive parameters. The gravid uterine weight, number of corpora lutea, implantations, early and late resorptions, and pre- and post-implantation loss were comparable across all groups, including the control group.

Necropsy/ Histopathology

At the scheduled cesarean, compared to controls, there were no drug-related gross pathology findings in the dams.

Toxicokinetics

On GDs 6 and 18, blood samples were collected at 0.25, 0.5, 1, 3, 8, and 24 hours postdose from TK animals[21]. The TK parameters of viloxazine were analyzed.

On both sampling days, after oral administration, viloxazine was rapidly absorbed, with a T_{max} of 0.25 to 1 hour postdose; and quickly eliminated, with a $T_{1/2}$ of 1.8 to 3.6 hours. The exposure (AUC) to viloxazine increased greater than dose proportionally. The exposure profiles were largely comparable between GD 6 and GD 18, and there was no significant accumulation.

[21] For control TK animals, blood samples were collected only at 0.25 hours postdose.

Reference ID: 4698714

Table 130. Toxicokinetic Parameters of Viloxazine in the Rabbit Embryo-Fetal Developmental Toxicity Study

Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0-24\,h}$ (hr•ng/mL)	AUC_{inf} (hr•ng/mL)	$t_{1/2}$ (h)	T_{last} (h)
GD 6	50 (G2TK)	0.5 (0.5 -1.0)	2730 ± 818	6650 ± 1680	6650 ± 1680	2.62 ± 0.372	24 (24-24)
	100 (G3TK)	0.25 (0.25 -0.25)	14600 ± 4480	41400 ± 4490	41400 ± 4490	1.77 ± 0.056	24 (24-24)
	150 (G4TK)	1.0 (1.0-1.0)	12200 ± 2720	84000 ± 29500	84000 ± 29500	1.86 ± 0.18	24 (24-24)
GD 18	50 (G2TK)	0.5 (0.25-1.0)	5460 ± 3000	10600 ± 3340	10885 [a]	3.37[a]	24 (24-24)
	100 (G3TK)	0.25 (0.25-0.5)	15100 ± 7010	36700 ± 7580	36700 ± 7580	1.89 ± 0.106	24 (24-24)
	150 (G4TK)	1.0 (0.25-3.0)	19100 ± 12000	65900 ± 2940	66000 [a]	3.56 [a]	24 (24-24)

AUC_{inf}: Area under the plasma concentration- time curve up to infinity
AUC_{0-24hr}: Area under the plasma concentration-time curve from time 0 to 24 hr
AUC_{0-last}: Area under the plasma concentration-time curve from time 0 to the last measurable concentration
C_{max}: Maximum concentration in plasma
$t_{½}$: Elimination phase half-life
T_{max}: Time to reach maximum plasma concentration
T_{last}: Time of last quantifiable concentration
[a] n=2 animal data

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 43, 87, and 130 mg/kg/day, respectively
Abbreviations: AUC = area under the curve; GD = gestation day; T = time

F_1 Offspring

Terminal Observations

Compared to controls, there was a slight but not statistically significant decrease in mean fetal weight in the HD group (7%), which correlated with the decrease in maternal weight gain during the gestational treatment period. Given the small magnitude and lack of other adverse fetal findings, it is not considered to be adverse. Other parameters were not affected, including the average number of fetuses, live fetuses, and sex ratio.

Fetal Malformations/ Variations (External, Visceral, Skeletal)

External

Compared to controls, there was no drug-related external fetal malformation or variation. A single fetus in the HD group had a moderately flexed left forelimb at the wrist (fetal incidence/group of 0.7%). However, the incidence value was within the historical control range at the test facility (0.81%); therefore, it is not considered to be drug related.

Reference ID: 4698714

Visceral

Compared to controls, there was no drug-related visceral malformation.

Skeletal

Compared to controls, there was no drug-related skeletal malformation. A slight increase in the incidence of incomplete ossification of the second sternebrae was observed in HD fetuses (4 fetuses in 4 litters, compared to 2 fetuses in 1 litter in the controls), which correlated with slightly decreased fetal weight in this group. They are not considered to be adverse.

13.2.7.3. Pre- and Post-natal Developmental Toxicity

Study title:	Study of Effects of Orally Administered SPN-812V on Pre- and Post-natal Development, including Maternal Function in Wistar Rats
Study no.:	821V-Tox2017-017
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Viloxazine; 5002946/130032; 100.5%
Enhanced PPND Study:	N

Key Findings

- Viloxazine, at 217 mg/kg/day, caused premature deaths in 4/20 dams and led to a dosing holiday between GD 20 to 23 in 9 dams.
- Viloxazine, at 217 mg/kg/day, caused significant decreases in maternal body weight, weight gain, and food consumption during the gestation and lactation periods. At 87 mg/kg/day, maternal body weight gain was also decreased during the gestation period.
- Viloxazine, at ≥87 mg/kg/day, reduced the live birth rate and decreased offspring viability during the early lactation period (day 1 to day 4).
- Viloxazine, at ≥87 mg/kg/day, caused delayed development in the offspring during the pre-weaning period. At 217 mg/kg/day, viloxazine also caused delayed growth and sexual maturation in the offspring during the postweaning period.
- Viloxazine, at doses up to 217 mg/kg/day, did not affect the neurobehavioral parameters, including learning and memory, or the reproductive capacity of the offspring.
- The NOAEL for maternal toxicity and developmental toxicity is 43 mg/kg/day. The corresponding maternal exposure levels are a C_{max} of 3600 ng/mL and an AUC of 7880 ng*hour/mL on lactation day 20.

Reference ID: 4698714

Table 131. Study of Effects of Orally Administered Viloxazine on Pre- and Post-natal Development, Including Maternal Function in Wistar Rats Methods

Methods	Details
Doses:	0 (control), 43 (LD), 87 (MD), and 217 (HD) mg/kg/day[22]
Frequency of dosing:	Once daily
Number/sex/group:	Main study: n=20/dose group for main study. TK: n=9/ dose group for viloxazine-treated groups and n=5 for the control group.
Dose volume:	10 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Wistar
Comment on study design and conduct:	Pregnant rats were orally treated with viloxazine at 0, 43, 87, and 217 mg/kg/day from GD 6 to weaning (lactation day 20). Parameters evaluated include: for F0 dams: mortality, clinical signs, body weight and food consumption, parturition, lactation, and gross pathology at scheduled necropsy; for F1 generation: viability, clinical signs, body weight and food consumption, sexual maturation, neurobehavioral assessment (sensory and motor activity, learning and memory), reproductive capacity, and gross pathology.
Dosing solution analysis:	The concentration and stability of the dosing formulation were within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

F_0 Dams

Mortality and Clinical Signs

During the gestation period, 4 HD dams died prematurely during GD 20 to 22; only one of these dams was observed with moribund signs of recumbency (Table 132). A post mortem necropsy showed non-glandular stomach thinning in 3 of the 4 dams, which is more likely a secondary change due to the general poor health of the animal, rather than the direct cause of death. Nevertheless, given the multiple incidences at HD, these deaths are considered to be drug related. Due to the premature deaths, dosing was paused for the remaining 11 dams that had not yet littered (GD 20 to 23) and resumed following littering. Of the 16 surviving dams, 5 dams littered before dosing was paused and 9 dams littered after dosing suspension; 2 females were not pregnant. There were no drug-related clinical signs in the dams that survived until littering and scheduled necropsy.

[22] Doses are presented as free base-equivalent doses. The original doses of 0, 50, 100, and 250 mg/kg/day viloxazine hydrochloride are converted to free base-equivalent doses using a correction factor of 0.867.

Reference ID: 4698714

Table 132. Drug-Related Premature Deaths in the Rat Pre- and Post-natal Developmental Toxicity Study

Rat No.	Clinical Signs	Unscheduled Mortality Type
Ru7521	None	Found dead on GD 22
Ru7527	None	Found dead on GD 20
Ru7528	Recumbent	Moribund sacrificed on GD 21
Ru7539	None	Found dead on GD 20

Source: Excerpted from the Applicant's study reports
Abbreviations: GD = gestation day

Body Weight and Food Consumption

During gestation, compared to controls, viloxazine caused dose-dependent decreases in maternal body weight, weight gain, and food consumption. The decreases were most profound in the HD group during the first 3 days after treatment initiation (up to 8%, 69%, and 23% in body weight, weight gain, and food consumption, respectively, Table 133). Weight gain in the MD group was also decreased (by 50.44%).

Table 133. Drug-Related Decreases in Maternal Body Weight, Weight Gain, and Food Consumption in the Rat Pre- and Post-natal Developmental Toxicity Study

Parameter	Dose (mg/kg/day)		
	50	100	250
Body Weights during Gestation			
GD 15	↓2.44	↓3.96	↓8.16*
GD 20	↓2.03	↓3.58	↓8.35*
Body Weight Gains (%) compared to control during Gestation			
GDs 6-9	↓20.39	↓50.44	↓68.56*
GDs 9-12	↓10.46	↓9.44	↓39.90*
GDs 0-20	↓4.11	↓7.31	↓20.66*
Parameter	**Dose (mg/kg/day)**		
	50	**100**	**250**
Food consumption (%) compared to control during Gestation			
GDs 6-9	↓9.65	↓9.15	↓22.52*
GDs 9-12	↓10.91	↓7.51	↓21.57*
GDs 12-15	↓8.20	↓9.32	↓20.54*
GDs 15-18	↓5.09	↓7.13	↓17.25*
GDs 0-20	↓6.60	↓4.74	↓14.47*

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 43, 87, and 217 mg/kg/day, respectively
* $p<0.01$
Abbreviations: GD = gestation day

Reference ID: 4698714

During the lactation period, compared to controls, maternal body weight and weight gain were decreased in the HD group (by 7% to 9% and 21% to 120%, respectively), which correlated with decreased food consumption (22% to 26%). The LD and MD groups were generally not affected during the lactation period.

Parturition and Litter Observations

At parturition, pregnancy was confirmed in 16 (80%), 20 (100%), 20 (100%), and 18 (90%) out of the 20 mated females in the control, LD, MD, and HD group, respectively. Compared to controls, MD and HD groups had increased number of dead pups (16 and 20 in the MD and HD groups, respectively, compared to 0 in the control group). The HD group had decreased gestation index (92.9% compared to 100% in the control group), due to 1 HD dam delivering all dead pups (3 pups in total) on GD 24 after 3 days of dosing holiday. In addition, the HD group had increased post-implantation loss (32.4%, compared to 11.5% in controls); this value was also out of the historical control range at the test facility.

From lactation days (LacDs) 0 to 4, compared to the control group, the MD and HD groups had increased number of total litter loss (3 in both the MD and HD groups, compared to 0 in the control group), which resulted in a lower survival index (80.8% and 86.5% in the MD and HD groups, respectively, compared to 97.8% in the control group). In addition, compared to controls, HD pups had decreased body weight (up to 32%) during the lactation period (Table 134). Values in the MD and HD groups were also out of the historical control range. Because maternal nursing behavior was not specifically evaluated in the study, it is unclear whether the decreases in pup survivability were due to direct drug effects on the pups via lactational exposure or indirect drug effects from deficits in maternal care. The LD group was not affected.

In addition, compared to the controls, HD pups had decreased body weight (by up to 32%) during the lactation period.

Table 134. Drug-Related Decreases in Offspring Survivability in the Rat Pre- and Post-natal Developmental Toxicity Study

Lactation Day	Mean viable litter size				Survival Index (%)			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	50	100	250	0	50	100	250
1	9.2	10.2	9.5	7.8	100	96.8	92.3*	79.8*
4	8.9	9.2	9.4	7.6	97.8	90	80.8*	86.5*
7	7.2	7.2	7.3	6.3	100	100	100	89.6*
14	7.2	7.2	7.3	6.2	100	100	100	98.5
21	7.2	7.2	7.3	6.2	100	100	100	100

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 43, 87, and 217 mg/kg/day, respectively
* $p<0.01$

Gross Pathology

At the scheduled necropsy, there were no drug-related gross pathology findings in the dam or in the pups that were culled on LacD 4.

Reference ID: 4698714

F_1 Generation

Mortality and Clinical Signs

Compared to controls, there were no drug-related changes in offspring mortality and clinical signs.

Post-natal Development

During the preweaning period, compared to controls, there were dose-dependent delays in offspring development, which correlated with decreased pup body weight (up to 8%, 13%, and 32% in the LD, MD, and HD groups, respectively, relative to the control group). Delayed growth/development was most profound in the HD group (Table 135).

Table 135. Drug-related Delay in Offspring Growth and Development in the Rat Pre- and Post-natal Developmental Toxicity Study

	Dose			
Postnatal Day	**Control**	**LD**	**MD**	**HD**
% Pups Reached Pinna Detachment/Litter				
2	27.7	16.9	11.8*	8.3*
3	58.2	46.7	51.1	29.2*
4	100	100	100	100
% Pups Reached Incision Eruption/Litter				
11	81.4	82.2	88.0	62.2*
12	100	100	100	81.0
13-14	NA	NA	NA	100
% Pups Reached Eye Opening/Litter				
14	16.4	4.3*	5.9	0*
15	43.6	26.3*	22.7*	15.2*
16	77.3	74.9	81.8	49.1*
17	100	100	100	95.6
18	NA	NA	NA	100
% Pups Reached Testes Descent/Litter				
19	20.3	30.8	12.3	5.0*
20	100	100	100	73.5*
21	NA	NA	NA	100

Source: Modified/reformatted based on the data in the Applicant's study reports
* p<0.05 compared to controls
Abbreviations: HD = high dose; LD = low dose; MD = mid dose

During the postweaning period, compared to controls, HD offspring had decreased body weight (up to 19% to postweaning day 22) and decreased weight gain (up to 20.1% to post-weaning day 8), which correlated with decreased food consumption (up to 14.5%).

Sexual Maturation

Compared to controls, HD offspring had delayed preputial separation (49 days compared to 46 days for the controls) and vaginal opening (36 days compared to 35 days for the controls). This delay is likely secondary to delayed growth rather than a direct drug effect, because the body weight at the time the offspring reached sexual maturation was similar across all groups.

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Neurobehavioral Assessment

Compared to controls, there were no drug-related changes in sensory observations, motor activity, or learning and memory (M-Watermaze performance) in the offspring.

Reproductive Capacity

Compared to controls, there were no drug-related changes in reproductive performance in the offspring. The precoital interval, mating and fertility indices, and litter data (litter size, live birth index, and survival index) were comparable across all groups. Maternal weight, weight gain, and food consumption during the gestation period were comparable.

Gross Pathology

At the scheduled necropsy, compared to controls, there were no drug-related findings in F1 dams or F2 offspring.

Toxicokinetics and Lactation (Exposures)

On GD 6, GD 20, and LacD 20, blood samples were collected at 0.25, 0.5, 1, 3, 8, and 24 hours postdose from the F0 dams.[23] A TK analysis of viloxazine was conducted.

On all three sampling days, after oral administration, viloxazine was rapidly absorbed with T_{max} values of 0.25 to 0.5 hours. The $T_{1/2}$ was 1.7 to 5.1 hours. The exposure to viloxazine increased dose proportionally. There was no significant accumulation after repeat dosing and the exposure profiles were generally comparable on all three sampling days (Table 136).

[23] Control samples were collected only at 0.25 hour postdose.

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Table 136. Toxicokinetic Parameters of Viloxazine in the Rat Pre- and Post-natal Developmental Toxicity Study

Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24hr} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	$t_{½}$ (hr)	T_{last} (hr)
GD 6	50 (G2TK)	0.250	4030	7230	7250	3.59	24.0
	100 (G3TK)	0.500	6390	11800	12300	1.73	8.00
	250 (G4TK)	0.500	9510	42700	42900	3.09	24.0
GD 20	50 (G2TK)	0.250	2600	4960	5130	4.61	24.0
	100 (G3TK)	0.250	4380	10800	10900	3.69	24.0
	250 (G4TK)	0.250	14600	37600	38400	5.10	24.0
LD 20	50 (G2TK)	0.250	3600	7880	7920	3.49	24.0
	100 (G3TK)	0.250	7740	19300	19500	4.11	24.0
	250 (G4TK)	0.250	8320	40600	42400	5.09	24.0

$AUC_{0-\infty}$: Area under the plasma concentration- time curve up to infinity
AUC_{0-24hr}: Area under the plasma concentration-time curve from time 0 to 24 hr
AUC_{last}: Area under the plasma concentration-time curve the last measurable concentration
C_{max}: Maximum concentration in plasma
$t_{½}$: Elimination phase half-life
T_{max}: Time to reach maximum plasma concentration
T_{last}: Time of last quantifiable concentration

Source: Excerpted from the Applicant's study reports
Doses are presented based on viloxazine hydrochloride; the free base-equivalent doses are 43, 87, and 217 mg/kg/day
Abbreviations: GD = gestation day; LD = lactation day

Viloxazine Hydrochloride: A Peri-natal and Post-natal Study in Rats (Study 723-0033, Non-GLP)[24]

Pregnant Sprague-Dawley rats were orally treated with viloxazine from GD 15 throughout lactation until weaning, at doses of 0 (water control), 13 (LD), 33 (MD), and 82 (HD) mg/kg/day (n=22/group for the control, LD, and HD groups; n=15 for the MD group). The maternal parameters evaluated included general health, body weight, weight gain, and parturition. The developmental parameters evaluated included offspring body weight and viability throughout the lactation period. In addition, at the scheduled necropsy, gross pathology was evaluated in the dams and offspring (two pups/sex/group).

Maternal Toxicity: Compared to controls, viloxazine at doses up to 82 mg/kg/day did not cause any significant maternal toxicity. A slight but nonsignificant decrease in maternal weight was observed at 82 mg/kg/day during the last week of lactation (~6%). Given the small magnitude, it is not considered to be adverse. The LD and MD groups were not affected.

Developmental Toxicity: Compared to controls, viloxazine, at 82 mg/kg/day, caused decreased body weight in the offspring (7% to 12%); the decreases in pup body weight persisted throughout the lactation period. No other developmental toxicities were observed. The LD and MD groups were not affected.

Based on the above findings, the NOAEL for maternal toxicity is 82 mg/kg/day and the NOAEL for developmental toxicity is 33 mg/kg/day.

[24] This is an abbreviated legacy study conducted in 1975, prior to implementation of GLP regulations, in which limited parameters were evaluated in the offspring.

Reference ID: 4698714

Viloxazine Hydrochloride: A Peri-natal and Post-natal Study in Mice (Study 723-0044, Non-GLP)[25]

Pregnant Swiss–Webster mice were orally treated with viloxazine at doses of 0 (water control, Group 1/G1), 13 (LD, G2), 33 (MD, G3), and 82 (HD, G4) mg/kg/day from GD 13 throughout lactation until weaning (n=22/group), or at 82 mg/kg/day (HD, G5, n=22) from GD 13 until parturition or from parturition until weaning (HD, G6, n=22). The maternal parameters evaluated included general health, body weight, parturition, and nursing behavior. The developmental parameters evaluated included offspring body weight and viability. In addition, at the scheduled necropsy, gross pathology was evaluated in the dams and offspring (two pups/sex/group).

Maternal Toxicity: Compared to controls, at 82 mg/kg/day, there was increased mortality in the dams when they were treated during the late gestation stage (5/22 deaths in each of the G4 and G5 groups, compared to 0/22 in the control group and 1/22 in G6 (treated at the same dose but only during the lactation stage). The causes of death could not be determined. Post mortem necropsy did not identify any abnormal findings except for glycogen depletion in the liver, which is possibly related to the slight decreases in maternal weight (up to 6% in G4 relative to controls), rather than a cause of death. More perplexing is that all deaths occurred during the lactation period, despite the fact that animals in the G5 group did not receive viloxazine during that period. Nevertheless, considering the large increases in the maternal death rate in G4 and G5, it is reasonable to conclude that viloxazine at 82 mg/kg/day during the late gestation stage (after GD 13), but not the lactation stage, increased the risk of maternal death. LD or MD animals were not affected. It should be noted that in other repeat-dose studies in mice, doses up to 130 mg/kg/day were generally tolerated. Drug effects at doses comparable to 82 mg/kg/day were limited to CNS hypoactivity and impaired gait. Therefore, the mortality observed in the current study was possibly due to increased sensitivity to drug effects during pregnancy.

Developmental Toxicity: Compared to controls, at 82 mg/kg/day, the offspring body weight was significantly decreased in the G4 and G6 groups (11.4% and 12.9%, respectively), in which the dams were treated throughout the lactation period, but not in the G5 group, in which the dams were treated at the same dose but only during the gestation period. Because no significant difference in maternal nursing behavior was observed, the decreases in offspring body weight during the lactation period are most likely a direct drug effect via lactational exposure. The LD and MD groups were not affected.

Based on the findings, the NOAEL for both maternal and developmental toxicity is 33 mg/kg/day.

[25] This is a legacy study conducted in 1976, prior to implementation of GLP regulations. This is an abbreviated study, in which limited parameters were evaluated in the offspring

Reference ID: 4698714

13.2.7.4. Juvenile Animal Study

Study title:	Eight-Week Oral Rat Juvenile Toxicity and Toxicokinetic Study with Recovery Evaluation
Study no.:	812V-Tox2012-001
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
Duration:	8
Duration units:	Weeks
GLP compliance:	Yes
Drug, lot #, and % purity:	Viloxazine; 110011 (L-8340-101-001); 99.9%

Key Findings

- A possible drug-related premature death occurred at 217 mg/kg/day.
- At 217 mg/kg/day, viloxazine caused ptosis in both sexes and transient decreases in motor activity in females. Both effects were reversible.
- At ≥130 mg/kg/day, viloxazine caused dose-dependent decreases in body weight, weight gain, and food consumption, which were reversible after recovery. The decreases at 130 mg/kg/day were generally mild and not considered to be adverse.
- Viloxazine, at doses up to 217 mg/kg/day, did not affect sexual maturation, reproductive capacity, or learning and memory in juvenile rats.
- The NOAEL in juvenile rats is 130 mg/kg/day. After 8 weeks of repeat treatment, the corresponding exposure levels are C_{max} values of 2760 and 5020 ng/mL and AUCs of 10,500 and 28,100 ng*hour/mL in males and females, respectively.

Table 137. 8-Week Oral Rat Juvenile Toxicity and Toxicokinetic Study with Recovery Evaluation Methods

Methods	Details
Doses:	0 (control), 43 (LD), 130 (MD), and 217 (HD) mg/kg/day[26]
Frequency of dosing:	Once daily
Number/sex/group:	Main study (subset A): n=15/sex/group Recovery study (subset B): n=20/sex/group TK study (subset C): n=18/sex for the LD, MD, and HD groups; n=3 for the control group
Dose volume:	10 mL/kg
Formulation/vehicle:	H_2O
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Sprague–Dawley (Crl:CD (SD))
Age at start of experiment:	PND 23
Period of development studied:	Juvenile rats were treated from PND 23 to PND 79, followed by an 8-week recovery period

[26] Doses are presented as free base-equivalent doses. The original doses of 0, 50, 150, and 250 mg/kg/day viloxazine hydrochloride are converted to free base-equivalent doses using a correction factor of 0.867

Reference ID: 4698714

Methods	Details
Comment on study design and conduct:	Dose selection was based on a 17-day DRF study (Study 812V-Tox2010-018), in which juvenile rats were orally treated with viloxazine from PND 23 to PND 40 at doses of 0, 21.7, 43, 87, 217, and 434 mg/kg/day. No significant drug-related toxicities were observed at doses up to 217 mg/kg/day. At 434 mg/kg/day, viloxazine caused transient hypoactivity, significant decreases in body weight (>24%), weight gain (~25%), and food consumption (>15%), and increases in liver weight (~25%). In addition, the absolute and relative weights of lymphoid organs (spleen and thymus) were decreased (~20% to 32%). Given the relatively large magnitude of decreases in body weight and weight gain, 434 mg/kg/day likely exceeded the MTD. In addition, in a previous 3-month general toxicity study in adult rats, doses up to 217 mg/kg/day were tolerated. Drug-related findings were mainly limited to increased liver weight with histopathology of hepatocellular hypertrophy and vacuolation. Based on these findings, 217 mg/kg/day was selected as the high dose in the definitive study.
Parameters and key endpoints evaluated:	Mortality, clinical signs, body weight, weight gain, food consumption, ophthalmology, growth and sexual maturation, neurobehavioral assessment (FOB, motor and sensory activity, learning and memory), clinical pathology, IGF-1, organ weights, gross pathology and histopathology, and reproductive capacity.
Dosing solution analysis:	The concentration of the dosing formulation was within the acceptable range.

Source: summarized from the Applicant's study reports

Observations and Results

Mortality

One possible drug-related death occurred in HDM (No. 2152) on postnatal day (PND) 28. Prior to death, this animal had clinical signs of mild dehydration, ptosis, decreased motor activity, loss of righting reflex, tremors, cold to touch, tachypnea, and urine-stained abdominal fur. A post mortem necropsy did not identify any abnormal findings. The Applicant considered it to be incidental; however, because a similar clinical sign (ptosis) was observed in other HD animals in this study or at the same dose in previous studies in adult rat (decreased motor activity, tremor), a potential drug-related effect could not be excluded.

Three incidental premature deaths occurred in 2 MDMs (Nos. 2208 and 2211) and 1 MDF (No. 2395). Animal 2208 (MDM) was euthanized on PND 66 due to a lesion in the left eye, which was first identified on PND 28 and continued to exacerbate. Given the unilateral nature of the eye lesion, it is not considered to be drug-related. Animal 2211 (MDM) was euthanized on PND 45 due to significant body weight loss. A post mortem necropsy identified urinary tract lesions and build-up of calculi in the bladder, which is a known but rare spontaneous finding in this strain of rat; therefore, it is not considered to be drug-related. Animal 2395 (MDF) was euthanized after it delivered a litter due to a mistimed pregnancy. Other than the mistimed pregnancy, there were no abnormal findings in this female; all the pups appeared normal. Therefore, there is no drug-related finding in this female.

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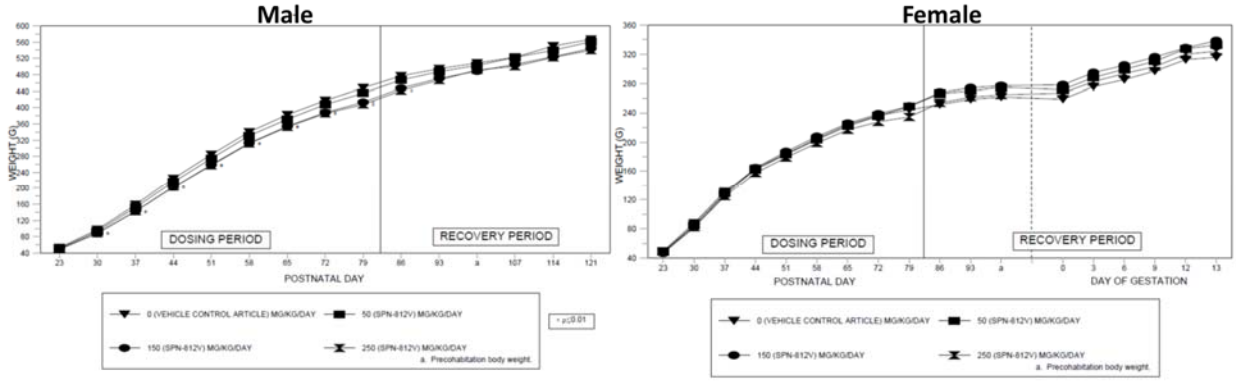
Clinical Signs

During the treatment period, compared to controls, ptosis occurred dose-dependently in the MD and HD groups (4, 5, 7, and 10 MDMs, MDFs, HDMs, and HDFs affected, respectively, compared to 0 controls). Drug-related ptosis primarily occurred during the first few days after treatment initiation and was no longer apparent thereafter. No other drug-related clinical signs were observed.

Body Weight and Food Consumption

During the treatment period, compared to controls, body weight and/or weight gain were decreased in MD and HD males and to a lesser extent in HD females (Figure 32), which correlated with decreased food consumption. At the end of the treatment period, cumulative weight gain was decreased by 7.7%, 9.5%, and 4.5% in MDMs, HDMs, and HDFs, respectively; and cumulative food consumption was decreased by 8.5%, 10.3%, and 6.4% in MDMs, HDMs, and HDFs, respectively. These decreases were reversible during the recovery period.

Figure 32. Drug-related Decreases in Body Weight and/or Weight Gain in the Juvenile Rat Study



Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 0, 43, 130, and 217 mg/kg/day
Abbreviations: SPN = viloxazine

Ophthalmoscopy

There were no drug-related ophthalmic findings. Incidental findings of unilateral uveitis and retinal degeneration were observed at comparable incidences and/or severity across all groups, including the controls.

Hematology

Compared to the controls, there were no drug-related changes in hematology parameters.

Clinical Chemistry

Compared to the controls, there were no drug-related changes in clinical chemistry parameters. At the end of the treatment period, HDMs had a slightly increased globulin concentration (11%). Given the small magnitude and lack of correlative findings, this is considered to be incidental.

Reference ID: 4698714

Urinalysis

Compared to controls, there were no drug-related changes in urinalysis parameters. A few incidental changes occurred; however, they are not considered to be drug-related or adverse due to their small magnitude and/or lack of a clear dose relationship.

Sexual Maturation

There were no drug-related effects on sexual maturation. Despite the slightly lower body weight and/or weight gain in the MD and HD groups, the average days of sexual maturation (preputial separation and vaginal opening) were comparable across all groups.

Reproductive Capacity

Compared to the controls, there were no drug effects on reproductive capacity. Sperm parameters (count, density, motility, and morphology) and estrous cycling were not affected. The fertility indices were 94.4%, 80%, 94.1%, and 100% in the control, LD, MD, and HD groups, respectively. At the scheduled cesarean, compared to the controls, no drug-related changes were observed; the numbers of corpora lutea, implantation sites, viable and nonviable embryos, and pre- and post-implantation loss were comparable across all groups.

CNS/ Neurobehavioral Assessment

Motor Activity

At the end of the treatment or recovery period, compared to the controls, there were no significant drug effects on motor activity. A decrease in motor activity was initially observed in HDFs at about 2 hours postdose on PND 74 or 75 (~25%, relative to controls); however, a reassessment prior to dosing on the next day (PND 76 or 77) did not show any difference, suggesting the decreases in motor activity to be transient rather than a long-term effect.

Functional Observational Battery

Compared to controls, there were no drug-related effects on the functional observational battery (FOB) during the treatment (PND 33 and 76) or recovery (PND 90) period.

Acoustic Startle

Compared to controls, there were no drug-related effects on acoustic startle during the treatment (PND 72) or recovery (PND 92) period.

Learning and Memory (M-Watermaze Performance)

Compared to controls, there were no drug-related effects on learning and memory (M-Watermaze performance) during the treatment (PND 68) or recovery (PND 83) period.

Reference ID: 4698714

Bone Evaluation

At the end of the treatment period, compared to controls, there were no drug-related effects on femur length. However, femur weights were slightly reduced (~8%) in male rats at all doses without a clear dose relationship. Nevertheless, the decreases were reversible after recovery. Therefore, they are not considered to be adverse. Females were not affected.

Gross Pathology

At the end of the treatment or recovery period, compared to controls, there were no drug-related gross pathology findings.

Organ Weights

Compared to controls, there were no drug-related changes in organ weights. A few incidental changes in organ weights were noted; however, there was no clear dose relationship or correlative histopathology findings; therefore, they are not considered to be drug-related.

Histopathology

At the end of the treatment or recovery period, histopathology evaluation was performed in organ/tissues collected from control and HD animals and any gross lesions. Compared to the controls, there were no drug-related changes in histopathology.

Toxicokinetics

On PNDs 23 and 72 (days 1 and 50 of dosing), blood samples were collected from designated animals at 0.5, 1, 2, 4, 8, and 24 hours postdose.[27] The TK parameters of viloxazine were analyzed. A single control sample on PND 72 had a low level of viloxazine (<3% of the C_{max} in the LD group), which is most likely due to cross-contamination. Given the small value, it does not affect TK data interpretation.

On both sampling days, after oral administration, viloxazine was absorbed relatively rapidly, with T_{max} values of 0.5 to 4 hours and $T_{1/2}$ values of 0.6 to 3.4 hours. In both sexes, the exposure (AUC) increased slightly greater than dose proportionally. On PND 23, the exposure levels were comparable between males and females, whereas on PND 72 the exposure levels were slightly higher in females than in males (female-to-male ratio, 1.46 to 2.32). Repeat administration led to slightly reduced exposure levels on PND 72 relative to PND 23 (Table 138).

[27] Blood samples were collected from TK animals on PND 23 and from main-study animals on PND 72. Control samples were collected only at 0.5 hour postdose.

Reference ID: 4698714

Table 138. Summary Toxicokinetic Parameters of Viloxazine in the Juvenile Rat Study

Gender	Day [a]	Dose (mg/kg/day)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	AUC_{0-24h} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	$T_{1/2}$ (h)
Male	1	50	1.00	3680	7130	7140	7130	0.57
		150	1.00	8880	29000	40800	35900	3.38
		250	4.00	10200	54600	62500	NR	NR
	50	50	1.00	1760	3550	3580	3560	0.77
		150	2.00	2760	10500	11900	10800	1.54
		250	0.50	4390	23500	27600	25000	1.87
Female	1	50	1.00	2880	7040	7080	7050	0.71
		150	0.50	6330	22700	27100	24200	1.91
		250	0.50	11400	52000	72800	65000	3.34
	50	50	1.00	1710	6500	6530	6510	0.69
		150	2.00	5020	28100	28100	28100	1.64
		250	2.00	5420	40900	40900	40900	1.89

NR- Not reportable due to insufficient time points in the terminal elimination phase

[a] Once daily by oral gavage from PND 23 (post natal day), the first day of dose administration and considered as Day 1 and PND 72 is considered as Day 50 of dosing

Source: Excerpted from the Applicant's study reports
Doses are presented as viloxazine hydrochloride; the free base-equivalent doses are 0, 43, 130, and 217 mg/kg/day
Abbreviations: AUC = area under the curve; T = time

13.2.8. Phototoxicity

In a spectral absorbance assay (Study 812-Tox2019-056), the maximal absorption for viloxazine was detected at 290 nm with a molar extinction coefficient of 56.62 L/mol*cm, which is below the threshold of 1000 L/mol*cm. Therefore, viloxazine is not considered to have significant phototoxicity potential.

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vitro Studies

Protein Binding (Study 809V-TOX2007-026)

Plasma protein binding was determined in plasma at concentrations of 0.5, 1, 3 and 10 µg/mL [^{14}C]-viloxazine by ultrafiltration. The results demonstrate that [^{14}C]SPN-809V was moderately bound to rat, dog and human plasma proteins (40.8% to 82.2%). In human, the mean plasma protein binding of [^{14}C]-viloxazine ranged from 82.2% at 0.5 µg/mL to 75.7% at 10 µg/mL.

Blood to Plasma Ratio (Study 812V-TOX2018-030)

Pooled male human (n=3) whole blood was dosed with viloxazine at nominal concentrations of 0.745, 7.45 and 74.5 µg/mL and incubated at 37°C on a rotary mixer for 0, 60 and 120 minutes. After incubation, a packed cell volume (hematocrit) determination was made and duplicate aliquots of blood were analyzed by LC-MS/MS (viloxazine) or radioactivity ([^{3}H]-chloroquine). The results indicated that viloxazine does not preferentially accumulate in human blood cells.

Reference ID: 4698714

Viloxazine is stable for up to 120 minutes in human blood at 37°C. The overall blood/plasma ratio for viloxazine at C_{max} in human (7450 ng/mL) was 0.509.

Metabolism of [^{14}C] Viloxazine (Report No. 809V-TOX2007-032)

The cytochrome P450 (CYP) isoenzymes involved in the metabolism of viloxazine were identified in human hepatic microsomes from human donors and recombinant (cDNA-expressing) human CYP Supersomes™. CYP450 isoenzymes were identified in inhibition studies with pooled human hepatic microsomes, CYP-specific inhibitory antibodies (or the CYP-selective chemical inhibitor sulfaphenazole for determination of CYP2C9 involvement), and microsomes containing individual cDNA-expressed human CYP isoenzymes. Incubation of [^{14}C]viloxazine with pooled human liver microsomes in the presence of NADPH resulted in the formation of several metabolites. The metabolites that could be identified by liquid chromatography-tandem mass spectrometry (LC/MS/MS) consisted of hydroxylation and de-ethylation products of viloxazine. M8 (hydroxy-SPN-809V) was the major in vitro metabolite in pooled human liver microsomes. A Michaelis–Menten (MM) kinetic analysis of M8 formation yielded a K_m of 35.2±9.4µM and a V_{max} of 64.3±4.7 pmol/minute/mg microsomal protein.

Incubations with inhibitors and with cDNA-expressed human CYP isoenzymes suggested that the major metabolite of [^{14}C]viloxazine, M8, was formed primarily by CYP2D6. One other metabolite, MB (unidentified) was also formed primarily by CYP2D6. Four other metabolites, MA (unidentified), M6 (hydroxy-viloxazine), M11 (hydroxy-viloxazine), and MC (unidentified), were formed by multiple CYP isoenzymes, primarily CYP1A2, 2B6, 2D6, and 3A4.

Inhibition of CYP Isozymes by Viloxazine (Study 812V-TOX2018-024)

The potential of viloxazine to act as a reversible competitive inhibitor (0-minute preincubation with test compound) and as a time-dependent inhibitor (30-minute preincubation with test compound in the presence and absence of NADPH cofactor) was determined. Viloxazine (0, 3.37, 10.1, 33.7, 101, 303, and 1010µM and 0.001, 0.003, 0.1, 0.3, 1 and 10µM [with CYP1A2 only]) was incubated with pooled human liver microsomes, β-NADPH, phosphate buffer, and CYP-selective chemical substrates. Following incubation, the levels of known metabolites from each CYP-catalyzed reaction were quantified by LC-MS/MS. The results suggested that viloxazine did not inhibit CYP2C8, 2C9, or 2C19; the IC_{50} values for these enzymes were >1010µM. The data suggested that viloxazine acts as a reversible inhibitor of CYP1A2, 2B6, 2D6, and 3A4/5 with IC_{50} values of 0.269, 184, 141 and 221 (midazolam) and 352 (testosterone) µM, respectively. No time-dependent inhibition by viloxazine was observed, except for CYP1A2. Viloxazine was potentially a time-dependent inhibitor of CYP1A2, with an IC_{50} value of 0.0436µM (~0.01 µg/mL) following a 30-minute preincubation with cofactor (NADPH).

Induction Potential of CYP1A2, 2B6, and 3A4 by Viloxazine (Study 812V-TOX2017-002)

The potential for viloxazine to induce CYP1A2, 2B6 and 3A4 was evaluated using cryopreserved human hepatocytes. Viloxazine at 1.4, 3.5, 14, 35, 70, 140 and 350µM was used to assess the effects on CYP1A2, 2B6, and 3A4 mRNA levels. Following exposure, RNA was extracted from the cells and the mRNA levels of the target genes analyzed. In addition to viloxazine, cultured hepatocytes from the same three donors were exposed to the prototypical

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inducing compounds omeprazole (CYP1A2), phenobarbital (CYP2B6), and rifampicin (CYP3A4), as well as the noninducing agent flumazenil and appropriate solvent controls. The overall induction response was assessed using the calculated R value (R3), where an R3 value of <1/1.1 (i.e., 0.9) would be considered indicative of enzyme induction.

The results indicated that there was no cytotoxic effect mediated by viloxazine at up to 140µM. R3 values were calculated using a worst-case scenario C_{max} of 7450 ng/mL and were found to be 0.068 and 0.0442 for CYP1A2 (donor 1 and 2, respectively) and 0.161 for CYP2B6.Viloxazine is a potential inducer of CYP1A2 if the C_{max} value is >38 ng/mL. Viloxazine is a potential inducer of CYP2B6 if the C_{max} value is >108 ng/mL. In this study, the values for omeprazole-mediated CYP1A2 induction (AhR-mediated), phenobarbital-mediated CYP2B6 induction (CAR-mediated), and rifampicin-mediated CYP3A4 induction (PXR-mediated), were acceptable at the concentrations dosed, therefore, the controls were suitable.

Another in vitro study (Supernus 809V-TOX2007-009, submitted under IND (b) (4)) suggests that viloxazine at ≤0.2 µg/mL is not an inducer of cytochrome P450. At ≥2 µg/mL, viloxazine may be an inducer of CYP1A1/1A2 (based on one of three donors), and at ≥20 µg/mL, viloxazine may be an inducer of CYP2B6 and CYP2C9. Based on the population PK analysis, the average C_{max} at steady state in adolescents with a daily dose of 600 mg is predicted to be approximately 6.5 µg/mL (refer to Section III.14.4). Therefore, viloxazine is considered a potential inducer of CYP1A2 but not of CYP2B6 in the clinical setting.

Evaluation of Drug Transporters Involved in the Disposition of Viloxazine

Viloxazine was evaluated as a potential substrate of OATP1B1*1a and OATP1B3. Viloxazine (at 0.659, 2.20, 6.59 and 19.8µM) was incubated with HEK293 cells singly transiently transfected with the transporters (Corning® Transporto Cells™). Incubations contained either viloxazine or the OATP1B probe substrate [^{3}H]estradiol 17β-glucuronide ([^{3}H]E17βGluc;2 µM) with and without the reference inhibitor cyclosporine A (10µM). Viloxazine was assessed with cyclosporine A at the lowest and highest test compound concentration only. [^{3}H]E17βGluc was assessed with and without cyclosporine A at a single concentration to determine the extent of inhibition and to demonstrate a fully functioning assay system. Probe substrate concentrations were quantified by radioactivity measurement using liquid scintillation counting and viloxazine concentrations were measured by LC-MS/MS.

There was no effect of cyclosporine A on the rate of uptake of viloxazine into transfected cells. The uptake ratio of viloxazine was <2 in all incubation conditions and so it is not considered an in vitro substrate for OATP1B1*1a. Cyclosporine A did not affect the viloxazine uptake ratio relative to the control at a viloxazine concentration of 19.8µM. The uptake ratio of viloxazine was <2 in all incubation conditions and it is not considered an in vitro substrate for OATP1B3. Viloxazine is not considered an in vitro substrate of the OATP1B1*1a or OATP1B3 transporters.

Viloxazine as an Inhibitor of Drug Transporters (Study 81V-TOX2018-026)

ABC transporters (P-gp and BCRP) inhibition by viloxazine was assessed in transfected MDCKII cells (PreadyPort™ Ready-to-use Transfected Monolayer (P-gp or BCRP)). Viloxazine was incubated with the cells in triplicate with a known P-gp or BCRP substrate in the presence of varying concentrations of test compound. At the end of an appropriate incubation period, the

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probe substrate concentrations in the samples (donor compartment sampled at 120 minutes; receiver compartment sampled at 60, 90, and 120 minutes) were quantified by radioactivity measurement using liquid scintillation counting. Viloxazine was also assessed as a potential inhibitor of the OATP1B1*1a, OATP1B3, MATE1, and MATE2-K SLC transporters. The potential of viloxazine to act as a direct inhibitor (0-minute preincubation in the absence of test compound) and as a time-dependent inhibitor (30-minute preincubation with test compound) was determined for OATP1B1*1a and OATP1B3. Incubations of viloxazine were conducted in the presence of probe substrates of the transporters.

There was concentration-dependent inhibition of the net efflux ratio of the P-gp substrate (digoxin) and BCRP substrate (prazosin), resulting in IC_{50} values of 1.50 and 1.68mM, respectively. The I_{gut}/IC_{50} value of viloxazine was calculated as 6.73 and 6.01 for P-gp and BCRP, respectively, based on a viloxazine maximum clinical dose of 600 mg. Therefore, viloxazine is not expected to be an inhibitor of Pgp or BCRP to cause clinically relevant drug interaction because the I_{gut}/IC_{50} values were <10.

Viloxazine was a direct inhibitor of the OATP1B1*1a and OATP1B3 transporters, with IC_{50} values of 1.84 and 2.70mM respectively. Furthermore, viloxazine was a time-dependent inhibitor of these transporters, with IC_{50} values of 0.903 and 0.585mM, respectively, following 30-minute preincubation. The calculated R value was <1.1; therefore, viloxazine is not expected to undergo clinically important interactions with OATP1B1*1a and OATP1B3 substrates.

Viloxazine was a weak inhibitor of the MATE1 transporter, with a reported IC_{50} value of 140µM. The calculated $I_{max,u}/IC_{50}$ ratio was 0.05. Therefore, a clinically important interaction is unlikely. MATE2-K was not inhibited by viloxazine (IC_{50} >330µM and $I_{max,u}/IC_{50}$ ratio <0.02).

Another transporter inhibition study (812V-TOX2012-005) determined whether viloxazine hydrochloride inhibits substrate transport by P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3. Viloxazine at 150µM did not inhibit the transport of probe substrate by OATP1B1, OATP1B3 or BCRP, but inhibited P-gp, OAT1-, OAT3-, and OCT2-mediated transport by 9.41%, 29.7%, 33.4%, and 43.9%, respectively. The tested concentration of viloxazine was about 50-fold the human unbound C_{max}. Because the inhibition of transporter activities was <50% in the presence of 150µM viloxazine, the unbound C_{max}/IC_{50} for viloxazine should be <0.1. Therefore, it is not expected to be clinically important.

14.2. Bioanalytical Analysis

The validated bioanalytical method (TR-10-034.00) used to determine the concentrations of viloxazine and its metabolite (5-hydroxyviloxazine glucuronide) in human plasma in the pivotal clinical and pharmacokinetic studies consisted of liquid extraction plus liquid chromatography-tandem mass spectrometry (LC/MS/MS). The concentration range was 0.01 to 10 µg/mL. The-inter-run precision and intra-run precision were ≤10%. The accuracy was 97% to 107%. An incurred sample reanalysis was conducted and met the acceptance criteria. The quality control samples were adequate. A bioanalytical method (TR-18-019.00) was used to determine the concentration of 5-hydroxyviloxazine glucuronide. The concentration range was 0.005 to 10 µg/mL. The inter- and intra-run precisions were ≤14%. The accuracy was 94% to 115%.

The viloxazine concentration in human urine was determined using an LC/MS/MS method. The concentration range in urine was 0.005 to 10 µg/mL. The inter- and intra-run precisions were

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≤8% and ≤7%, respectively. The accuracy was 88% to 114%. The 5-hydroxyviloxazine glucuronide concentration in human urine was measured by LC/MS/MS with a concentration range of 10 to 10,000 ng/mL. The inter- and intra-run precisions were ≤4.5% and ≤4.9%, respectively. The accuracy was 92% to 102.6%.

An LC/MS/MS method was used to determine the concentration of methylphenidate in human plasma with a concentration range of 0.05 to 5.0 ng/mL. The inter- and intra-run precisions were ≤3% and the accuracy was 89% to 98%. An LC/MS/MS bioanalytical method was validated to determine the concentrations of d-amphetamine and l-amphetamine in human plasma over the range of 0.500 to 80.0 ng/mL for d-amphetamine and 0.200 to 32.0 ng/mL for l-amphetamine. The inter- and intra-run precisions were ≤2.9% and ≤3.0%, respectively. The accuracy was 96.2% to 110%. A bioanalytical method (ATM-2380) was validated to determine the concentration of moxifloxacin in human plasma over the range 25.0 to 5000 ng/mL. The inter- and intra-run precisions were ≤4.1% and ≤5.9%, respectively. The accuracy was 99.6% to 104.2%. A bioanalytical LC/MS/MS method was validated to determine the concentrations of dextromethorphan in human plasma over the range 0.0300 to 30.0ng/mL. The inter- and intra-run precisions for dextromethorphan were ≤5.4% and ≤6.4%, respectively. The accuracy was 98.3% to 105.9%. An LC/MS/MS bioanalytical method was validated to determine the concentrations of caffeine in human plasma over the range 50.0 to 15,000 ng/mL. The inter- and intra-run precisions were ≤3% and ≤3.2%. The accuracy was 99.2% to 105%. A validated LC/MS/MS bioanalytical method was used to determine the concentration of midazolam in human plasma over the range 0.200 to 40.0 ng/mL. The inter- and intra-run precisions were ≤3.8%. The accuracy was 97.8% to 102.7%.

All acceptance criteria were met for assay methodologies and validation of viloxazine, 5-hydroxyviloxazine glucuronide, in plasma and urine. The acceptance criteria for caffeine, dextromethorphan, midazolam, d-amphetamine, methylphenidate, and moxifloxacin were met. The validation data demonstrated that the methods were precise, accurate, sensitive, specific, and reproducible. The validated assays are, therefore, acceptable.

14.3. In Vivo Studies

14.3.1. ADME Studies

Mass Balance Study

Study 812P111 was a single-center, open-label, nonrandomized, single-dose study in 7 healthy male subjects. Subjects received a single oral dose of [^{14}C]-viloxazine solution (20 mL) containing 100 mg of viloxazine (as free base) and not more than (NMT) 8.7 MBq (236 µCi) [^{14}C]-viloxazine. Blood, urine, and feces samples were taken for determination of the concentrations of viloxazine and its metabolites in each matrix by LC-MS/MS.

Two major components (P1 and P2) accounted for ≥10% of the total sample radioactivity in plasma in at least one subject. P1 accounted for 10% to 16% of the total sample radioactivity in plasma. P1 was identified as 5-hydroxyviloxazine glucuronide. P2 accounted for 53% to 72% of the total sample radioactivity in plasma. P2 was identified as unchanged viloxazine. Plasma concentrations of total radioactivity were higher than those of total viloxazine, with geometric mean C_{max} and AUC values approximately 1.5- and 2.0-fold greater, respectively.

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Two major components (U1 and U3) accounted for ≥10% of the total sample radioactivity in urine. A mean of 99.8% of the dose was excreted in the urine. U1 accounted for 22% to 33% of the total sample radioactivity. U1 was detected (>10% of sample radioactivity) in all of the 7 urine samples analyzed and was also detected in plasma (referred to as P1). U3 accounted for 17% to 28% of the total sample radioactivity in urine. U3 was identified as unchanged viloxazine (referred to as P2) and was detected (>10% of sample radioactivity) in all 7 of the urine samples analyzed. Following administration of a single oral dose of [^{14}C]-viloxazine, a mean of 103.165% (range 101.72% to 104.29%) of the radioactivity administered was recovered by the end of the sampling period (96 hours postdose), with approximately 90% of the dose recovered within the first 24 hours of dosing. An average of 102.495% of the total radioactivity was recovered from urine and 0.670% from feces. Urinary excretion is the major route of elimination of viloxazine and its metabolites. Unchanged viloxazine and its 5-hydroxy glucuronide metabolite were the only moieties excreted in urine in amounts >10% of total radioactivity.

Bioavailability Study

Study 812P103 was a single-center, open-label, randomized, 2-period, 2-sequence, crossover study in healthy adult subjects that evaluated the steady-state PK and relative bioavailability under fasted conditions. Subjects received a single dose of the assigned medication (SPN-812 ER or SPN-812 IR) on the morning of the first dosing day. PK blood samples were collected over the next 48 hours. On days 3 to 6, Treatment A (200 mg SPN-812 ER) was administered once daily and Treatment B (66.7 mg SPN-812 IR) thrice daily starting in the morning. PK blood sampling continued up to 24 hours after the morning dose on day 6. Predose PK blood samples were collected on days 4 and 5. Subjects were re-entered after an 8-day washout period and ≥10 hours prior to the first dose of period 2. The dosing schedule and study procedures were as for period 1. A validated LC/MS/MS analytical method was used to determine viloxazine (SPN-812) concentrations (calibration range 0.01 to 10.0 µg/mL).

The PK parameters after administration of single and multiple doses of SPN-812 (viloxazine) are provided in Table 139, Table 140, and Table 141.

Table 139. SPN-812 (Viloxazine) Pharmacokinetic Parameters after a Single Dose on Day 1, Mean ± SD (%CV)

Parameter	N	Treatment A (SPN-812 ER)	Treatment B (SPN-812 IR)
C_{max} (µg/mL)	28	1.33±0.335 (25.2)	3.42±0.802 (23.4)
T_{max} (hours)[a]	28	5 (3.00, 9.00)	1.75 (0.50, 6.00)
$AUC_{(0-t)}$ (h*µg/mL)	28	26.0±9.94 (38.2)	30.9±9.87 (31.9)
$AUC_{(0-inf)}$ (h*µg/mL)	28	27.3±12.2 (44.8) [N=27]	31.2±9.88 (31.6)
$T_{½}$ (hours)	28	7.02±4.74 (67.5) [N=27]	4.26±1.30 (30.4)

Source: Applicant's study 812P103, page 45
[a] T_{max} = Median (range)
Abbreviations: AUC = area under the curve; ER = extended release; IR = immediate release; SPN = viloxazine

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Table 140. SPN-812 (Viloxazine) Steady-State Pharmacokinetic Parameters on Day 6 after Multiple Doses, Mean ± SD

	SPN-812 ER (qd) (N=27)	SPN-812 IR (q8h) (N=28)	
Parameter	**0-24 h**	**0-24 h**	**0-8 h**
$C_{max,ss}$ (µg/mL)	1.66±0.503 (30.4)	1.92±0.496 (25.8)	1.89±0.506 (26.7)
$T_{max,ss}$ (hours)[a]	5.0 (2.0, 9.0)	1.5 (0.50, 10.0)	1.0 (0.50, 3.00)
$C_{min,ss}$ (µg/mL)	0.388±0.230 (59.3)	0.611±0.289 (48.9)	0.738±0.346 (46.9)
C_{avg} (µg/mL)	1.03±0.355 (34.5)	1.14±0.359 (31.6)	1.25±0.392 (31.3)
$AUC_{(0-24h)}$ (h*µg/mL)	24.7±8.52 (34.5)	27.3±8.62 (31.6)	9.90±3.10 (31.3)
%FL (%)	128±27.8 (21.7)	121±32.8 (27.1)	97.3±29.9 (30.7)

Source: Applicant's study 812P103, page 46[a] T_{max} = Median (range)
Abbreviations: AUC = area under the curve; ER = extended release; IR = immediate release; SPN = viloxazine

Table 141. Viloxazine Steady-State Relative Bioavailability Following Administration of SPN-812 ER vs. IR

	Geometric LS Mean		LS Mean Ratio (Test/Ref)		
PK Parameter	**SPN-812 ER (Test)**	**SPN-812 IR (Ref)**	**Estimate (%)**	**CV (%)**	**90% CI**
$C_{max,ss}$ (µg/mL)	1.593	1.844	86.4	15.7	(80.3, 92.9)
C_{avg} (µg/mL)	0.981	1.071	91.6	12.5	(86.4, 91.1)
$AUC_{(0-24)}$ (h*µg/mL)	23.5	25.7	91.6	12.5	(86.4, 97.1)
C_{min} (µg/mL)	0.320	0.534	60.0	41.3	(49.9, 72.1)
%FL (%)	124.9	119.0	105.0	16.4	(97.3, 113.2)

Source: Applicant's study 812P103, page 48
Abbreviations: AUC = area under the curve; CV = covariance; ER = extended release; FL = peak-to-trough fluctuation; IR = immediate release; LS = least squares; PK = pharmacokinetic; SPN = viloxazine

Following a single-dose administration, the PK profiles of once-daily (1×200 mg) SPN-812 ER showed similar exposures (AUCs) but lower C_{max} values compared to SPN-812 IR. The T_{max} and $T_{1/2}$ values of viloxazine (SPN-812 ER capsules) were about 5 and 7 hours, respectively.

There was no significant difference in systemic exposure to viloxazine after multiple-dose administration of the ER and IR SPN-812 formulations for 6 days. Steady state was reached after 2 days of daily dosing of SPN-812 ER. The peak-to-trough fluctuation, % FL, was about 128% for SPN-812 ER.

Food Effect

Study 812P105 was a single-center, randomized, open-label, single-dose, 3-period, 3-treatment, 3-sequence crossover in study in 27 healthy adult subjects. For Treatment A, subjects swallowed an intact 200 mg viloxazine capsule after 10 hours overnight fast. For Treatment B, subjects consumed the contents of a 200 mg viloxazine capsule sprinkled on applesauce. For Treatment C, subjects swallowed an intact 200 mg viloxazine capsule after a high-fat (50% total caloric content), high-calorie (800 to 1000 calories) meal. The washout period between drug administrations was 4 days. Plasma PK samples were collected up to 48 hours. A validated LC/MS/MS method was used to determine viloxazine concentrations (calibration range 0.01 to 10 µg/mL).

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Table 142. Effect of Food on Viloxazine (SPN-812)

	B vs. A (Sprinkled vs. Intact)				
	Geometric Mean[a]		Ratio (%)[b]	90% CI	
PK Parameter	B	A	B/A	Lower	Upper
C_{max}	1.21	1.34	90.10	83.35	97.40
AUC_{last}	23.00	24.54	93.71	89.09	98.57
AUC_{inf}	24.45	25.64	95.37	89.80	101.28
	C vs. A (Fed vs Fasted)				
	C	A	C/A	Lower	Upper
C_{max}	1.22	1.34	90.86	84.05	98.21
AUC_{last}	22.01	24.54	89.68	85.26	94.33
AUC_{inf}	23.68	25.64	92.35	86.96	98.07

Source: Applicant's study 812P105, pages 44–45[a] Geometric means for intact 200 mg SPN-812 ER capsule–fasted (A); sprinkled 200 mg ER capsule–fasted (B); and 200 mg SPN-812 ER capsule–fed (C) based on the least squares mean of log-transformed parameter values
[b] Ratio (%)=geometric mean (GM) B/GM A or GM C/GM A
Abbreviations: AUC = area under the curve; ER = extended release SPN = viloxazine

Sprinkling of the contents of viloxazine on applesauce decreased the C_{max} and total exposure (AUC_{last} and AUC_{inf}) by about 10%, and 5% to 6%, respectively. Administration of viloxazine capsule after a high-fat meal (800 to 1000 kcal) reduced the C_{max} and total exposure by about 9% and 8% to 10%, respectively. These differences are not expected to be clinically meaningful. The T_{max} values after administration of viloxazine sprinkled on applesauce, and in an intact capsule under fed and fasted conditions, were 5, 7, and 5 hours, respectively. Therefore, viloxazine can be taken with or without food and can be administered sprinkled on applesauce.

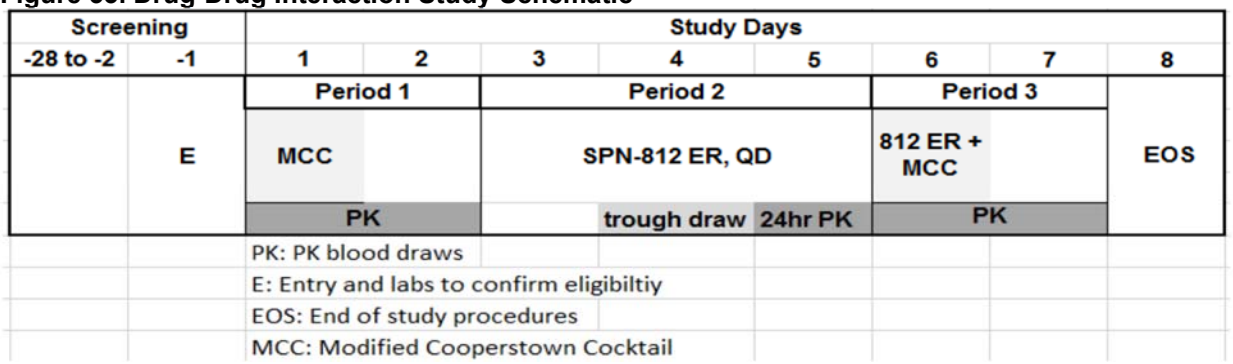
14.3.2. Drug-Drug Interactions

Effect of Viloxazine on the Pharmacokinetics of Other Drugs

Effect of Viloxazine on Select CYP Substrates

Study 812P113.1 evaluated the effect of multiple-dose viloxazine ER on the PK of CYP1A2, CYP2D6, and CYP3A4 substrates given as a single dose to healthy adults under fasting conditions in an open-label, 3-period, 3-treatment, 1-sequence crossover study (Figure 33).

Figure 33. Drug-Drug Interaction Study Schematic



Source: Applicant's study 812P113.1, page 39
Abbreviations: ER = extended release; PK = pharmacokinetic; SPN = viloxazine

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MCC contained a caffeine 200 mg tablet, dextromethorphan 30 mg capsule, and midazolam 0.025 mg/kg syrup. The viloxazine ER dose was 900 mg QD. PK blood draws were performed over a 48-hour period.

Table 143. Statistical Analysis of Caffeine and Its Metabolite (Paraxanthine) Pharmacokinetic Parameters Following Administration of MCC Alone and Coadministration with Viloxazine ER

Caffeine: Period 3 vs. Period 1 (SPN-812 ER + Caffeine vs. Caffeine alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	34	5230.71	34	5277.89	99.11	95.84	102.49
AUC_{0-t}	34	187131.00	34	42904.85	436.15	398.87	476.92
AUC_{0-inf}	3	179103.43	3	30702.80	583.35	262.41	1296.80
Paraxanthine: Period 3 vs. Period 1 (SPN-812 ER + Paraxanthine vs. Paraxanthine alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	27	251.32	27	1188.65	21.14	16.22	27.56
AUC_{0-t}	27	4962.73	27	24022.30	20.66	18.07	23.61

[a] Geometric Mean for Period 3 (Test) and Period 1 (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Period 1 = Modified Cooperstown Cocktail: (MCC) as a single dose on Day 1 200 mg Caffeine + 30 mg Dextromethorphan + 0.025 mg/kg Midazolam (MCC)
Period 3 = 900 mg SPN-812 Extended release on Day 6, followed by MCC 4.5 hours later

Source: Applicant's study 812P113.1, page 73
Abbreviations: AUC = area under the curve; ER = extended release; SPN = viloxazine

Table 144. Statistical Analysis of Dextromethorphan and Its Metabolite (Dextrorphan) Pharmacokinetic Parameters Following Administration of MCC Alone and Coadministration with Viloxazine ER

Dextromethorphan: Period 3 vs. Period 1 (SPN-812 ER + Dextromethorphan vs. Dextromethorphan alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	29	1.18	29	0.78	150.76	126.03	180.35
AUC_{0-t}	29	11.73	29	6.32	185.76	155.01	222.61
AUC_{0-inf}	27	12.45	27	6.56	189.71	160.37	224.42
Dextrorphan: Period 3 vs. Period 1 (SPN-812 ER + Dextrorphan vs. Dextrorphan alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	28	3.54	28	3.70	95.51	85.75	106.38
AUC_{0-t}	28	14.03	28	11.95	117.36	103.68	132.83
AUC_{0-inf}	8	30.23	8	32.75	92.31	79.71	106.92

[a] Geometric Mean for Period 3 (Test) and Period 1 (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Period 1 = Modified Cooperstown Cocktail: (MCC) as a single dose on Day 1 200 mg Caffeine + 30 mg Dextromethorphan + 0.025 mg/kg Midazolam (MCC)
Period 3 = 900 mg SPN-812 Extended release on Day 6, followed by MCC 4.5 hours later
Source: Study 812P113.1, page 79
Abbreviations: AUC = area under the curve; ER = extended release; SPN = viloxazine

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Table 145. Statistical Analysis of Midazolam and Its Metabolite (1-Hydroxymidazolam) Pharmacokinetic Parameters Following Administration of MCC Alone and Coadministration with Viloxazine ER

Midazolam: Period 3 vs. Period 1 (SPN-812 ER + Midazolam vs. Midazolam alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	35	11.61	35	10.29	112.81	104.71	121.54
AUC_{0-t}	35	39.15	35	23.36	167.56	153.05	183.45
AUC_{0-inf}	35	41.93	35	24.82	168.91	154.38	184.80
1-Hydroxymidazolam: Period 3 vs. Period 1 (SPN-812 ER + 1-Hydroxymidazolam vs. 1-Hydroxymidazolam alone)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N Test	Test	N Ref	Ref	(Test/Ref)	Lower	Upper
C_{max}	35	2.69	35	5.64	47.66	43.81	51.86
AUC_{0-t}	35	7.44	35	13.07	56.95	53.35	60.78
AUC_{0-inf}	22	7.68	22	12.74	60.24	55.24	65.69

[a] Geometric Mean for Period 3 (Test) and Period 1 (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Period 1 = Modified Cooperstown Cocktail: (MCC) as a single dose on Day 1 200 mg Caffeine + 30 mg Dextromethorphan + 0.025 mg/kg Midazolam (MCC)
Period 3 = 900 mg SPN-812 Extended release on Day 6, followed by MCC 4.5 hours later
Source: Study 812P113.1, page 85
Coadministration of viloxazine ER with midazolam increased the midazolam AUC about 1.7-fold but did not affect the C_{max}. therefore, viloxazine is a weak inhibitor of CYP3A4.
Abbreviations: AUC = area under the curve; ER = extended release; SPN = viloxazine

Effect of Viloxazine on Stimulants (d-Amphetamine and Methylphenidate)

Study 812P113.2 evaluated the interaction of lisdexamphetamine (Vyvanse®) coadministered with viloxazine ER. The study was a randomized, single-dose, 3-period, 3-treatment, 6-sequence crossover study in healthy adults. Subjects were administered their treatment after an at least 10-hour overnight fast according to a randomized schedule. There was a 4-day washout period between treatments. Blood samples for PK analysis were collected over a 96-hour period.

Treatment A: Vyvanse 50 (1×50) mg capsule, single dose (n=35)

Treatment B: Viloxazine ER 700 (3×200+1×100) mg capsules, single dose (n=34)

Treatment C: Viloxazine ER 700 mg+Vyvanse 50 mg capsules, single dose (n=34)

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Table 146. Statistical Analysis of d-Amphetamine Pharmacokinetic Parameters Following Administration of Vyvanse Alone (Treatment A) and Coadministration with Viloxazine ER (Treatment C)

Dependent Variable (n=34)	GeoMean[a]		Ratio (%)[b] (C/A)	90% CI [c] Lower	90% CI [c] Upper
	C	A			
C_{max}	61.0865	54.1642	112.78	109.93	115.71
AUC_{0-t}	935.6568	853.3514	109.64	105.25	114.22
AUC_{inf}	947.0406	864.7033	109.52	105.19	114.03

[a] Geometric Mean for (A); (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (C)/Geometric Mean (A)
[c] Confidence Interval

Source: Applicant's study 812P113.2, page 58d-amphetamine is the active moiety in lisdexamphetamine (Vyvanse)
Source: Applicant's study 812P113.2, page 58Abbreviations: AUC = area under the curve; ER = extended release
Abbreviations: AUC = area under the curve; ER = extended release

Study 812P113.3 evaluated the interaction of 36 mg methylphenidate (Concerta®) coadministered with 700 mg of viloxazine ER. The study was a randomized, open-label, single-dose, 3-period, 3-treatment, 6-sequence crossover study in healthy adults. The treatments were administered after an overnight fast of at least 10 hours. There was a washout period of 4 days between treatments. Blood samples for PK analysis were collected over a 96-hour period.

Treatment A: Concerta 36 (1×36) mg single-dose oral tablet (n=34)

Treatment B: Viloxazine ER 700 (3×200 + 1×100) mg single-dose oral capsules (n=34)

Treatment C: Concerta 36 mg+viloxazine ER 700 mg (n=34)

Table 147. Statistical Analysis of Methylphenidate Pharmacokinetic Parameters Following Administration of Concerta Alone (Treatment A) and Coadministration with Viloxazine ER (Treatment C)

Dependent Variable (n=34)	GeoMean[a]		Ratio (%)[b] (C/A)	90% CI [c] Lower	90% CI [c] Upper
	C	A			
C_{max}	10.4048	10.0480	103.55	97.42	110.07
AUC_{0-t}	124.6372	116.8464	106.67	101.01	112.64
AUC_{inf}	125.1913	117.4327	106.61	100.99	112.54

[a] Geometric Mean for (A); (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (C)/Geometric Mean (A)
[c] Confidence Interval

Source: Applicant's study 812P113.3, page 59
Abbreviations: AUC = area under the curve; ER = extended release

There was no significant effect of viloxazine of the PK of d-amphetamine, the active moiety in lisdexapmhetamine, after single-dose coadministration of Vyvanse and viloxazine ER. There was no significant effect of viloxazine on the PK of methylphenidate after single-dose coadministration of Concerta and viloxazine ER.

Effects of Other Drugs on Viloxazine

Studies 812P113.2 and 812P113.3 evaluated the effects of d-amphetamine and methylphenidate on the PK of viloxazine following their coadministration (Table 148 and Table 149).

Reference ID: 4698714

Table 148. Statistical Analysis of Viloxazine Pharmacokinetic Parameters Following Administration of Viloxazine ER Alone (Treatment B) and Coadministration with Vyvanse (Treatment C)

Dependent Variable (n=33)[a]	GeoMean[b]		Ratio (%)[c] (C/B)	90% CI [d] Lower	90% CI [d] Upper
	C	B			
C_{max}	4.7078	4.9060	95.96	91.33	100.82
AUC_{0-t}	100.4693	101.2948	99.19	96.53	101.91
AUC_{inf}	101.6324	102.4197	99.23	96.61	101.93

[a] n=32 for AUC_{inf}, Treatment C, Subject (b) (6) excluded from λ_z related parameters of viloxazine in Treatment C due to non-determinable elimination rate.
[b] Geometric Mean for (B); (C) based on Least Squares Mean of log-transformed parameter values
[c] Ratio(%) = Geometric Mean (C)/Geometric Mean (B)
[d] Confidence Interval
Source: Applicant's study 812P113.2, page 64
Abbreviations: AUC = area under the curve; ER = extended release

Table 149. Statistical Analysis of Viloxazine Pharmacokinetic Parameters Following Coadministration of Viloxazine ER and Concerta

Dependent Variable (n=33)	GeoMean[a]		Ratio (%)[b] (C/B)	90% CI [c] Lower	90% CI [c] Upper
	C	B			
C_{max}	4.7001	4.6545	100.98	96.21	105.99
AUC_{0-t}	98.1257	99.5027	98.62	96.21	101.08
AUC_{inf}	99.2735	100.3126	98.96	96.55	101.44

[a] Geometric Mean for (B); (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (C)/Geometric Mean (B)
[c] Confidence Interval
Source: Applicant's study 812P113.3, page 64
Abbreviations: AUC = area under the curve; ER = extended release

d-Amphetamine and methylphenidate did not significantly affect the PK of viloxazine when Vyvanse or Concerta was coadministered with viloxazine ER.

Effect of Alcohol on Viloxazine ER

Study 812P115 evaluated the effect of alcohol on the bioavailability of viloxazine after administration of viloxazine ER. The study assessed the effect of 0%, 4%, 20%, and 40% alcohol in orange juice taken with viloxazine ER 200 mg by healthy male subjects. The study was of a randomized, open-label, single-dose, 4-period, 4-treatment, 4-sequence, crossover design. There was a 4-day washout period between treatments. Blood samples for PK analysis were collected over a 48-hour period.

Reference ID: 4698714

Table 150. Statistical Analysis of Viloxazine Pharmacokinetic Parameters Following Administration of Viloxazine ER with Alcohol

Treatment B vs. Treatment A (200 mg SPN-812 ER + 4% Alcohol vs. 200 mg SPN-812 ER + 0% Alcohol, N = 31)					
Dependent Variable	Geometric Mean[a] B	A	Ratio (%)[b] (B/A)	90% CI[c] Lower	Upper
C_{max}	1.4061	1.3848	101.54	97.52	105.73
AUC_{0-t}	27.8991	27.0240	103.24	97.45	109.37
AUC_{inf}	29.9587	28.3439	105.70	102.17	109.35
Treatment C vs. Treatment A (200 mg SPN- 812 ER + 20% Alcohol vs. 200 mg SPN- 812 ER + 0% Alcohol, N = 30)					
Dependent Variable	Geometric Mean[a] C	A	Ratio (%)[b] (C/A)	90% CI[c] Lower	Upper
C_{max}	1.3247	1.3920	95.16	90.35	100.23
AUC_{0-t}	29.5156	27.3126	108.07	102.35	114.11
AUC_{inf}	30.9325	28.7051	107.76	101.46	114.45
Treatment D vs. Treatment A (200 mg SPN-812 ER + 40% Alcohol vs. 200 mg SPN-812 ER + 0% Alcohol, N = 27)					
Dependent Variable	Geometric Mean[a] D	A	Ratio (%)[b] (D/A)	90% CI[c] Lower	Upper
C_{max}	0.9288	1.3729	67.65	62.60	73.11
AUC_{0-t}	21.6905	27.0422	80.21	71.34	90.18
AUC_{inf}	23.1130	28.4596	81.21	72.00	91.60

Note: AUC_{inf} values that resulted from >20% extrapolation were excluded from the comparisons.
[a]Geometric Mean based on Least Squares Mean
[b]Ratio(%) = Geometric Mean (B) (C) (D)/Geometric Mean (A)
[c]90% Confidence Interval

Source: Applicant's study 812P115, page 58
Abbreviations: AUC = area under the curve; ER = extended release; SPN = viloxazine

The T_{max} was 2 hours after administration of viloxazine ER with 40% alcohol, which is 3 hours less than that without alcohol. The C_{max} and AUC were reduced about 32% and 20% compared to no alcohol, respectively. Higher alcohol poisoning was noted when viloxazine ER was administered with orange juice containing 20% (5/31) and 40% (11/31) alcohol. (b) (4)

14.3.3. Intrinsic Factors

Renal Impairment

Study 812P112 evaluated the effect of renal impairment on the PK of viloxazine after a single administration of viloxazine ER (Table 151). It was an open-label, single-dose, non-randomized, 1-treatment, parallel study. Subjects with normal renal function were matched to renal impairment subject(s) by dose, gender, age (±10 years), and body mass index (BMI) (±20%). Subjects with mild (eGFR 60 to 89 mL/min/1.73m^2, Modification of Diet in Renal Disease [MDRD]), moderate (eGFR 30 to 59 L/min/1.73m^2, MDRD), and severe (eGFR <30 mL/min/1.73m^2 without dialysis, MDRD) renal impairment were administered a single dose of 400 (2×200) mg of viloxazine ER on study day 1 after an overnight fast of ≥10 hours. Matched subjects with normal renal function (creatine clearance ≥90 mL/min, Cockcroft-Gault) received the same dose. PK blood draws were performed predose and for 72 hours postdose.

Reference ID: 4698714

Table 151. Summary of Viloxazine Pharmacokinetics After Single-Dose Administration to Subjects with Mild, Moderate, and Severe Renal Impairment and Matched Normal-Renal-Function Controls

Mild Renal Impairment vs. Normal Healthy Matches (400 mg)					
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]
	Group 1	Group 6	(Group 1/Group 6)	Lower	Upper
C_{max}	3.06	2.83	108.24	85.37	137.23
AUC_{0-t}	65.27	59.68	109.35	83.48	143.24
AUC_{inf}	67.59	61.84	109.31	83.56	143.00
CL/F	98.63	107.81	91.48	69.93	119.68
CL_R	18.43	21.28	86.58	62.74	119.50
Moderate Renal Impairment vs. Normal Healthy Matches (400 mg)					
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]
	Group 2	Group 6	(Group 2/Group 6)	Lower	Upper
C_{max}	3.25	2.83	114.86	90.59	145.63
AUC_{0-t}	78.67	59.68	131.81	100.62	172.66
AUC_{inf}	80.38	61.84	129.98	99.36	170.04
CL/F	82.94	107.81	76.93	58.81	100.64
CL_R	14.49	21.28	68.10	49.34	93.99
Severe Renal Impairment vs. Normal Healthy Matches (400 mg)					
Dependent Variable	GeoMean[a]		Ratio (%)[b]	90% CI [c]	90% CI [c]
	Group 4	Group 6	(Group 4/Group 6)	Lower	Upper
C_{max}	4.65	2.83	164.38	122.91	219.84
AUC_{0-t}	116.54	59.68	195.25	140.28	271.77
AUC_{inf}	117.50	61.84	190.02	136.74	264.05
CL/F	56.74	107.81	52.63	37.87	73.13
CL_R	6.39	21.28	30.02	20.23	44.54

[a] Geometric Mean based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test, Groups 1, 2, and 4)/Geometric Mean (Reference, Group 6)
[c] Confidence Interval

Source: Applicant's study 812P112.1, page 101
Abbreviations: AUC = area under the curve; CL = clearance

Mild or moderate renal impairment does not have a clinically significant effect on the PK of viloxazine. However, severe renal impairment increased the viloxazine AUC about 2-fold. Dose adjustment is recommended for patients with severe renal impairment.

Hepatic Impairment

Hepatic impairment studies were not conducted for this application. Viloxazine ER should not be used in this patient population. A postmarketing requirement (PMR) would be issued as part of the action items.

CYP2D6 Phenotypes

Study 812P113.1 evaluated the effect of CYP2D6 phenotype on the PK of viloxazine. The design was an open-label, 3-period, 3-treatment, 1-sequence crossover study in healthy adults to assess the PK of multiple doses of viloxazine ER in CYP2D6 poor metabolizers (PMs) and extensive metabolizers (EMs). Subjects were administered 900 mg of viloxazine ER once daily. The PK of viloxazine at steady state in PMs compared to EMs are listed in Table 152.

Reference ID: 4698714

Table 152. Summary of Viloxazine PK in CYP2D6 Poor Metabolizers and Extensive Metabolizers Following Multiple, Once-Daily Doses of 900 mg Viloxazine ER

CYP 2D6 Poor Metabolizers vs. CYP2D6 Extensive Metabolizers (PM vs. EM)							
Dependent Variable	Geometric Mean[a]				Ratio (%)[b]	90% CI[c]	
	N PM	PM	N EM	EM	(PM/EM)	Lower	Upper
C_{max}	7	8.00	29	6.59	120.70	102.33	142.37
C_{min}	7	3.05	29	2.29	132.95	103.99	169.98
AUC_{0-24}	7	134.32	29	106.89	125.66	105.36	149.87

[a] Geometric Mean for PM (Test) and EM (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (PM, Test)/Geometric Mean (EM, Ref)
[c] 90% Confidence Interval
Source: Applicant's study 812P133.1, page 89
Abbreviations: AUC = area under the curve; ER = extended release; EM = extensive metabolizers; PM = poor metabolizers

The C_{max}, C_{min}, and AUC at steady state were about 21% to 33% higher in PM compared to EM subjects. This is not expected to be clinically meaningful. The median T_{max} was about 5 hours for both PM and EM subjects.

14.4. Pharmacometrics Review

14.4.1. Executive Summary

The Applicant's population pharmacokinetic (PPK) analysis which supports labeling statements is reviewed. Few changes to Section 12 of the proposed label are suggested. Supportive information is provided for the proposed changes.

14.4.2. Applicant's Analysis

Objectives: (i) To simultaneously characterize the PPK of viloxazine and its metabolite 5-hydroxy-viloxazine glucuronide; and (ii) to test for covariate effects to identify potential sources of variability.

Data: The PK data of 495 subjects from 4 studies (812P301, 812P302, 812P303, and 812P304) were used to develop PPK models for viloxazine.

Method: Nonlinear mixed effect PK modeling was conducted using NONMEM software and the FOCE-I method. The base structural PK model was first developed to describe the PK profiles of viloxazine and its metabolite. Covariate modeling was conducted using forward addition ($p<0.01$ for 1 degree of freedom) and backward elimination ($p<0.001$ for 1 degree of freedom). Covariates including age, BMI, weight, height, gender, race, ethnicity, ALT, AST, and creatinine were tested. Alternative models were compared using the log-likelihood ratio test for nested models or the Akaike information criterion for non-nested models. The final model was evaluated using goodness-of-fit plots, visual predictive checks, and bootstrapping.

Results: The PK of viloxazine was described by a one-compartment model with first-order absorption and elimination of the parent drug, and first-order metabolite formation and elimination (Figure 34). Body weight was added on volume of distribution of viloxazine and its metabolite, its metabolite clearance, viloxazine metabolic clearance. The parameter estimates of the final PPK model for viloxazine are shown in Table 153.

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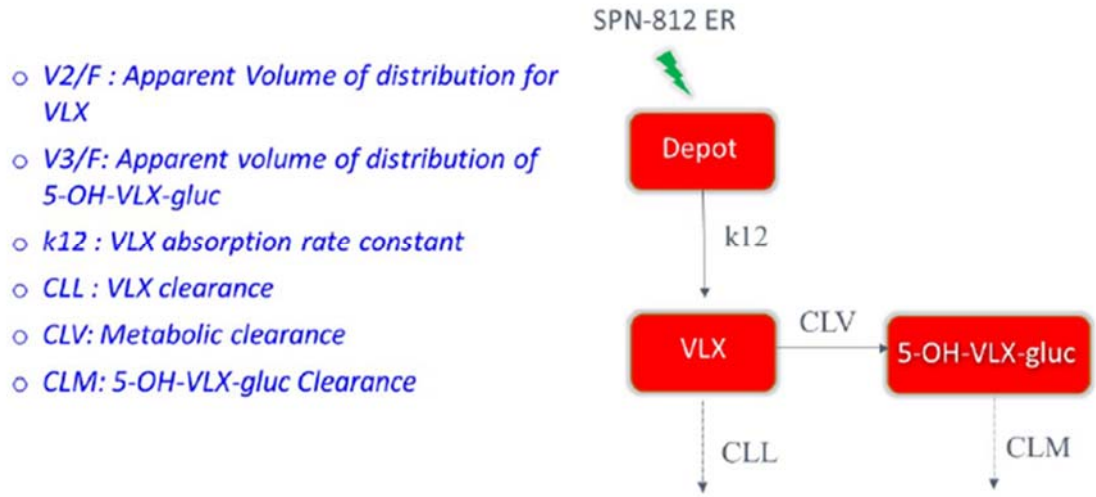
Figure 34. Schematic Representation of the PK Model of Viloxazine



Source: Supernus population PK report: Figure 3, page 25
Abbreviations: ER = extended release; PK = pharmacokinetic; SPN = viloxazine

Table 153. Parameter Estimates of the Applicant's Final PPK Model

	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: Supernus PPK report: Table 9, page 34
Abbreviations: CLL = VLX clearance; CLM = serotonin-VLX-glucose clearance; CLV = metabolic clearance; CV = covariance; k12 = VLX absorption rate constant; PPK = population pharmacokinetic; V2/F = apparent volume of distribution for VLX; VLX = viloxazine

The PPK model for viloxazine and its metabolite was assessed with diagnostics plots including goodness-of-fit (Figure 35) and visual predictive checks. Overall, goodness-of-fit plots adequately describe the PK data of viloxazine and its metabolite. The final pop PK model was

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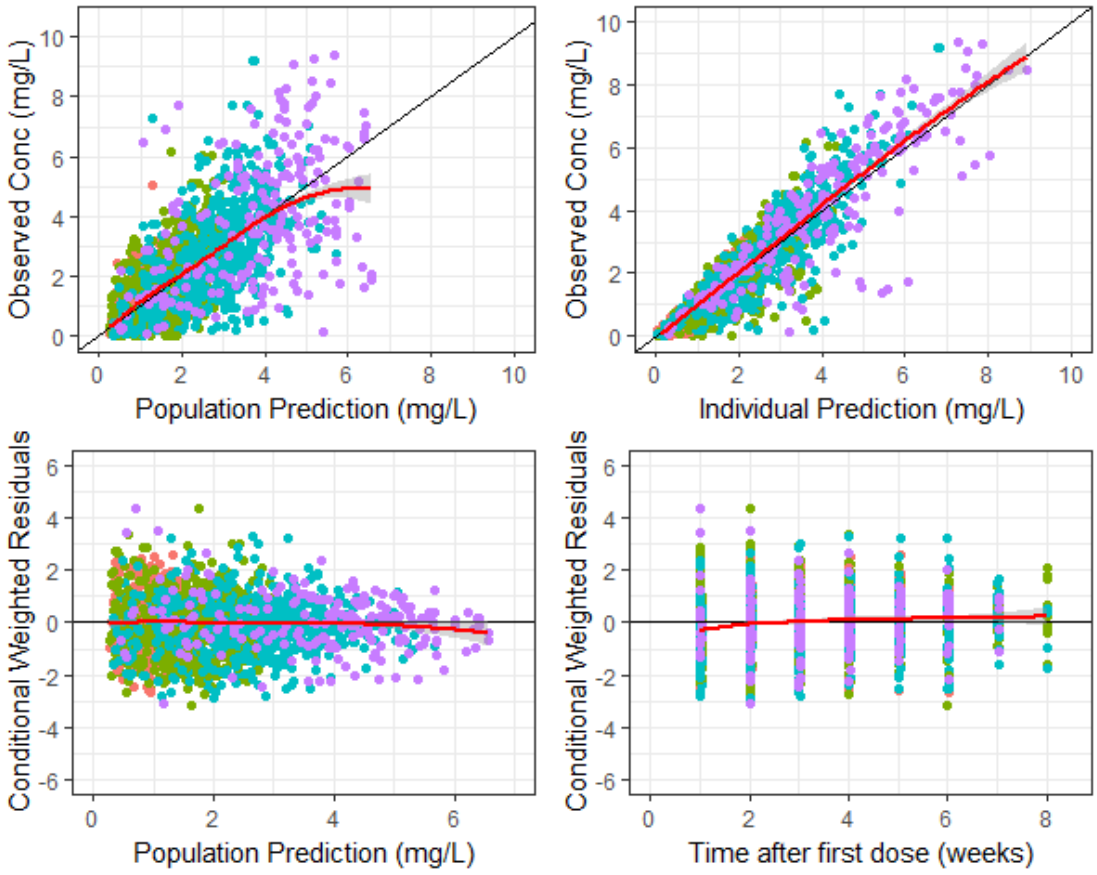
used to simulate steady-state PK profiles of viloxazine, and NCA analysis was then performed to evaluate the impact of body weight on viloxazine exposure.

14.4.3. Reviewer's Analysis

Evaluation of the Applicant's PPK Model

The reviewer was able to run the Applicant's final PPK model and obtained similar results. Model diagnostics for viloxazine are shown in Figure 35. The effect of the covariates on the PK of viloxazine was evaluated based on the PPK modeling results and the observed data. The impact of covariates was evaluated using PK data of viloxazine 400 mg for the following reasons: (i) Linear PK from 300 to 2100 mg/day, (ii) viloxazine 400 mg is a recommended dose for both age groups (children and adolescent), and (iii) adequate PK data for viloxazine 400 mg in both age groups with rich PK sampling (up to 6 hours postdose).

Figure 35. Goodness-of-Fit Plots of the Applicant's PPK Model for Viloxazine



Source: M:\Viloxazine_NDA211964_VS\Reviewer\Rscripts\pk_analysis_viloxazine.R
Abbreviations: PPK = population pharmacokinetic

Effect of Body Weight

The PK data of 130 subjects dosed with viloxazine 400 mg were distributed into quartiles (i.e., first quartile: n=36, 21 to 45; second quartile: n=31, 45 to 53; third quartile: n=33, 53 to 63; and

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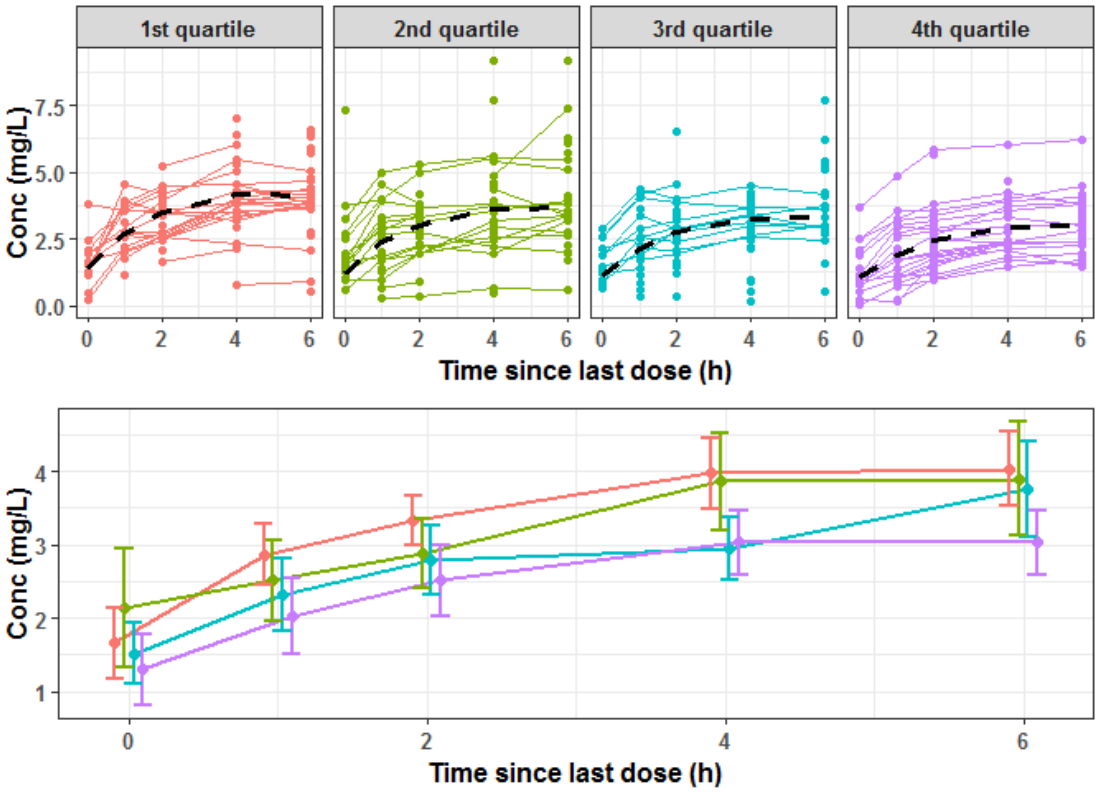
fourth quartile: n=30, 63 to 92.5) based on their weight distribution and plotted together with the corresponding median population predictions (Figure 36). Overall, the AUC and C_{max} of viloxazine decreased with increasing body weight.

Figure 36. Body Weight PK Data of Subjects Dosed with 400 mg Viloxazine



Source: M:\Viloxazine_NDA211964_VS\Reviewer\Rscripts\pk_analysis_viloxazine.R

Top row, Individual PK profiles of viloxazine by body-weight quartile; black dashed line indicates median population predictions from the Applicant's final PPK model. Bottom row, mean (95% CI) PK profiles of viloxazine by body-weight quartile. Red, green, cyan, and purple—first, second, third, and fourth quartiles of body weight, respectively.
Abbreviations: PK = pharmacokinetic; PPK = population pharmacokinetic

The effect of body weight on viloxazine and its major metabolite exposure was quantified by the Applicant by conducting PK simulations. The PK data of 263 children (median body weight 31.5 kg) and 199 adolescents (median body weight 57.25 kg) dosed with 100 to 600 mg were simulated and the resulting PK parameters were compared (Table 154). The estimated steady-state C_{max} and AUC_{0-24} of viloxazine and its major metabolite at doses of 100 to 600 mg were approximately 40% to 50% higher in children compared to adolescents. However, the ADHD-RS-5 total scores of children and adolescents were similar (Refer to the Medical Officer's review).

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Table 154. Estimated Viloxazine and Metabolite PK Parameters (C_{max} and AUC_{0-24}) at Steady-State in Children and Adolescents at Doses of 100, 200, 400, and 600 mg

	C_{max} (µg/mL)			AUC_{0-24} (µg*h/mL)		
Dose	Children of 31.5 kg	Adolescent of 57.3 kg	Change (%)	Children of 31.5 kg	Adolescent of 57.3 kg	Change (%)
Viloxazine						
100	1.6	1.f16	38	19.29	14.5	33
200	4.04	2.89	40	71.45	52.41	36
400	8.15	5.77	41	143.61	105.51	36
600	8.89	6.49	37	106.96	79.97	34
Viloxazine metabolite: 5-hydroxy-viloxazine glucuronide						
100	1.04	0.74	41	13.17	9.24	43
200	2.66	1.79	49	47.8	32.36	48
400	5.17	3.49	48	93.72	63.94	47
600	5.2	3.56	46	70.14	48.94	43

Source: Adapted from the Supernus population PK report: Tables 13–20, pages 43–50
Abbreviations: AUC = area under the curve; PK = pharmacokinetic

Sex Effect

The PK data of 91 males and 39 females dosed with viloxazine 400 mg were plotted with the corresponding population predictions (Figure 37). The overlapping 95% CIs of the PK profiles by sex suggest a lack of a clinically relevant influence of sex on the PK of viloxazine.

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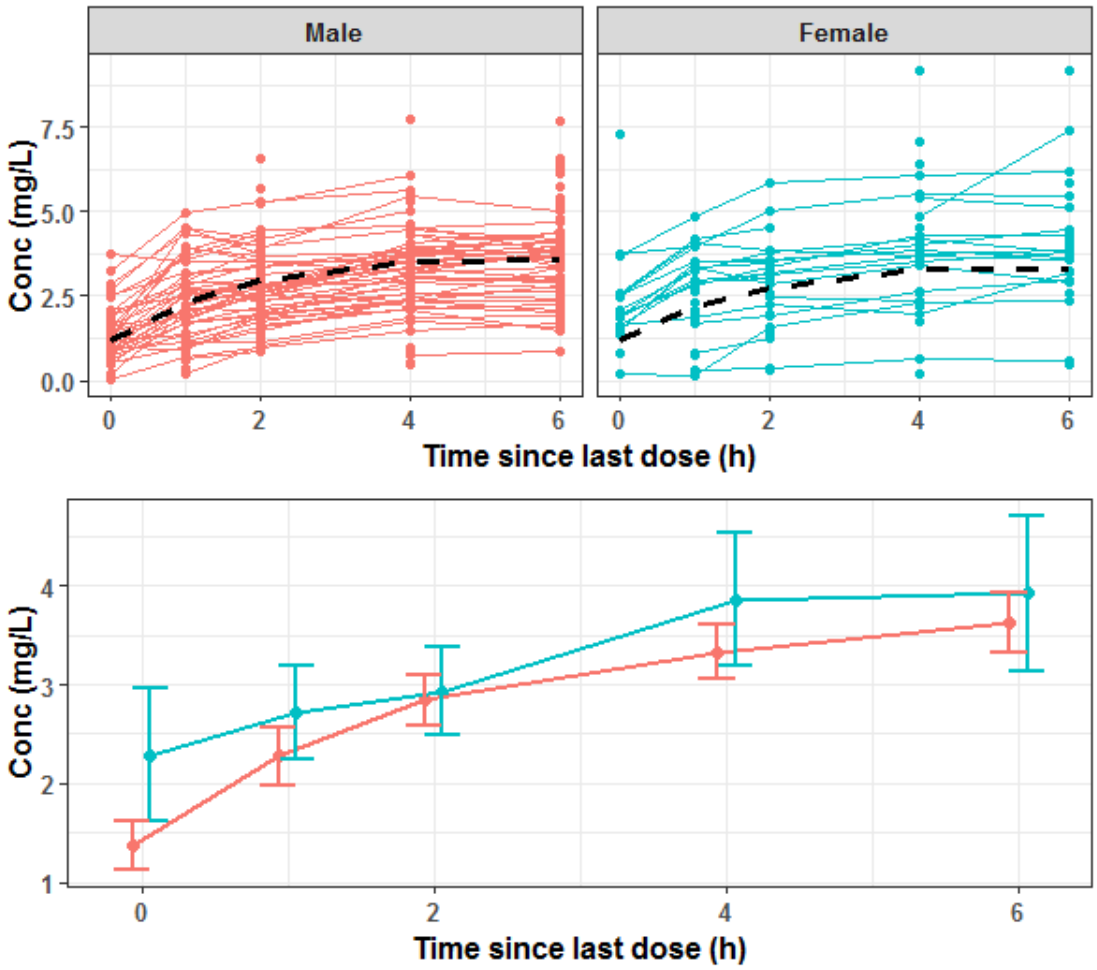
Figure 37. PK Data of Subjects Dosed with 400 mg Viloxazine by Sex



Source: M:\Viloxazine_NDA211964_VS\Reviewer\Rscripts\pk_analysis_viloxazine.R
Top row, individual PK profiles of viloxazine by sex; black dashed line indicates median population predictions from the Applicant's final PK model. Bottom row, mean (95% CI) PK profiles of viloxazine by sex. Red indicates male and cyan, female subjects.
Abbreviations: PK = pharmacokinetic

Race Effect

The PK data of 48 black, 76 white, and 6 other subjects dosed with viloxazine were plotted with the corresponding median population predictions (Figure 38). The data for 'other' were sparse, resulting in wider confidence intervals. Overall, the overlapping 95% CIs of the PK profiles by race suggest a lack of a clinically relevant influence of race on the PK of viloxazine. The population PK model developed from a larger dataset (white [n=258], black [n=214], and other [n=23]) confirmed the above findings.

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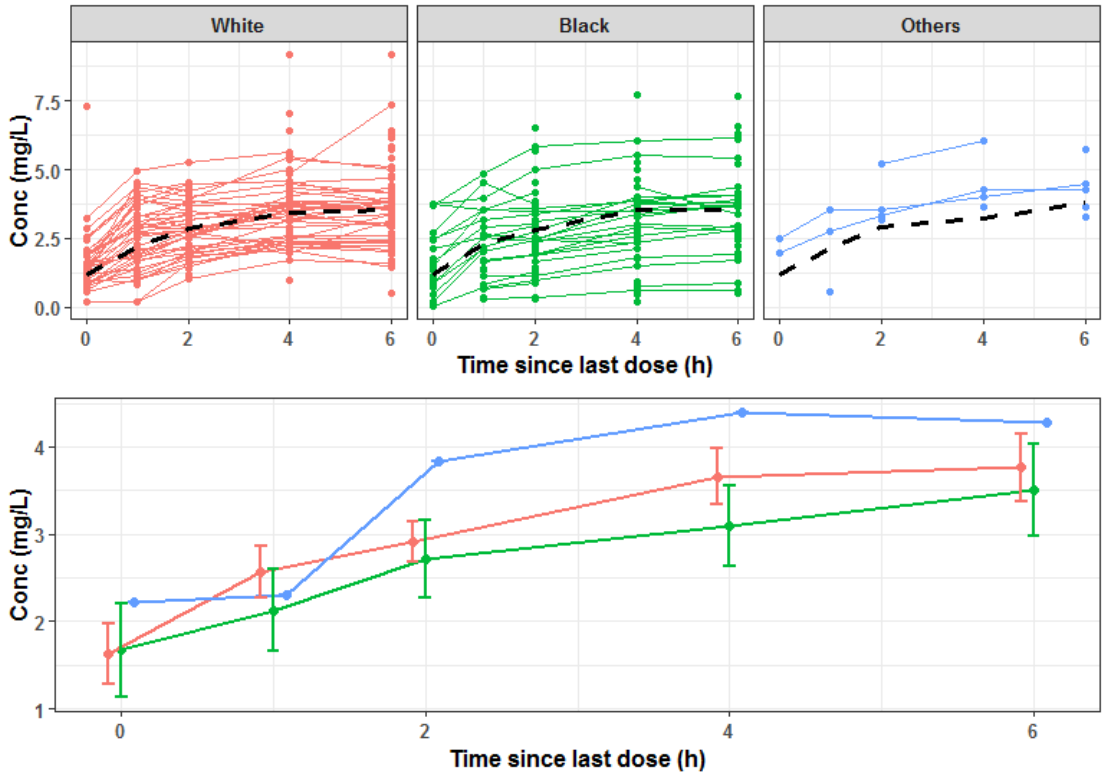
Figure 38. PK Data of Subjects Dosed with Viloxazine by Race



Source: M:\Viloxazine_NDA211964_VS\Reviewer\Rscripts\pk_analysis_viloxazine.R
Top row, individual PK profiles of viloxazine by race. Black dashed line indicates the median population predictions from the Applicant's final PK model; Bottom row, mean (95%CI) PK profiles of viloxazine by race. Red, green, and blue indicate white, black, and other, respectively. Error bars for others are not shown due to the small sample size.
Abbreviations: PK = pharmacokinetic

15. Trial Design: Additional Information and Assessment

This section describes the study design of the four phase 3 placebo-controlled studies (812P301, 812P302, 812P303, 812P304) that were submitted as evidence of safety and efficacy. These four studies have many design elements in common, so Study 312P301 is described in detail and then notable differences in the other studies are highlighted. In addition, this section briefly describes Study 812P202, a phase 2 dose-ranging study, and Study 812P310, a phase 3, open-label, long-term safety study.

812P301

Overview and Objective

The primary objective of the study was to evaluate the efficacy of viloxazine ER compared to placebo as monotherapy for ADHD in children ages 6 to 11 years.

Reference ID: 4698714

Study Design

812P301 was a multicenter, randomized, double-blind, three-arm, placebo-controlled study to evaluate the safety and efficacy of viloxazine ER (SPN-812) 100 mg and 200 mg in children with ADHD. The study was conducted entirely in the United States and included 34 research centers that spanned all geographic regions of the country.

Patients ages 6 to 11 years weighing at least 20 kg with a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM 5), confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents, were eligible to enroll. In addition, a baseline ADHD-RS-5 score of at least 28 and a baseline Clinical Global Impression-Severity (CGI-S) score of at least 4 were required. The ADHD-RS-5 is a validated rating scale that assesses symptoms that correspond to the DSM 5 criteria for ADHD. The scale consists of 18 questions, divided into hyperactivity/impulsivity and inattention subscales. Each question assesses the frequency of a symptom on a 4-point Likert scale. Raw scores are converted to percentile scores based on age and gender. The CGI-S is a clinician-completed, single-item assessment of the severity of a patient's symptoms. Possible responses on the CGI-S are: 1=Not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill.

Patients entering the study must have been free of medication for ADHD for at least 1 week prior to randomization and be considered medically healthy by the Investigator (as assessed by physical examination, medical history, clinical laboratory tests, vital signs, and ECG). Female patients of childbearing potential had to be either abstinent or had to agree to use effective methods of birth control throughout the study.

The exclusion criteria were:

- Current diagnosis of a major psychological disorder. Patients with major depressive disorder were allowed in the study if free of episodes currently and for the last 6 months.
- Current diagnosis of a major neurological disorder. Patients with seizures or a history of seizure disorder within the immediate family (siblings, parents), or a history of seizure-like events were excluded.
- Current diagnosis of significant systemic disease.
- Evidence of suicidality (defined as either active suicidal plan/intent or active suicidal thoughts or more than one lifetime suicide attempt) within 6 months of or at screening.
- A BMI greater than the 95th percentile for age and gender.
- History of an allergic reaction to viloxazine or related drugs.
- Any food allergy, intolerance, restriction, or special diet that, in the opinion of the Investigator, could contraindicate the subject's participation in this study.
- Subjects who received any investigational drug within the longer of 30 days or 5 half-lives prior to day-1 dosing of the study medication.
- Any reason, which, in the opinion of the Investigator, would prevent the subject from participating in the study.

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- Positive drug screen at the screening visit. A positive test for amphetamines was allowed for subjects receiving a stimulant ADHD medication at screening; the subject was required to discontinue the stimulant at least 1 week prior to the baseline visit.
- Pregnancy, breastfeeding, or refusal to practice abstinence or acceptable birth control during the study (for female patients of childbearing potential).

Treatment assignment was conducted via an interactive web response system (IWRS), using a randomization schedule to determine the kit assignment for each patient being randomized. Patients, investigators, study site personnel, the Applicant, and the Contract Research Organization (CRO) clinical staff were blinded to the treatment assignments. The personnel who conducted the PPK analysis had access to data on plasma drug levels but were not otherwise associated with the conduct of the study and did not communicate with clinical site personnel about treatment assignments. The randomization schedule was filed securely by the IWRS vendor. Viloxazine ER and placebo were provided as capsules that were identical in appearance and were packaged in identical blister packs. Compliance with treatment was tracked using accountability logs.

Criteria for withdrawal included withdrawal of consent, noncompliance, occurrence of unmanageable adverse events, loss to follow-up, or other personal reasons. No dietary restrictions were required. As noted above, any medications for ADHD must have been discontinued at least 1 week prior to randomization. Additional concomitant medications were prohibited during the study except nutritional supplements, numbing cream for venipuncture, and common over-the-counter remedies (e.g., acetaminophen and ibuprofen). Known CYP1A2 substrates were specifically prohibited.

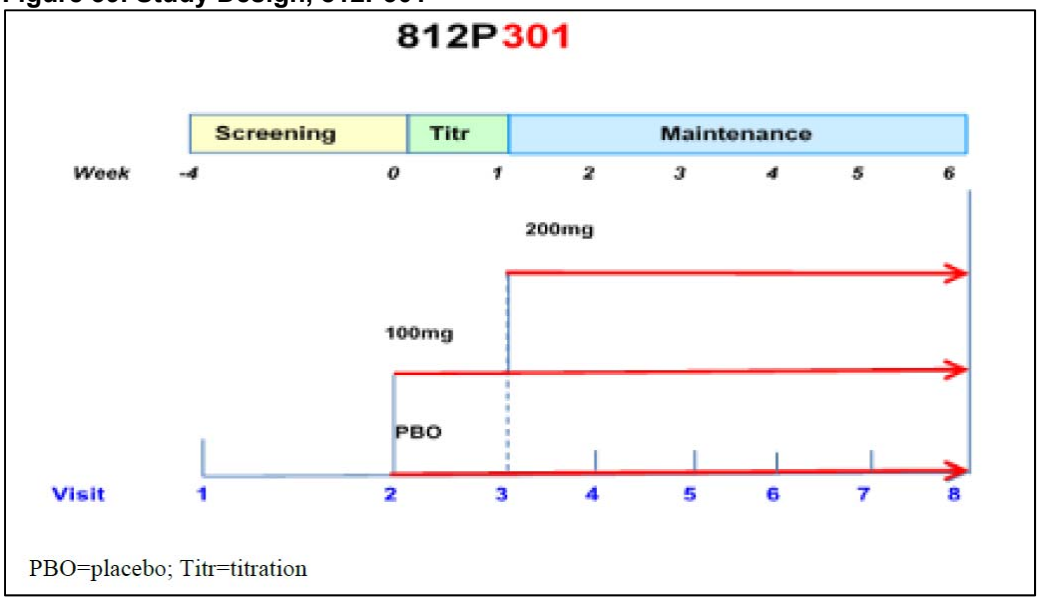
The investigational study drug (viloxazine ER or placebo) was administered once daily as intact placebo capsules, intact viloxazine ER 100 mg capsules, or as capsule content sprinkled on soft food. Treatment could be administered with or without food.

The study protocol, protocol amendments, and the Informed Consent Form (ICF) were reviewed and approved by an Institutional Review Board (IRB). The CRO ([redacted] (b) (4)) was involved in system set-up, monitoring, pharmacovigilance, data entry, data management, data security, statistical analysis, and medical writing.

Patients were randomly assigned in a 1:1:1 ratio to receive either placebo, viloxazine ER 100 mg, or viloxazine ER 200 mg. The selected doses were based on the results of a phase 2 dose-ranging study (812P202), from which the Applicant concluded that the 100 mg and 200 mg doses were well tolerated in this age group. After a 4-week screening period, patients entered a 1-week dose titration phase and then a 5-week maintenance phase (Figure 39).

Reference ID: 4698714

Figure 39. Study Design, 812P301



Source: Applicant's Clinical Study Protocol, Figure 1: Study Schematic, page 19

Study Endpoints

The primary efficacy endpoint was the change from baseline (CFB) in the ADHD-RS-5 Total Score at the end of study (EOS). This study used the ADHD-RS-5 Home Version: Child Instrument, which was completed at each weekly visit by the Investigator from baseline to EOS.

The key secondary endpoints were the Clinical Global Impression-Improvement (CGI-I) scale score at EOS, the CFB in the Conners 3-Parent Composite T-score at EOS, and the CFB in the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) Total Average Score at EOS.

The CGI-I assesses whether a patient's illness has improved or worsened over time. Responses on the CGI-I are rated on a 7-point Likert scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse). The CGI-I was assessed at each study visit and patients were asked to evaluate their symptoms relative to their condition at baseline.

The Conners 3 is a diagnostic tool intended to assess ADHD and associated learning and emotional problems in patients ages 6 to 18 years. It includes parent and teacher reports for all patients and self-reports for patients ages 8 to 18 years. The Conners 3 domains are inattention, hyperactivity, impulsivity, executive functioning, learning problems, and relationships. The parent composite T-score was calculated by averaging the scores on the 6 domains.

The WFIRS-P assesses functional impairment associated with ADHD. This scale includes 50 items grouped into six domains: Family, School, Life Skills, Child's Self-Concept, Social Activities, and Risky Activities. Each item is rated on a 4-point Likert scale (0=never or not at all; 1=sometimes or somewhat; 2=often or much; and 3=very often or very much) over a 1-month recall period. Parents completed this instrument at baseline and EOS.

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The other secondary endpoints were:

- The 50% responder rate, defined as the proportion of patients with a ≥50% reduction in the ADHD-RS-5 total score at EOS
- CFB in the Parenting Stress Index (PSI-4) SF total score at EOS
- CFB in the ADHD-RS-5 Inattention subscale score at EOS and Hyperactivity/Impulsivity subscale score at EOS
- CFB in the Conners 3-Self Composite T-score at EOS (ages 8 to 11 years only)
- Categorical CGI-I defined as the proportion of patients with a score of 1 ("very much improved") or 2 ("much improved") by visit

The exploratory endpoints were:

- CFB in the Conners 3-Parent T-score at EOS by individual domain
- CFB in the Conners 3-Self T-score at EOS by individual domain
- CFB in the WFIRS-P average score at EOS by individual subdomain
- CFB in the Parenting Stress Index, Fourth Edition score at EOS by individual domain
- PK of viloxazine and its metabolite, 5-hydroxy-viloxazine glucuronide
- Pharmacogenomics of viloxazine ER

The safety endpoints were:

- Adverse events
- Clinical laboratory tests
- Vital signs
- Physical examinations
- ECGs
- Columbia Suicide Severity Rating Scale (C-SSRS)

Table 155 (provided by the Applicant) summarizes the schedule of assessment activities in the study. Physical examinations, ECGs, and laboratory assessments were conducted at screening and at EOS. Vital sign monitoring, adverse event tracking, and monitoring for suicidal ideation and behavior (using the C-SSRS) were performed at every visit.

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Table 155. Schedule of Assessments (Study 812P301)

		Treatment Phase[g]		
	Screening	Baseline, Randomization	Maintenance	End of Study[i]
Visit #	**1**	**2**	**3-7**	**8**
Week #	-	**0**	**1-5**	**6**
Visit Day		**1**	**7, 14, 21, 28, 35**	**42**
Visit Window (days)	≤28d before V2		±2	±2
Informed Consent/Assent[a]	X			
Medical and Psychiatric History[j]	X			
Mini-KID	X			
Demographics	X			
Urine Drug Screen	X			
Randomization		X		
Physical Exam[b]	X			X[c]
Inclusion/Exclusion Criteria	X	X		
ECG (12-lead)	X			X
Vital Signs[d]	X	X	X	X
Hematology	X			X
Serum Chemistry	X			X
Pharmacogenomic sample	X			
Urine Pregnancy Test, FOCP only		X		X
CGI-S	X	X		
CGI-I			X	X
C-SSRS	X	X	X	X
ADHD-RS-5	X	X	X	X
WFIRS-P, PSI-4-SF		X		X
Conners 3[e] – parent, self		X		X
Concomitant Medication	X	X	X	X
Adverse Events		X[f]	X	X
Drug Dispensed		X[g]	X	
Drug Return, Compliance			X	X
Optional PK Blood Sampling[h]			←	→

Source: Applicant's Clinical Study Report, Time and Events Schedule, pages 35–36
[a] To be obtained prior to performing any study procedures.
[b] Includes height and weight, excludes genitourinary system
[c] Changes from screening only
[d] Seated (5 minutes) heart rate and blood pressure, temperature, and respiratory rate
[e] Self-report, only patients ages 8 to 11 years
[f] At baseline, AEs were recorded only after SM was administered. Subjects with SAEs at EOS were followed until the event resolved or considered stable.
[g] Titration began after the first dose of SM was administered
[h] Optional PK substudy was performed between visits 3 and 8, inclusive. Samples were taken predose and postdose at hours 1, 2, 4, and 6.
[i] EOS or last visit in the case of early discontinuation
[j] Including any medical occurrences in the period from screening to first SM intake
Abbreviations: ADHD-RS-5 = Attention Deficit Hyperactivity Disorder Rating Scale-5; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FOCP = female of childbearing potential; Mini-KID = Mini International Neuropsychiatric Interview for Children and Adolescents; PK = pharmacokinetics; PSI-4-SF = Parenting Stress Index, Fourth Edition, Short Form; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report

Reference ID: 4698714

Patients were considered study completers if they completed all study visits up to and including visit 8 (EOS).

The Applicant defined four patient populations for analysis purposes:

- Randomized population: All enrolled patients that had a baseline visit scheduled and were randomized via the IWRS.
- Safety population: All patients randomized into the study, who received at least one dose of study drug. Patients were analyzed according to the treatment they actually received.
- Intent-to-treat (ITT) population: All patients who received at least one dose of study drug and had a baseline and at least one postrandomization ADHD-RS-5 assessment. Patients were analyzed according to the treatment to which they had been randomized.
- Per-protocol population: All patients in the ITT population who had completed all 8 visits with no missing ADHD-RS-5 assessments and no major protocol violations. Patients were analyzed according to the treatment they received.

812P302

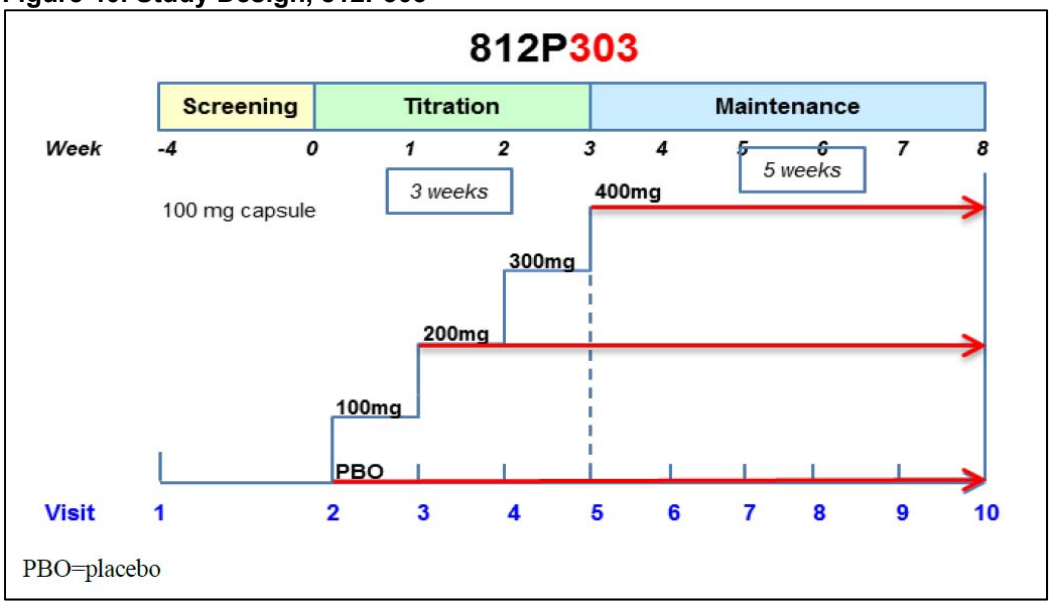
The primary objective of Study 812P302 was to evaluate the efficacy of viloxazine ER 200 mg and 400 mg compared to placebo as monotherapy for ADHD in adolescents ages 12 to 17 years. The design of this study was identical to that of Study 812P301 except for the age range, weight requirement (minimum weight for enrollment was 35 kg), and doses. The primary and secondary endpoints were also identical, except that the age-appropriate Stress Index for Parents of Adolescents was substituted for the Parenting Stress Index (PSI). This study was conducted at 33 research centers in the United States.

812P303

Study 812P303 evaluated the viloxazine ER 200 mg and 400 mg doses in children ages 6 to 11 years. The design of this study was also nearly identical to Study 812P301, except for the higher dose range and a longer (3 weeks) titration period (Figure 40). Patients were considered study completers if they attended all visits up to and including visit 10. This study was conducted at 28 research centers in the United States.

Reference ID: 4698714

Figure 40. Study Design, 812P303

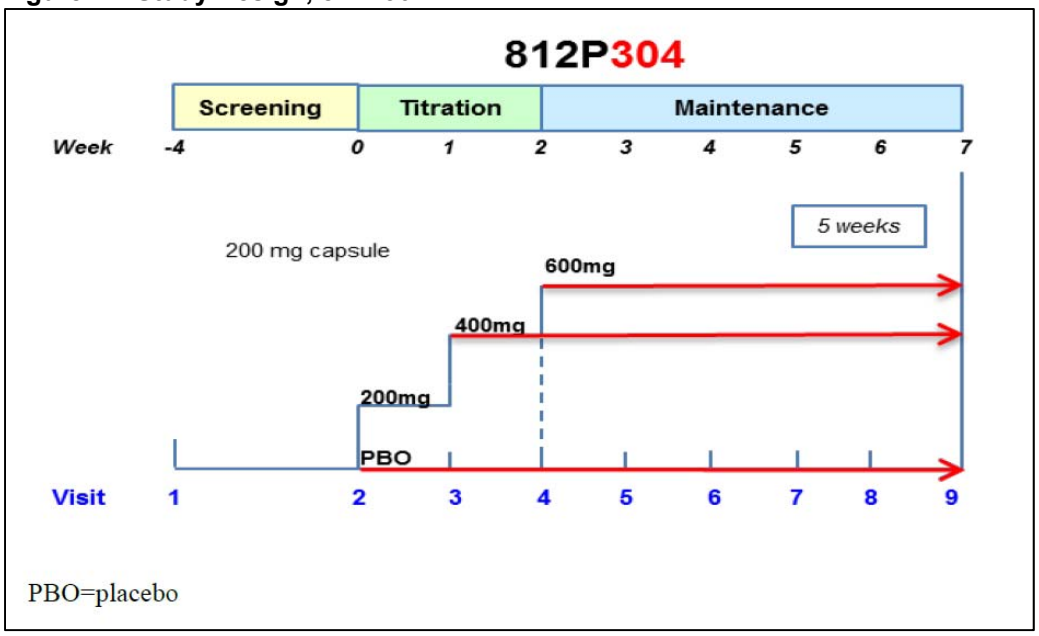


Source: Applicant's Clinical Study Protocol, Figure 1: Study Schematic, page 19

812P304

Study 812P304 evaluated viloxazine ER 400 mg and 600 mg in adolescents ages 13 to 17 years. This study included slightly different exploratory endpoints and a 2-week dose titration phase. Otherwise, the study design mirrored those of the other phase 3 studies.

Figure 41. Study Design, 812P304



Source: Applicant's Clinical Study Protocol, Figure 1: Study Schematic, page 20

Reference ID: 4698714

Overall Assessment of Phase 3 Study Designs

Overall, these phase 3 studies were appropriately designed to meet their stated objectives. The design was typical of studies used to evaluate the safety and efficacy of psychiatric drugs and did not include any novel elements. The Applicant and the Agency reached agreement on the primary endpoint prior to submission of the NDA. However, the Agency did not agree with the use of the CGI-I as a key secondary endpoint because of its vulnerability to recall bias.

The inclusion and exclusion criteria were appropriate to select a representative patient population and to mitigate the potential risks to patients in the studies. ADHD diagnosis in clinical practice is based on application of the DSM-5 criteria, which were also used in the phase 3 studies. The study excluded patients with a known history of seizure disorder or at high risk of seizures given that the risk of seizures in humans was unknown (convulsions occurred in multiple species in nonclinical studies). The protocol required reporting of seizures and seizure-like events as adverse events of special interest. The protocol also included appropriate prospective monitoring for potential safety signals of interest in this population, including cardiovascular adverse events, negative impacts on growth, and suicidal ideation.

812P202

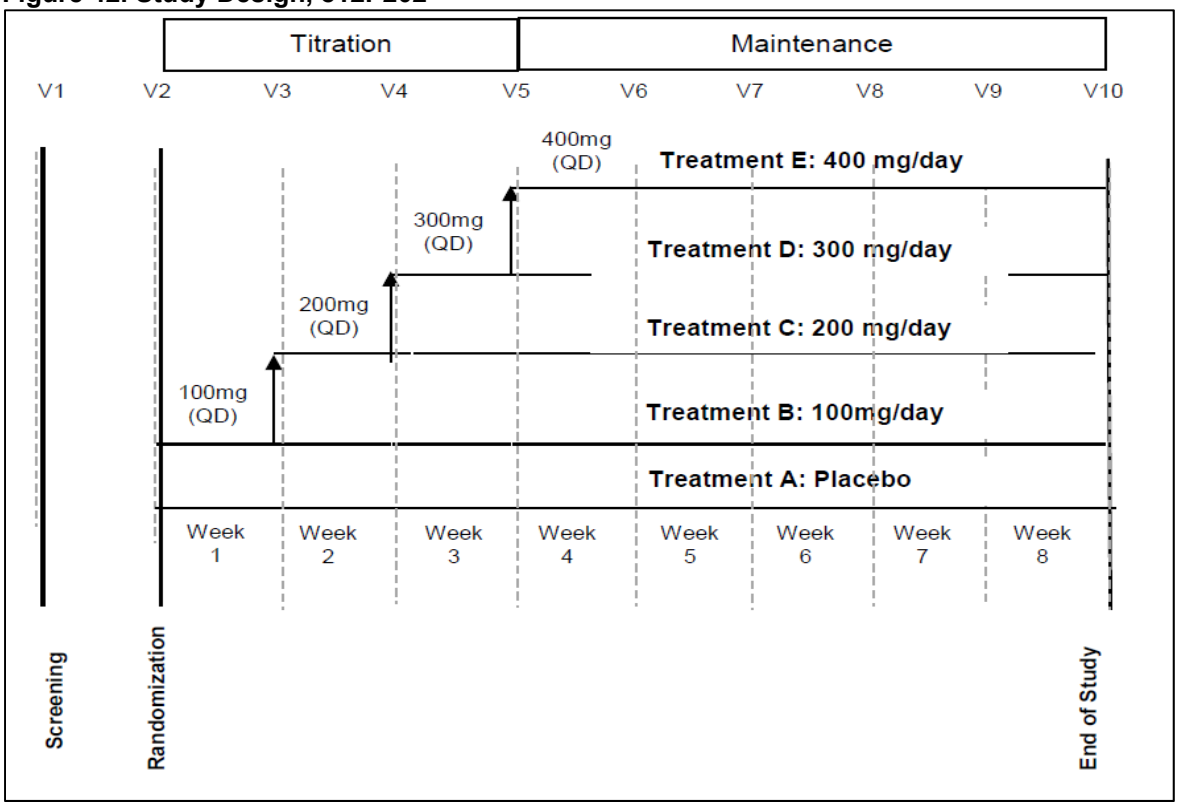
Study 812P202 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study that evaluated the efficacy and safety of viloxazine ER in pediatric patients ages 6 to 12 years. The study was conducted at 32 centers in the United States.

The primary objective was to assess the effectiveness of viloxazine ER in reducing the symptoms of ADHD as measured by the ADHD Rating Scale–IV (ADHD-RS-IV). The secondary objectives were to assess the safety and tolerability in this patient population, effects on the CGI-I and CGI-S, effects on the hyperactivity/impulsivity and inattentive subscales of the ADHD-RS-IV, and to perform a responder analysis based on the ADHD-RS-IV total score. The study randomized patients (1:2:2:2:2) to receive placebo or viloxazine ER 100, 200, 300, or 400 mg once daily. The study included a 3-week titration phase and a 5-week maintenance phase (Figure 42).

The inclusion criteria were: age 6 to 12 years, ADHD-RS-IV total score of ≥26, CGI-S of ≥4, and weight ≥20 kg. Patients must have stopped any ADHD medications at least 1 week before participation. The exclusion criteria were a history of major depressive disorder, obsessive compulsive disorder, posttraumatic stress disorder, or other anxiety disorder; significant physical illness; active suicidal ideation or >1 suicide attempt within the last 6 months; BMI ≥95%; substance or alcohol use within the last 3 months or positive toxicology screen; and pregnancy. The primary endpoint was the CFB to EOS in the ADHD-RS-IV total score. The schedule of assessments was similar to those in the phase 3 studies.

Reference ID: 4698714

Figure 42. Study Design, 812P202



Source: Applicant's Clinical Study Report, Figure 1, page 12

Overall Assessment of Phase 2 Study Design

Study 812P202 was appropriately designed to meet its stated objectives. The primary differences between Study 812P202 and the phase 3 trials were the smaller study size, the inclusion of the 300 mg dose, the randomization ratio, the lack of an adolescent population, and the use of the ADHD-RS-IV (rather than the ADHD-RS-5) as the primary endpoint. Study 812P202 provides supportive data on the safety and efficacy of viloxazine ER in pediatric patients with ADHD.

<u>812P310</u>

Study 812P310 was a phase 3, multicenter, single-arm, open-label extension study to evaluate the long-term safety and efficacy of viloxazine ER in pediatric patients with ADHD. Patients who completed Studies 812P202, 812P301, 812P302, 812P303, and 812P304 and who met minimum weight criteria (at least 20 kg for patients ages 6 to 11 years and 35 kg for patients ages 12 to 17 years) were eligible to enroll. The initial dose of viloxazine ER was 100 mg once daily for patients ages 6 to 11 years and 200 mg for those ages 12 to 17 years. Over the course of a 12-week optimization period, doses could be titrated up or tapered down by 100 mg per week in patients ages 6 to 11 years or by 200 mg in older patients. The target dose range was 100 mg to 400 mg daily for patients ages 6 to 11 years and 200 mg to 600 mg daily for patients ages 12 to 17 years. The study is ongoing; patients may continue to receive viloxazine ER for 72 months or until it becomes commercially available. Safety parameters, including adverse events, laboratory assessments, vital signs, weight, ECGs, and C-SSRS were monitored every 3 months.

Reference ID: 4698714

Overall Assessment of Open-Label Safety Extension Study

Study 812P310 lacked a placebo arm and was not designed to determine whether observed adverse events or other clinical findings were likely associated with viloxazine ER exposure. However, changes from baseline in growth parameters, vital signs, and laboratory assessments were examined for long-term trends. In addition, the adverse event data were examined for any unexpected safety signals emerging with long-term use.

16. Efficacy Assessment Additional Information and Assessment

16.1. Gender, Race, Age

This reviewer conducted an exploratory subgroup analysis by race, gender, and age. The primary efficacy analysis model, mixed model repeated measures (MMRM), was used to investigate the treatment effect. The subgroup analyses were post hoc and any findings could be due to chance.

Study 301: Whites had a numerically better treatment effect than non-whites for both doses of SPN-812 ER compared to placebo; there were no substantial differences between males and females. Subjects ages 10 to 11 years, who were markedly fewer in number, had a numerically slightly smaller treatment effect.

Study 302: Whites and males had a numerically better treatment effect than non-whites and females, respectively, for both doses of SPN-812 ER compared to placebo. This may have been due to the smaller sample size. Subjects ages 12 to 14 years versus those 15 to 17 years had a numerically greater treatment effect.

Study 303: In general, there were no substantial differences among the subgroups. However, for the highest dose (SPN-812 ER 400 mg/day) the treatment effect in those ages 10 to 11 years was approximately half that in patients ages 6 to 9 years.

Study 304: Non-whites (about half the sample size of whites) had a numerically better treatment effect than whites for both doses of SPN-812 ER compared to placebo; similarly, females had a numerically better treatment effect than males. Despite the smaller sample size, SPN-812 ER 400 mg/day showed a numerically better treatment effect in patients ages 15 to 17 years than in those ages 12 to 14 years. Conversely, SPN-812 ER 600 mg/day in patients ages 15 to 17 years showed a numerically worse treatment effect than in those ages 12 to 14 years.

Study 301

Table 156. Study 301 Subgroup Analysis by Race: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
White							
Placebo	77	43.0 (7.62)	73	-10.6	1.64	--	--
SPN-812 ER 100 mg/day	76	45.1 (6.46)	73	-17.9	1.66	-7.2	2.33
SPN-812 ER 200 mg/day	83	44.0 (7.09)	80	-18.4	1.58	-7.8	2.27

Reference ID: 4698714

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Non-white							
Placebo	78	44.1 (6.44)	68	-11.5	1.59	--	--
SPN-812 ER 100 mg/day	71	44.9 (6.64)	66	-15.2	1.62	-3.7	2.24
SPN-812 ER 200 mg/day	75	44.0 (6.52)	66	-17.0	1.58	-5.5	2.21

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 157. Study 301 Subgroup Analysis by Gender: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Male							
Placebo	97	43.4 (7.19)	87	-10.6	1.48	--	--
SPN-812 ER 100 mg/day	94	45.2 (6.77)	87	-15.2	1.49	-4.6	2.09
SPN-812 ER 200 mg/day	99	44.4 (6.90)	95	-18.0	1.44	-7.3	2.05
Female							
Placebo	58	43.8 (6.85)	54	-11.0	1.78	--	--
SPN-812 ER 100 mg/day	53	44.8 (6.13)	52	-18.7	1.84	-7.6	2.51
SPN-812 ER 200 mg/day	59	43.4 (6.65)	51	-17.4	1.77	-6.4	2.48

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 158. Study 301 Subgroup Analysis by Age: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Age 6-9							
Placebo	103	44.6 (6.22)	92	-9.8	1.44	--	--
SPN-812 ER 100 mg/day	103	45.9 (6.02)	97	-16.5	1.42	-6.7	2.03
SPN-812 ER 200 mg/day	107	44.3 (6.58)	96	-17.5	1.38	-7.7	2.01
Age 10-11							
Placebo	52	41.4 (8.11)	49	-12.4	1.80	--	--
SPN-812 ER 100 mg/day	44	43.0 (7.24)	42	-16.0	1.96	-3.6	2.67
SPN-812 ER 200 mg/day	51	43.3 (7.27)	50	-17.5	1.81	-5.1	2.56

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Study 302

Table 159. Study 302 Subgroup Analysis by Race: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
White							
Placebo	63	40.5 (6.64)	62	-12.3	1.73	--	--
SPN-812 ER 200 mg/day	53	40.3 (7.04)	53	-19.7	1.87	-7.3	2.54
SPN-812 ER 400 mg/day	55	38.8 (7.41)	54	-16.5	1.85	-4.1	2.52

Reference ID: 4698714

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Non-white							
Placebo	41	40.5 (7.11)	40	-9.9	2.19	--	--
SPN-812 ER 200 mg/day	41	39.4 (7.51)	35	-10.3	2.28	-0.4	3.10
SPN-812 ER 400 mg/day	48	40.0 (7.82)	44	-16.3	2.05	-6.4	2.96

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 160. Study 302 Subgroup Analysis by Gender: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Male							
Placebo	58	40.7 (6.48)	57	-8.70	1.77	--	--
SPN-812 ER 200 mg/day	66	40.2 (7.14)	60	-15.8	1.66	-7.0	2.39
SPN-812 ER 400 mg/day	67	39.3 (7.77)	62	-18.0	1.64	-9.3	2.38
Female							
Placebo	46	40.3 (7.23)	45	-14.7	2.15	--	--
SPN-812 ER 200 mg/day	28	39.3 (7.52)	28	-16.5	2.77	-1.9	3.50
SPN-812 ER 400 mg/day	36	39.4 (7.35)	36	-13.9	2.43	0.8	3.25

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 161. Study 302 Subgroup Analysis by Age: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Age 12-14							
Placebo	70	41.6 (6.36)	68	-9.7	1.62	--	--
SPN-812 ER 200 mg/day	63	41.0 (6.80)	58	-16.9	1.73	-7.1	2.37
SPN-812 ER 400 mg/day	64	40.3 (7.37)	60	-16.4	1.71	-6.7	2.36
Age 15-17							
Placebo	34	38.3 (7.21)	34	-15.1	2.44	--	--
SPN-812 ER 200 mg/day	31	37.8 (7.70)	30	-14.4	2.57	0.7	3.55
SPN-812 ER 400 mg/day	39	37.8 (7.77)	38	-16.7	2.30	-1.7	3.35

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Study 303

Table 162. Study 303 Subgroup Analysis by Race: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
White							
Placebo	53	43.8 (6.79)	52	-13.7	2.05	--	--
SPN-812 ER 200 mg/day	54	43.9 (6.27)	51	-20.1	2.07	-6.4	2.90
SPN-812 ER 400 mg/day	52	45.0 (6.65)	49	-20.4	2.12	-6.7	2.92

Reference ID: 4698714

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Non-white							
Placebo	44	43.2 (6.86)	40	-9.2	2.08	--	--
SPN-812 ER 200 mg/day	53	43.7 (6.85)	48	-15.0	1.92	-5.8	2.80
SPN-812 ER 400 mg/day	45	45.0 (6.49)	36	-13.9	2.12	-4.7	2.95

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 163. Study 303 Subgroup Analysis by Gender: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Female							
Placebo	36	44.4 (6.95)	35	-13.7	2.52	--	--
SPN-812 ER 200 mg/day	33	44.8 (6.78)	31	-20.3	2.67	-6.6	3.63
SPN-812 ER 400 mg/day	38	43.5 (6.45)	32	-18.3	2.54	-4.6	3.55
Male							
Placebo	61	43.0 (6.71)	57	-10.8	1.85	--	--
SPN-812 ER 200 mg/day	74	43.4 (6.42)	68	-16.6	1.71	-5.7	2.50
SPN-812 ER 400 mg/day	59	46.0 (6.46)	53	-16.9	1.93	-6.0	2.66

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 164. Study 303 Subgroup Analysis by Age: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Age 6-9							
Placebo	64	44.0 (6.76)	61	-11.2	1.84	--	--
SPN-812 ER 200 mg/day	71	44.3 (6.40)	64	-17.4	1.79	-6.2	2.56
SPN-812 ER 400 mg/day	68	45.6 (6.29)	59	-18.5	1.83	-7.3	2.60
Age 10-11							
Placebo	33	42.7 (6.88)	31	-11.6	2.43	--	--
SPN-812 ER 200 mg/day	36	42.8 (6.78)	35	-17.5	2.32	-5.9	3.36
SPN-812 ER 400 mg/day	29	43.7 (7.04)	26	-14.3	2.63	-2.7	3.58

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

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Table 165. Study 304 Subgroup Analysis by Race: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
White							
Placebo	64	39.3 (7.64)	62	-15.4	1.70	--	--
SPN-812 ER 400 mg/day	63	40.8 (8.05)	60	-19.6	1.70	-4.2	2.40
SPN-812 ER 600 mg/day	66	40.6 (7.74)	64	-18.1	1.69	-2.7	2.36

Reference ID: 4698714

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Non-white							
Placebo	32	37.8 (8.88)	27	-8.1	2.26	--	--
SPN-812 ER 400 mg/day	36	41.9 (7.41)	31	-16.4	2.16	-8.3	3.10
SPN-812 ER 600 mg/day	31	38.1 (9.40)	26	-12.9	2.34	-4.8	3.19

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 166. Study 304 Subgroup Analysis by Gender: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Male							
Placebo	61	37.9 (8.22)	56	-12.2	1.76	--	--
SPN-812 ER 400 mg/day	66	42.5 (7.72)	60	-18.4	1.66	-6.2	2.42
SPN-812 ER 600 mg/day	71	40.1 (7.69)	65	-16.9	1.63	-4.7	2.34
Female							
Placebo	35	40.2 (7.66)	33	-14.8	2.33	--	--
SPN-812 ER 400 mg/day	33	38.7 (7.43)	31	-18.5	2.41	-3.8	3.36
SPN-812 ER 600 mg/day	26	38.9 (10.02)	25	-15.9	2.74	-1.2	3.60

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

Table 167. Study 304 Subgroup Analysis by Age: ADHD-RS-5 Total Score (ITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	**N**	**Mean (SD*)**	**N**	**Mean**	**SE#**	**Mean**	**SE#**
Age 12-14							
Placebo	63	39.5 (8.05)	58	-14.4	1.74	--	--
SPN-812 ER 400 mg/day	61	42.2 (7.95)	55	-18.2	1.78	-3.9	2.50
SPN-812 ER 600 mg/day	72	40.5 (8.71)	66	-18.1	1.63	-3.7	2.38
Age 15-17							
Placebo	33	37.3 (8.00)	31	-11.0	2.20	--	--
SPN-812 ER 400 mg/day	38	39.6 (7.39)	36	-18.5	2.04	-7.5	3.01
SPN-812 ER 600 mg/day	25	37.9 (6.96)	24	-12.7	2.53	-1.8	3.35

Source: Reviewer-generated
* Standard deviation, # standard error, ◊ least squares
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ER = extended release; ITT = intent-to-treat; RS = rating scale; SPN = viloxazine

16.2. Other Special/Subgroup Populations: U.S. versus Non-U.S.

All of the studies were conducted in the United States, and so a subgroup exploration of extra-U.S. sites is infeasible.

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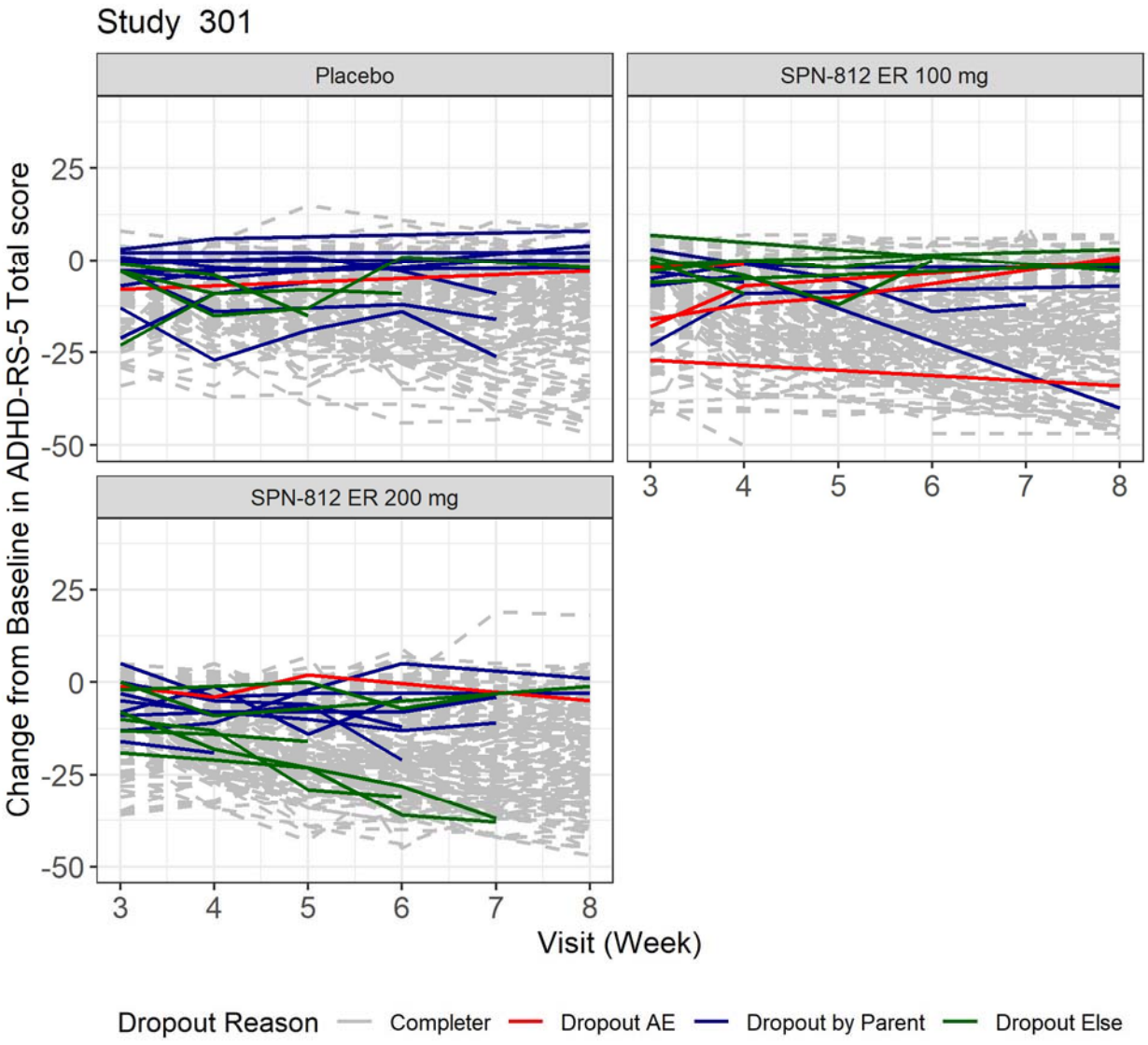
16.3. Graphical Exploration of Missing Data Patterns

The missing data pattern plots (Figure 43, Figure 44, Figure 45, Figure 46) suggest that the missing at random assumption might be reasonable because the dropouts, within each treatment group, may not depend on unobserved ADHD-RS-5 total scores.

Figure 43. Missing Data Patterns (Study 301)



Source: Statistical Reviewer
Dropout AE, dropout due to adverse events; dropout by parent, withdrawal by parent/guardian; dropout Else: withdrawal by subject, loss to follow-up, or dropout due to non-compliance
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; ER = extended release; RS = rating scale

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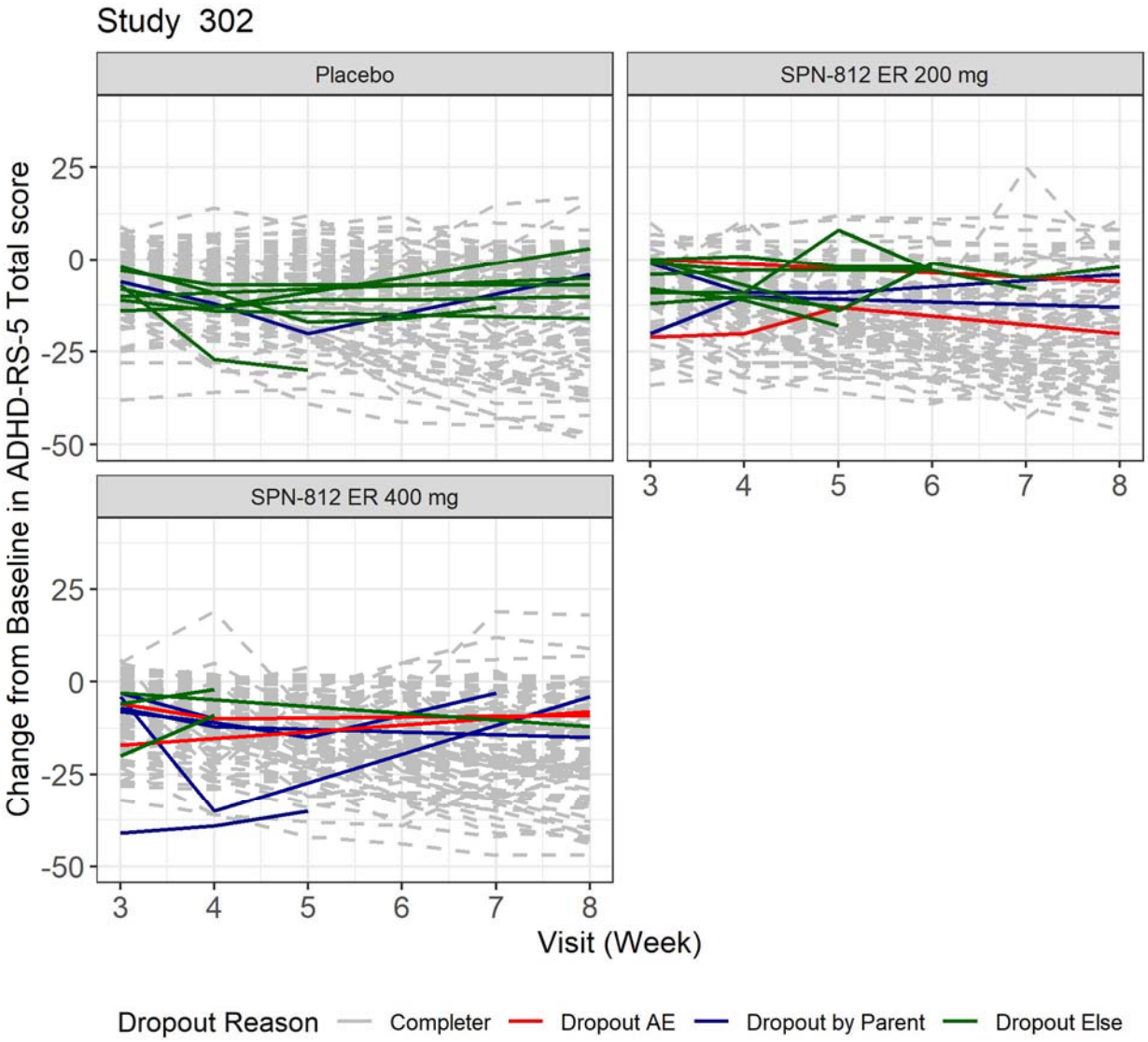
Figure 44. Missing Data Patterns (Study 302)



Source: Statistical Reviewer
Dropout AE, dropout due to adverse events; dropout by parent, withdrawal by parent/guardian; dropout Else: withdrawal by subject, loss to follow-up, or dropout due to non-compliance
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; ER = extended release; RS = rating scale

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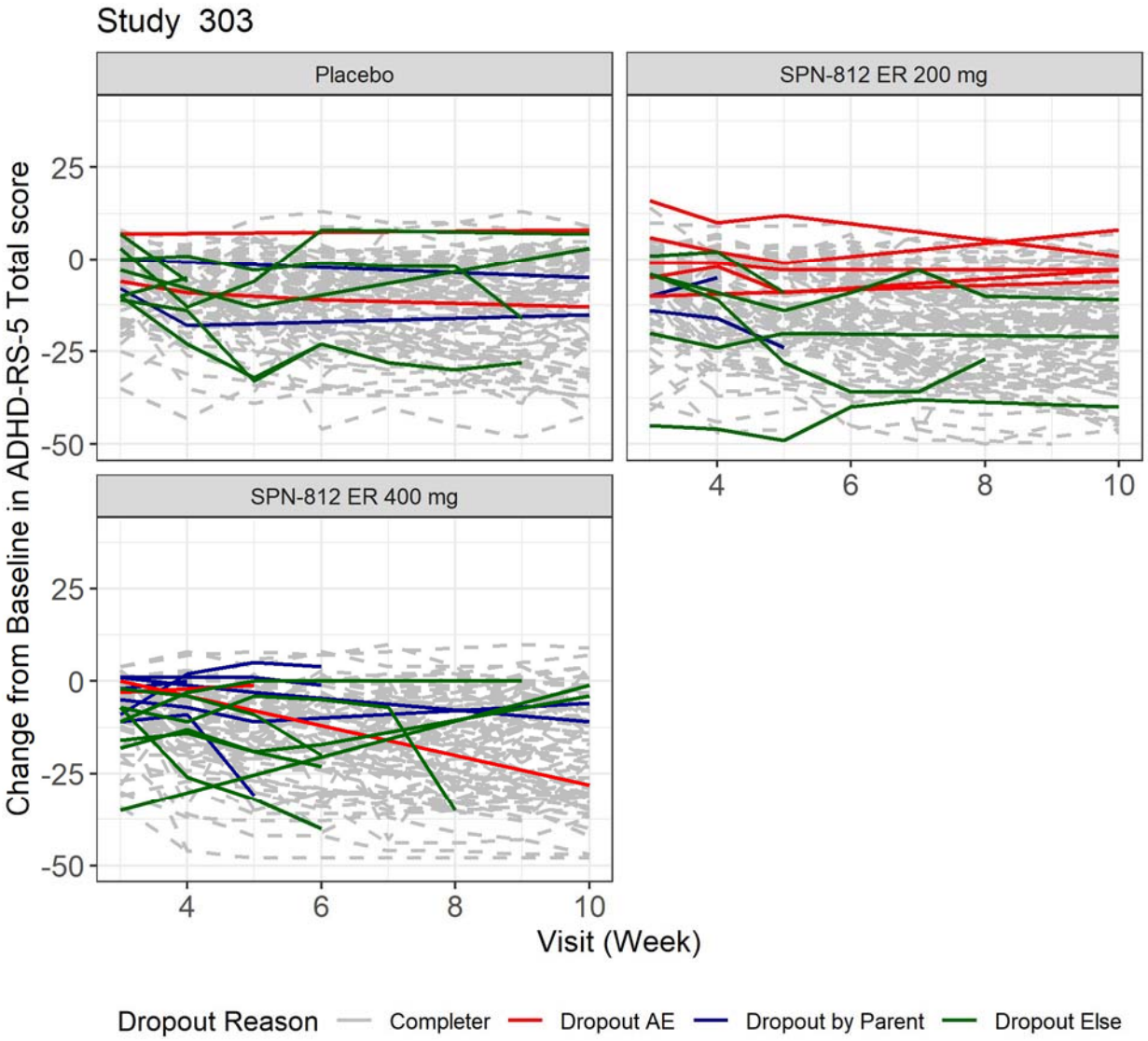
Figure 45. Missing Data Patterns (Study 303)



Source: Statistical Reviewer
Dropout AE, dropout due to adverse events; dropout by parent, withdrawal by parent/guardian; dropout Else: withdrawal by subject, loss to follow-up, or dropout due to non-compliance
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; ER = extended release; RS = rating scale

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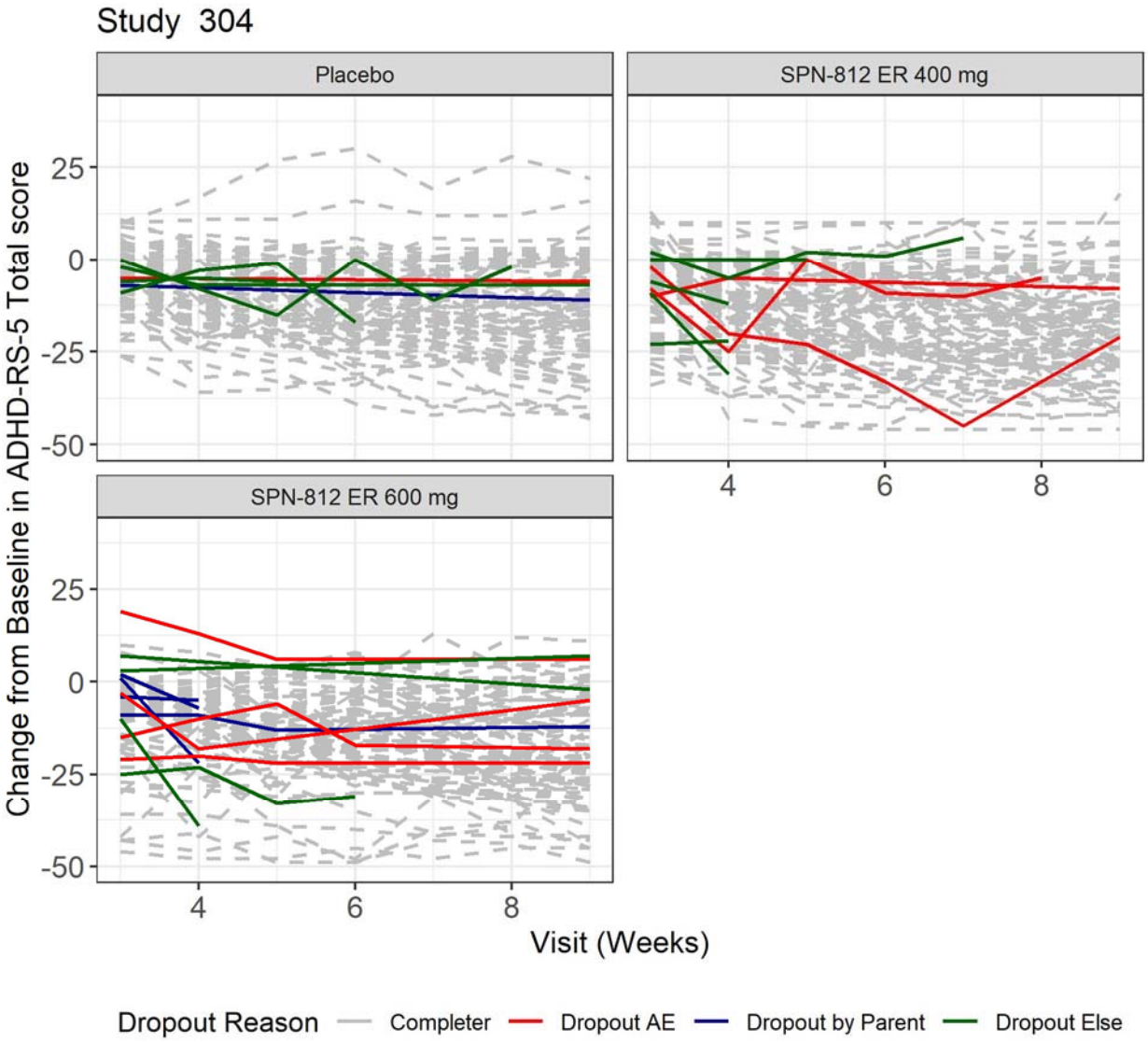
Figure 46. Missing Data Patterns (Study 304)



Source: Statistical Reviewer
Dropout AE, dropout due to adverse events; dropout by parent, withdrawal by parent/guardian; dropout Else: withdrawal by subject, loss to follow-up, or dropout due to non-compliance
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; ER = extended release; RS = rating scale

17. Clinical Safety Assessment Additional Information and Assessment

This section includes additional information and analyses that were considered in the overall safety review. Treatment-emergent adverse events (TEAEs) from the phase 3 placebo-controlled studies (812P301, 812P302, 812P303, and 812P304) were analyzed using customized grouped terms developed by the clinical review team. AEs with a high degree of overlap (e.g., abdominal pain and upper abdominal pain) were grouped to ensure that clinically meaningful safety signals

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could be detected. This grouping of AE terms was used to inform the safety data presented in labeling. In addition, the review team determined the system organ classes (SOCs) that accounted for the most AEs. This section also lists the AEs that led to discontinuation in the controlled clinical studies and summarizes subgroup analyses of safety signals. Detailed results from analysis of the laboratory assessment and ECG databases from the phase 3 placebo-controlled studies are also presented. Additional AE data from Studies 812P202 and 812P310 are described in this section (see Appendix 15)for a description of the study designs). Finally, the consultative reviews from the Interdisciplinary Review Team for Cardiac Safety and the Controlled Substances Staff are included here.

Treatment-Emergent Adverse Events (Division of Psychiatry Grouped Terms)

The AEs based on customized Division of Psychiatry (DP) Grouped Terms is presented in Table 168. The DP grouped terms aligned closely with FDA MedDRA Queries (FMQs). The FMQ of dyspepsia contains a preferred term (abdominal pain upper) that is also included in the abdominal pain FMQ. The FMQ of fatigue contains a preferred term (lethargy) that is also included in the somnolence FMQ. The FMQ for insomnia does not include sleep disorder, but sleep disorder is included in the DP insomnia grouped term. The FMQ for irritability includes agitation, which is not included in the DP irritability grouped term. These discrepancies did not appreciably alter the calculated frequency of AEs in the clinical trials. (b) (4)

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Table 168. Adverse Events With Grouped Terms, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Patients 6 to 11-Years-Old (Trials 812P301 and 812P303)					Patients 12 to 17-Years-Old (Trials 812P302 and 812P304)					Total	
Adverse Event (Preferred Term[1,2] or Grouped Term[3])	**100 mg N=154 %**	**200 mg N=268 %**	**400 mg N=100 %**	**reatment N=522 %**	**Placebo N=262 %**	**200 mg N=99 %**	**400 mg N=205 %**	**600 mg N=99 %**	**Γreatment N=403 %**	**Placebo N=201 %**	**Γreatment N=925 %**	**Placebo N=463 %**
Somnolence[4]	12	16	18	15	2	15	19	23	19	7	17	4
Headache[5]	10	11	7	10	5	10	14	9	12	10	11	7
Decreased appetite	5	9	9	8	0	5	7	6	7	1	7	0.4
Upper respiratory tract infection[6]	5	8	10	7	7	3	7	8	6	7	7	7
Fatigue	4	6	9	6	2	4	9	10	8	3	7	2
Pyrexia	3	2	3	12	0.3	1	1	1	1	0	2	0.2
Abdominal pain[7]	3	6	11	6	5	6	4	6	5	3	6	4
Nausea	1	3	2	3	2	7	9	9	8	4	5	3
Insomnia[8]	2	6	7	5	2	2	4	4	4	0.5	4	1
Vomiting	5	3	7	4	2	2	5	4	4	2	4	2
Irritability	3	2	6	3	2	3	4	5	4	1	4	1

Source: adae.xpt; Software: Python. Created by the Clinical Data Scientist and Clinical Reviewer.
[1] TEAEs defined as AEs with onset or increase in severity at any time from the first exposure to study drug.
[2] Coded as MedDRA preferred terms.
[3] Grouped terms were specified by the Division of Psychiatry and each is footnoted.
[4] Somnolence: somnolence, lethargy, and sedation
[5] Headache: headache, migraine, migraine with aura, tension headache
[6] Upper respiratory tract infection: nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
[7] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
[8] Insomnia: initial insomnia, insomnia, middle insomnia, poor-quality sleep, sleep disorder, terminal insomnia

Abbreviations: AE = adverse event; N, number of subjects in a group; n, number of subjects with an AE; TEAE = treatment-emergent adverse event.

(b) (4)

Table 169

(b) (4)

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(b) (4) lists adverse reactions that occurred in ≥2% of viloxazine ER–treated patients (and in whom they were more frequent than in placebo-treated patients).

Table 169. Adverse Reactions in ≥2% of Viloxazine ER–Treated Patients (More Frequently than Placebo) in Phase 3 Placebo-Controlled Trials

	Viloxazine ER				
Body System/ Adverse Reaction	**100mg N=154 %**	**200mg N=367 %**	**400mg N=305 %**	**All Viloxazine N=826 %**	**Placebo N=463 %**
Nervous system disorders					
Somnolence	12	16	19	16	4
Headache	10	11	12	11	7
Metabolic and nutritional disorders					
Decreased appetite	5	8	8	7	0.4
Infections and Infestations					
Upper Respiratory Tract Infection	5	7	8	7	6
Body as a Whole: General disorders					
Fatigue	4	5	9	6	2
Pyrexia	3	2	1	2	0.2
Gastrointestinal system disorders					
Abdominal Pain	3	6	7	5	4
Nausea	1	4	7	5	3
Vomiting	5	3	6	4	2
Psychiatric disorders					
Insomnia	2	5	5	4	1
Irritability	3	2	5	3	1

Source: adae.xpt; Software: Python. Created by the Clinical Data Scientist and Clinical Reviewer.
Somnolence: somnolence, lethargy, sedation
Headache: headache, migraine, migraine with aura, tension headache
Upper respiratory tract infection: nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
Insomnia: initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia
Abbreviations: ER = extended release

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Adverse Events by System Organ Class

Patients treated with viloxazine ER in the phase 3 placebo-controlled trials were most likely to experience adverse events in the following SOCs: nervous system disorders, gastrointestinal disorders, psychiatric disorders, general disorders and administration site conditions, infections and infestations, metabolism and nutrition disorders, and investigations (Table 170).

Table 170. Adverse Events by System Organ Class, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

	Patients 6 to 11 Years (Trials 812P301 and 812P303)					Patients 12 to 17 Years (Trials 812P302 and 812P304)					Total	
System Organ Class	100 mg N=154 %	200 mg N=268 %	400 mg N=100 %	Treatment N=522 %	Placebo N=262 %	200 mg N=99 %	400 mg N=205 %	600 mg N=99 %	Treatment N=403 %	Placebo N=201 %	Treatment N=925 %	Placebo N=463 %
Nervous system disorders	22	24	28	24	6	25	31	30	29	16	27	11
Gastrointestinal disorders	10	13	22	14	10	14	15	19	16	9	15	9
Psychiatric disorders	8	12	23	13	9	7	12	13	11	4	12	7
General disorders and administration site conditions	7	9	10	9	3	8	11	11	10	3	9	3
Infections and infestations	7	12	16	11	12	4	11	11	9	10	10	11
Metabolism and nutrition disorders	5	10	9	8	2	5	9	7	8	2	8	2
Investigations	3	4	8	4	2	4	5	3	4	2	4	2
Respiratory, thoracic and mediastinal disorders	3	3	4	3	2	0	6	1	3	4	3	3
Ear and labyrinth disorders	2	0.4	0	1	0	0	1	0	0.2	1	1	0.2
Injury, poisoning and procedural complications	1	3	2	3	4	3	2	4	3	3	3	4
Cardiac disorders	1	2	1	1	0.4	0	2	1	1	0	1	0.2
Musculoskeletal and connective tissue disorders	1	1	1	1	1	1	2	3	2	1	1	1

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	Patients 6 to 11 Years (Trials 812P301 and 812P303)					Patients 12 to 17 Years (Trials 812P302 and 812P304)					Total	
System Organ Class	**100 mg N=154 %**	**200 mg N=268 %**	**400 mg N=100 %**	**Treatment N=522 %**	**Placebo N=262 %**	**200 mg N=99 %**	**400 mg N=205 %**	**600 mg N=99 %**	**Treatment N=403 %**	**Placebo N=201 %**	**Treatment N=925 %**	**Placebo N=463 %**
Blood and lymphatic system disorders	1	1	0	1	0	0	0	0	0	0	0.3	0
Immune system disorders	1	0.4	1	1	0.4	0	0	0	0	0	0.3	0.2
Skin and subcutaneous tissue disorders	0	1	3	1		1		1	1	1	1	1
Vascular disorders	0	1	0	0.4	0	0	1	3	1	0	1	0
Eye disorders	0	0.4	0	0.2 2	0	1 2	0	0	0.2	0	0.2	0
Reproductive system and breast disorders	0	0.4	0	0.2	0	0	0	0	0	1	0.1	0.2
Surgical and medical procedures	0	0.4	0	0.2	0	0	0	0	0	0	0.1	0
Endocrine disorders	0	0	0	0	0.4	0	0	0	0	0	0	0.2
Renal and urinary disorders	0	0	0	0	0	0	1	1	1	1	0.2	0.2

Source: adae.xpt; Software: Python. Created by the Clinical Data Scientist
Abbreviations: N, number of subjects in the treatment arm; n, number of subjects with at least one event

The most commonly reported nervous system disorders were somnolence, headache, and sedation. The most commonly reported gastrointestinal disorders were nausea, vomiting, and abdominal pain. Psychiatric AEs were closely examined because patients with ADHD are at increased risk of other psychiatric disorders and because psychiatric AEs are associated with exposure to other adrenergic agents. Viloxazine ER–treated patients in the phase 3 controlled studies were more likely than placebo-treated patients to report psychiatric AEs (12.3% versus 6.9%).
Table 171 and Table 172 list the psychiatric AEs that occurred in ≥3 patients in the two age groups studied in the phase 3 placebo-controlled studies. Insomnia and irritability were the most common psychiatric AEs in patients ages 6 to 11 years and 12 to 17 years, respectively.

Table 171. Psychiatric Adverse Events in ≥3 Patients Ages 6 to 11 Years in Phase 3 Studies and at a Frequency Greater than in Placebo-Treated Patients

Adverse Event	Treatment (N=522)	Placebo (N=262)
Insomnia	26 (5%)	5 (2%)
Irritability	15 (3%)	4 (2%)
Mood swings	5 (1%)	2 (1%)
Depressed mood	4 (1%)	0
Nightmare	4 (1%)	1 (0.4%)

Source: adae.xpt. Created by the Clinical Reviewer
Insomnia: initial insomnia, insomnia, middle insomnia, poor-quality sleep, sleep disorder, terminal insomnia
Depressed mood: adjustment disorder with mixed anxiety and depressed mood, depressed mood, depressive symptom

Table 172. Psychiatric Adverse Events Occurring in ≥3 Patients Ages 12 to 17 Years in Phase 3 Trials and at a Frequency Greater than in Placebo-Treated Patients

Adverse Event	Treatment (N=403)	Placebo (N=201)
Irritability	17 (4%)	2 (1%)
Insomnia	14 (4%)	1 (1%)
Affect lability	5 (1%)	2 (1%)
Anxiety	3 (0.7%)	0

Source: adae.xpt. Created by the Clinical Reviewer
Insomnia: initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia
Anxiety: adjustment disorder with mixed anxiety and depressed mood, anxiety, panic attack, separation anxiety disorder

Irritability was reported more commonly in patients receiving viloxazine ER than in those receiving placebo. In addition to irritability, patients reported a constellation of preferred terms suggestive of pediatric depression or mood disturbance. These were affect lability, depressed mood, crying, tearfulness, emotional disorder, emotional poverty, emotional distress, self-esteem decreased, flat affect, mood altered, and mood swings. In the viloxazine ER group, 3.7% reported experiencing at least one of these AEs, compared to 2.6% of the placebo group. Although irritability was more common among viloxazine ER–treated patients, the difference between the viloxazine ER and placebo groups in the frequency of other mood-related AEs was small.

The psychiatric AE profile in the phase 2 dose-ranging study (812P202) was comparable to that in the phase 3 studies (Table 173). Insomnia and irritability were the most commonly reported psychiatric AEs.

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Table 173. Psychiatric Adverse Events Occurring in ≥2 Patients in Study 812P202

Adverse Event	Total Viloxazine (N=193) n (%)	Placebo (N=24) n (%)
Insomnia	12 (6)	0
Irritability	8 (4)	0
Agitation	5 (3)	0
Suicidal ideation	4 (2)	0
Tearfulness	4 (2)	0
Aggression	2 (1)	0
Abnormal dreams	2 (1)	0

Source: adae.xpt. Created by the Clinical Reviewer
Insomnia: terminal insomnia, middle insomnia, initial insomnia, insomnia
Agitation: agitation, anger

Psychiatric AEs were commonly reported in the open-label extension study (812P310). Of the 1097 patients treated with viloxazine ER in that study, 155 (14.1%) reported at least one psychiatric AE. Mood-related AEs (preferred terms affective disorder, affect lability, blunted affect, flat affect, irritability, depressed mood, depression, depressive symptom, major depression, mood altered, mood swings, persistent depressive disorder, and tearfulness) were reported by 89 (8.1%) of the patients in Study 812P310. A high rate of psychiatric symptomatology is expected in patients with ADHD. This uncontrolled study is not designed to determine whether the rate of mood-related symptoms is higher in patients treated chronically with viloxazine ER.

Of note, no events suggestive of psychosis or mania occurred in the phase 3 placebo-controlled studies. In Study 812P202, confusional state was reported as an AE by one patient. In the open-label safety extension (812P310), the following AEs possibly suggestive of psychosis occurred in 6 (0.5%) patients (ages 7 to 11 years): abnormal behavior (2 patients), hallucination auditory, hallucination visual, psychotic disorder, and confusional state. The lack of a strong psychosis or mania signal may represent a safety advantage of viloxazine ER over stimulant medications and atomoxetine. However, patients with psychosis and mania were specifically excluded in the study, so the effect of viloxazine ER in patients with bipolar or psychotic disorders is unknown. Depressive symptoms co-occur frequently in patients with ADHD and pediatric bipolar disorder may first present as a depressive episode. Therefore, patients receiving viloxazine ER should be carefully screened for risk factors for bipolar disorder prior to treatment.

The proposed labeling for viloxazine ER will include a recommendation to screen for bipolar disorder risk factors and a boxed warning regarding the risk of suicidal ideation and behavior. The most frequently occurring psychiatric AEs, irritability, and insomnia, are listed in Section 6.

Adverse Events Leading to Discontinuation

Table 174 provides additional information on the TEAEs that led to discontinuation in the phase 3 controlled studies. Of the 32 AEs leading to discontinuation, 19 occurred within the first 21 days of drug exposure.

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Table 174. Adverse Events Leading to Discontinuation, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

Study Arm	Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[1]	Study Day of AE Onset	Duration of Adverse Event (Days)	Duration of Exposure (Days)	Relatedness[2]
Placebo-adolescents	304 (b) (6)	16	F	Suicidal ideation	Exacerbation of suicidal ideation	N	17	0	16	Not related
Placebo-children	301	7	M	Aggression	Aggressive behavior	N	1	5	5	Possibly related
Placebo-children	303	9	F	Tic	Motor tic, facial	N	3	6	8	Possibly related
Placebo-children	303	11	F	Affect lability	Emotional meltdown	N	21	15	29	Possibly related
Placebo-children	303	6	M	Aggression	Physical aggression	N	11	24	14	Possibly related
Placebo-children	301	7	M	Agitation	Agitation	N	2	16	11	Possibly related
SPN-812 ER 100 mg-children	301	8	F	Tachycardia	Tachycardia	N	14	6	15	Possibly related
SPN-812 ER 100 mg-children	301	7	F	Electrocardiogram t wave inversion	Abnormal ecg-inverted t waves	N	14		14	Possibly related
SPN-812 ER 100 mg-children	301	10	M	Pyromania	Arson, inpatient behavioral health	Y	2	0	3	Unlikely related
SPN-812 ER 100 mg-children	301	11	M	Conduct disorder	Conduct disorder	Y	16	1	15	Unlikely related
SPN-812 ER 100 mg-children	301	7	M	Aggression	Aggression	N	1		30	Possibly related
SPN-812 ER 200 mg-adolescents	302	14	F	Diarrhoea	Diarrhea	N	0	3	4	Definitely related
SPN-812 ER 200 mg-adolescents	302	17	M	Somnolence	Daytime drowsiness	N	2	13	15	Possibly related

Reference ID: 4698714

Study Arm	Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[1]	Study Day of AE Onset	Duration of Adverse Event (Days)	Duration of Exposure (Days)	Relatedness[2]
SPN-812 ER 200 mg-adolescents	302 (b) (6)	13	F	Syncope	Syncopal episode	Y	23	0	25	Unlikely related
SPN-812 ER 200 mg-adolescents	302	16	M	Anxiety	Anxiety	N	3	4	6	Possibly related
SPN-812 ER 200 mg-children	301	8	M	Decreased appetite	Decreased appetite	N	22	1	24	Possibly related
SPN-812 ER 200 mg-children	301	10	M	Sleep terror	Night terrors	N	0	10	6	Possibly related
SPN-812 ER 200 mg-children	303	7	M	Nausea	Nausea	N	13	13	21	Possibly related
SPN-812 ER 200 mg-children	303	9	F	Hyperacusis	Hypersensitivity to sound	N	4	13	15	Possibly related
SPN-812 ER 200 mg-children	303	7	M	Irritability	Irritable	N	22	6	29	Possibly related
SPN-812 ER 200 mg-children	303	11	M	Hot flush	Hot flashes	N	0	2	1	Definitely related
SPN-812 ER 200 mg-children	303	11	M	Fatigue	Fatigue	N	0	32	22	Possibly related
SPN-812 ER 200 mg-children	303	7	M	Affect lability	Emotional lability	N	9	18	26	Not related
SPN-812 ER 400 mg-adolescents	304	16	M	Headache	Intermittent headaches	N	1	3	4	Definitely related

Reference ID: 4698714

Study Arm	Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[1]	Study Day of AE Onset	Duration of Adverse Event (Days)	Duration of Exposure (Days)	Relatedness[2]
SPN-812 ER 400 mg-adolescents	302 (b) (6)	12	M	Terminal insomnia	Terminal insomnia	N	4	6	9	Definitely related
SPN-812 ER 400 mg-adolescents	304	15	M	Suicide attempt	Suicidal attempt	Y	46	0	48	Possibly related
SPN-812 ER 400 mg-adolescents	304	13	M	Abdominal pain upper	Stomach ache	N	5	31	43	Definitely related
SPN-812 ER 400 mg-adolescents	302	12	F	Somnolence	Somnolence	N	11	8	18	Possibly related
SPN-812 ER 400 mg-adolescents	304	12	F	Vomiting	Intermittent vomiting	N	14	3	18	Definitely related
SPN-812 ER 400 mg-children	303	6	M	Flat affect	Flattened affect	N	5	7	9	Possibly related
SPN-812 ER 400 mg-children	303	6	M	Gastroenteritis	Gastroenteritis	N	21	11	22	Possibly related
SPN-812 ER 400 mg-children	303	6	M	Sedation	Excessive sedation	N	7	14	14	Possibly related
SPN-812 ER 400 mg-children	303	8	F	Mood altered	Coarsening of mood	N	0	11	8	Definitely related
SPN-812 ER 600 mg-adolescents	304	12	M	Fatigue	Fatigue	N	0	27	24	Possibly related
SPN-812 ER 600 mg-adolescents	304	14	M	Depressed mood	Depressed mood	N	21	17	35	Possibly related

Reference ID: 4698714

Study Arm	Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[1]	Study Day of AE Onset	Duration of Adverse Event (Days)	Duration of Exposure (Days)	Relatedness[2]
SPN-812 ER 600 mg-adolescents	304 (b) (6)	16	M	Somnolence	Somnolence	N	1	19	30	Definitely related
SPN-812 ER 600 mg-adolescents	304	14	M	Somnolence	Sleepiness	N	0	7	7	Possibly related
SPN-812 ER 600 mg-adolescents	304	13	M	Vitiligo	Vitiligo-like rash	N	22	0	23	Possibly related

Source: adae.xpt; Software: Python. Created by the Clinical Data Scientist.
[1] SAEs defined as AEs resulting in any of the following: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
[2] Scale of relatedness: not related, possibly related, definitely related, and related.
Abbreviations: AE, adverse event; ER = extended release; ID, identification; SAE, serious adverse event; SPN = viloxazine

Laboratory Assessments—Additional Information

Table 175 and Table 176 list the age-specific reference ranges for laboratory assessments used in the phase 3 controlled studies.

Table 175. Laboratory Reference Ranges-Patients Ages 6 to 11 Years

Alanine Aminotransferase (U/L)	U/L	5	30
Alkaline Phosphatase (U/L)	U/L	155	420
Aspartate Aminotransferase (U/L)	U/L	0	47
Bilirubin (µmol/L)	µmol/L	2	21
Creatinine (µmol/L)	µmol/L	21	68
Glucose (mmol/L)	mmol/L	3.9	7.8
Hemoglobin (g/L)	g/L	114	151
Leukocytes (10^9/L)	10^9/L	3.5	10.5
Neutrophils (10^9/L)	10^9/L	2.1	8.9
Platelets (10^9/L)	10^9/L	175	420
Potassium (mmol/L)	mmol/L	3.5	5.3
Sodium (mmol/L)	mmol/L	135	148

Source: ad b.xpt. Created by the Clinical Data Scientist.

Table 176. Laboratory Reference Ranges-Patients Ages 12 to 17 Years

Alanine Aminotransferase (U/L)	U/L	5	20
Alkaline Phosphatase (U/L)	U/L	110	630
Aspartate Aminotransferase (U/L)	U/L	0	41
Bilirubin (µmol/L)	µmol/L	2	21
Creatinine (µmol/L)	µmol/L	41	88
Glucose (mmol/L)	mmol/L	3.9	7.8
Hemoglobin (g/L)	g/L	113	156
Leukocytes (10^9/L)	10^9/L	3.5	10.5
Neutrophils (10^9/L)	10^9/L	2.1	7.8
Platelets (10^9/L)	10^9/L	140	370
Potassium (mmol/L)	mmol/L	3.5	5.3
Sodium (mmol/L)	mmol/L	135	148

Source: ad b.xpt. Created by the Clinical Data Scientist.

Table 177, Table 178, Table 179, and Table 180 summarize the mean values and mean changes from baseline (by treatment group) in the phase 3 controlled trials. The mean values remained within the normal range. Mean changes from baseline were small and unlikely to be clinically meaningful.

Table 177. Laboratory Values[1] (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	153	15.3 (6.5)		161	15 (5.2)		158	15.2 (6.9)	
Alanine Aminotransferase (U/L)	Week 6 (EOS)	136	15.8 (8.3)	0.4 (7.6)	138	16.9 (14.1)	2 (13.8)	139	15.3 (5.8)	0.1 (7)
Alkaline Phosphatase (U/L)	Baseline	153	251.9 (74)		161	250.6 (71)		158	249.1 (61.4)	

Reference ID: 4698714

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alkaline Phosphatase (U/L)	Week 6 (EOS)	136	250.5 (69.5)	1.3 (35.7)	137	249.5 (68)	3.2 (57.9)	137	253.4 (63.1)	5.9 (39.4)
Aspartate Aminotransferase (U/L)	Baseline	153	26.4 (6.2)		161	25.7 (5.3)		158	25.8 (5.5)	
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	136	26 (6.8)	-0.3 (5.1)	138	26.5 (16.8)	1 (17.1)	139	26.1 (6.3)	0.3 (5.5)
Bilirubin (umol/L)	Baseline	153	5.7 (3.6)		161	5.6 (3.3)		158	5.9 (4)	
Bilirubin (umol/L)	Week 6 (EOS)	136	5.4 (2.8)	-0.3 (2.7)	138	5.3 (3)	-0.5 (2.5)	139	5.3 (2.8)	-0.6 (2.7)
Blood Urea Nitrogen (mmol/L)	Baseline	153	4.3 (1.2)		161	4.1 (1.2)		158	4.3 (1.2)	
Blood Urea Nitrogen (mmol/L)	Week 6 (EOS)	136	4.2 (1.3)	-0.2 (1.2)	138	4.2 (1.1)	0 (1.1)	139	4.5 (1.3)	0.2 (1.3)
Calcium (mmol/L)	Baseline	153	2.4 (0.1)		160	2.4 (0.1)		158	2.4 (0.1)	
Calcium (mmol/L)	Week 6 (EOS)	136	2.4 (0.1)	0 (0.1)	137	2.4 (0.1)	0 (0.1)	137	2.4 (0.1)	0 (0.1)
Chloride (mmol/L)	Baseline	153	100.2 (1.9)		161	99.8 (2.3)		158	99.6 (2.2)	
Chloride (mmol/L)	Week 6 (EOS)	136	100.1 (2.1)	-0.2 (2.6)	138	99.7 (2.1)	-0.1 (2.6)	139	100 (2.3)	0.4 (2.9)
Creatinine (umol/L)	Baseline	153	43.5 (7.5)		161	43.6 (8.2)		158	43.6 (8.4)	
Creatinine (umol/L)	Week 6 (EOS)	136	44.8 (7.4)	1.6 (7.2)	138	47.1 (8.9)	3.6 (9.1)	139	44 (8.3)	0.7 (7.6)
Direct Bilirubin (umol/L)	Baseline	153	3.1 (0.3)		159	3.1 (0.3)		158	3.1 (0.5)	
Direct Bilirubin (umol/L)	Week 6 (EOS)	136	3 (0.3)	0 (0.3)	138	3.1 (0.3)	0 (0.3)	139	3 (0.3)	0 (0.4)
Eosinophils (10^9/L)	Baseline	153	0.3 (0.3)		161	0.3 (0.4)		159	0.2 (0.2)	
Eosinophils (10^9/L)	Week 6 (EOS)	136	0.3 (0.4)	0 (0.2)	138	0.3 (0.2)	0 (0.2)	139	0.3 (0.3)	0 (0.2)
Glucose (mmol/L)	Baseline	153	4.9 (0.6)		161	4.9 (0.7)		158	4.8 (0.7)	
Glucose (mmol/L)	Week 6 (EOS)	136	4.8 (0.7)	-0.1 (0.9)	138	4.9 (0.8)	0.1 (0.9)	138	4.9 (0.7)	0 (0.8)
Hematocrit (fraction of 1)	Baseline	153	0.4 (0)		161	0.4 (0)		159	0.4 (0)	
Hematocrit (fraction of 1)	Week 6 (EOS)	136	0.4 (0)	0 (0)	138	0.4 (0)	0 (0)	139	0.4 (0)	0 (0)
Hemoglobin (g/L)	Baseline	153	130.2 (8.9)		161	130.2 (9)		159	129.3 (9.6)	
Hemoglobin (g/L)	Week 6 (EOS)	136	129.3 (9.8)	-0.9 (7.5)	138	131.3 (9.5)	0.1 (7.3)	139	127.5 (10)	-2 (6.7)

Reference ID: 4698714

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Leukocytes (10^9/L)	Baseline	153	6.4 (1.9)		161	6.7 (1.8)		159	6.6 (2.1)	
Leukocytes (10^9/L)	Week 6 (EOS)	136	6.1 (1.9)	-0.4 (1.6)	138	6.3 (1.9)	-0.4 (2)	139	6.3 (1.8)	-0.4 (2.1)
Neutrophils (10^9/L)	Baseline	153	3.2 (1.4)		161	3.3 (1.5)		159	3.2 (1.6)	
Neutrophils (10^9/L)	Week 6 (EOS)	136	3 (1.3)	-0.3 (1.3)	138	3.1 (1.6)	-0.3 (1.8)	139	2.9 (1.3)	-0.3 (1.7)
Platelets (10^9/L)	Baseline	153	306 (61.8)		161	312.1 (68.6)		159	312.7 (69.4)	
Platelets (10^9/L)	Week 6 (EOS)	136	287.9 (53.1)	-15.7 (45.6)	138	288 (69.8)	-17.5 (45.3)	139	307.9 (65.6)	-6.8 (51.3)
Potassium (mmol/L)	Baseline	153	4.4 (0.4)		160	4.3 (0.4)		158	4.4 (0.4)	
Potassium (mmol/L)	Week 6 (EOS)	136	4.3 (0.4)	-0.1 (0.5)	137	4.4 (0.4)	0.1 (0.5)	137	4.4 (0.4)	0 (0.5)
Sodium (mmol/L)	Baseline	153	140.2 (1.9)		161	140 (2.1)		158	140.1 (2.1)	
Sodium (mmol/L)	Week 6 (EOS)	136	140.1 (2.1)	-0.2 (2.6)	138	140.2 (1.8)	0.3 (2.6)	139	140.1 (2.3)	0 (2.9)

Source: ad b.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Abbreviations: EOS = end of study; SPN = viloxazine

Table 178. Laboratory Values[1] (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Alanine Aminotransferase (U/L)	Baseline	98	14.8 (5)		104	16.1 (8.2)		104	14.8 (8.9)	
Alanine Aminotransferase (U/L)	Week 6 (EOS)	86	15.6 (7.4)	0.8 (6.6)	96	18.1 (12.4)	1.9 (11.1)	102	14.6 (7.8)	-0.2 (6.4)
Alkaline Phosphatase (U/L)	Baseline	98	210.5 (112.9)		103	207.7 (104.9)		104	206.2 (113)	
Alkaline Phosphatase (U/L)	Week 6 (EOS)	86	207 (106.8)	-4.5 (34.3)	95	197.7 (104)	-5.6 (31.9)	101	201.1 (109.6)	-2.1 (41.6)
Bilirubin (µmol/L)	Baseline	98	8.7 (6)		104	7.2 (5.7)		104	8.1 (6.4)	
Bilirubin (µmol/L)	Week 6 (EOS)	86	8.1 (7.4)	-0.7 (6.3)	96	6.2 (5)	-1.2 (3.6)	102	7.9 (6.9)	-0.3 (4.1)
Aspartate Aminotransferase (U/L)	Baseline	98	21.3 (5.8)		104	21.5 (6.2)		104	20.4 (6.2)	

Reference ID: 4698714

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Aspartate Aminotransferase (U/L)	Week 6 (EOS)	86	21.3 (6.4)	-0.3 (4.8)	96	21.5 (7.3)	0.2 (7.5)	102	20 (5.8)	-0.4 (4.7)
Blood Urea Nitrogen (mmol/L)	Baseline	98	3.7 (1)		104	4.2 (1.4)		104	4.1 (1.1)	
Blood Urea Nitrogen (mmol/L)	Week 6 (EOS)	86	4 (1)	0.2 (1.1)	96	4 (1.2)	-0.2 (1.5)	102	4 (1.3)	-0.1 (1.3)
Calcium (mmol/L)	Baseline	98	2.4 (0.1)		103	2.4 (0.1)		104	2.4 (0.1)	
Calcium (mmol/L)	Week 6 (EOS)	86	2.4 (0.1)	0 (0.1)	95	2.4 (0.1)	0 (0.1)	101	2.4 (0.1)	0 (0.1)
Chloride (mmol/L)	Baseline	98	100.5 (2)		104	99.8 (2.8)		104	100.5 (2.2)	
Chloride (mmol/L)	Week 6 (EOS)	86	100 (2.1)	-0.5 (2.4)	97	100.5 (2.1)	0.7 (3.3)	102	100.6 (2.2)	0.1 (2.8)
Creatinine (µmol/L)	Baseline	98	61 (12.4)		104	59.6 (13.8)		104	58.2 (12.6)	
Creatinine (µmol/L)	Week 6 (EOS)	86	64.4 (12.7)	3.1 (6.9)	96	65.2 (17.5)	5.7 (15.8)	102	57.5 (11.8)	-0.6 (7.8)
Direct Bilirubin (µmol/L)	Baseline	98	3.3 (0.7)		104	3.2 (0.6)		104	3.2 (0.7)	
Direct Bilirubin (µmol/L)	Week 6 (EOS)	86	3.2 (0.6)	-0.1 (0.7)	95	3.1 (0.4)	-0.1 (0.6)	102	3.2 (0.6)	0 (0.7)
Eosinophils (10^9/L)	Baseline	99	0.2 (0.2)		105	0.2 (0.2)		104	0.2 (0.2)	
Eosinophils (10^9/L)	Week 6 (EOS)	87	0.2 (0.1)	0 (0.1)	97	0.3 (0.5)	0 (0.4)	101	0.2 (0.2)	0 (0.1)
Glucose (mmol/L)	Baseline	98	5 (0.7)		104	4.8 (0.6)		104	4.9 (0.7)	
Glucose (mmol/L)	Week 6 (EOS)	86	5.2 (0.8)	0.2 (0.9)	96	4.9 (0.7)	0.1 (0.8)	102	5 (0.7)	0.1 (0.8)
Hematocrit (fraction of 1)	Baseline	99	0.4 (0)		105	0.4 (0)		104	0.4 (0)	
Hematocrit (fraction of 1)	Week 6 (EOS)	87	0.4 (0)	0 (0)	97	0.4 (0)	0 (0)	101	0.4 (0)	0 (0)
Hemoglobin (g/L)	Baseline	99	138.8 (13.8)		105	138.9 (13)		104	136.2 (12)	
Hemoglobin (g/L)	Week 6 (EOS)	87	137.8 (13.3)	-1.9 (8.9)	97	138.4 (13.1)	-0.9 (7.4)	101	134 (12)	-2.4 (6.8)
Leukocytes (10^9/L)	Baseline	99	6.3 (2)		105	6.3 (1.9)		104	6.2 (1.8)	
Leukocytes (10^9/L)	Week 6 (EOS)	87	6.1 (1.7)	-0.3 (1.5)	97	6.1 (1.9)	-0.3 (1.6)	101	6.1 (1.9)	-0.1 (1.5)
Neutrophils (10^9/L)	Baseline	99	3.5 (1.6)		105	3.3 (1.5)		104	3.3 (1.4)	
Neutrophils (10^9/L)	Week 6 (EOS)	87	3.2 (1.3)	-0.3 (1.2)	97	3.2 (1.4)	-0.1 (1.5)	101	3.2 (1.5)	-0.1 (1.2)

Reference ID: 4698714

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Platelets (10^9/L)	Baseline	99	272.2 (72.4)		105	277.3 (55.4)		104	276.6 (54.4)	
Platelets (10^9/L)	Week 6 (EOS)	87	267.9 (63.2)	-4.7 (50.9)	97	269 (53.5)	-9.2 (40.8)	101	274.2 (57.1)	-3 (33.4)
Potassium (mmol/L)	Baseline	98	4.5 (0.4)		103	4.5 (0.5)		104	4.5 (0.4)	
Potassium (mmol/L)	Week 6 (EOS)	86	4.4 (0.5)	-0.1 (0.5)	96	4.5 (0.5)	-0.1 (0.5)	101	4.5 (0.4)	0 (0.6)
Sodium (mmol/L)	Baseline	98	141.1 (1.8)		104	140.4 (2.4)		104	140.9 (2)	
Sodium (mmol/L)	Week 6 (EOS)	86	140.7 (1.8)	-0.5 (2.2)	97	140.9 (1.9)	0.4 (2.9)	102	140.5 (1.9)	-0.4 (2.4)

Source: ad b.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Abbreviations: EOS = end of study; SPN = viloxazine

Table 179. Laboratory Values[1] (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	107	14.4 (4.9)		100	15 (6.1)		103	15.7 (6.3)	
Alanine Aminotransferase (U/L)	Week 8 (EOS)	97	15.1 (6)	0.7 (6.1)	81	16.2 (10.5)	1.1 (8.4)	92	15.6 (6.6)	-0.3 (7.1)
Alkaline Phosphatase (U/L)	Baseline	107	240.2 (63.5)		100	253.6 (76.8)		103	238 (55.2)	
Alkaline Phosphatase (U/L)	Week 8 (EOS)	97	240.7 (65.8)	5.5 (42.9)	81	247 (67.3)	-1.8 (52.7)	92	246.5 (60.5)	11.5 (39.6)
Aspartate Aminotransferase (U/L)	Baseline	107	25.8 (5.4)		100	26 (5.2)		103	26.8 (6)	
Aspartate Aminotransferase (U/L)	Week 8 (EOS)	97	26.5 (8.6)	0.8 (7.7)	81	25.8 (6.4)	-0.2 (5.4)	92	26.3 (6.5)	-0.4 (5.5)
Bilirubin (µmol/L)	Baseline	107	5.5 (3.2)		100	6.1 (3.5)		103	5.8 (3.2)	
Bilirubin (µmol/L)	Week 8 (EOS)	97	4.8 (2.4)	-0.7 (2.8)	81	5.7 (3.7)	-0.8 (2.9)	92	5.9 (3.6)	0.5 (2.5)
Blood Urea Nitrogen (mmol/L)	Baseline	107	4.4 (1.4)		100	4.3 (1.2)		103	4.3 (1)	
Blood Urea Nitrogen (mmol/L)	Week 8 (EOS)	97	4.4 (1.3)	0 (1.4)	81	4.4 (1.3)	0 (1.3)	92	4.6 (1.2)	0.3 (1.2)
Calcium (mmol/L)	Baseline	107	2.4 (0.1)		100	2.4 (0.1)		103	2.4 (0.1)	

Reference ID: 4698714

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Calcium (mmol/L)	Week 8 (EOS)	97	2.4 (0.1)	0 (0.1)	81	2.4 (0.1)	0 (0.1)	92	2.4 (0.1)	0 (0.1)
Chloride (mmol/L)	Baseline	107	100 (1.9)		100	99.9 (1.8)		103	99.9 (1.9)	
Chloride (mmol/L)	Week 8 (EOS)	97	100 (2.5)	0.1 (2.5)	81	100 (1.9)	0.1 (2)	92	100.6 (2.8)	0.8 (2.9)
Creatinine (µmol/L)	Baseline	107	44 (7.5)		100	43.5 (10.4)		103	42.9 (7.5)	
Creatinine (µmol/L)	Week 8 (EOS)	97	45.8 (8)	1.5 (5.8)	81	47.3 (13.4)	4.2 (14.2)	92	45.3 (8.7)	2 (7.3)
Direct Bilirubin (µmol/L)	Baseline	107	3 (0.2)		100	3.1 (0.3)		103	3.1 (0.4)	
Direct Bilirubin (µmol/L)	Week 8 (EOS)	97	3 (0.1)	0 (0.2)	81	3.1 (0.4)	0 (0.4)	92	3.1 (0.4)	0 (0.4)
Eosinophils (10^9/L)	Baseline	106	0.3 (0.3)		100	0.3 (0.3)		102	0.3 (0.3)	
Eosinophils (10^9/L)	Week 8 (EOS)	98	0.3 (0.2)	0 (0.2)	81	0.2 (0.2)	0 (0.2)	92	0.3 (0.4)	0 (0.3)
Glucose (mmol/L)	Baseline	107	4.8 (0.7)		100	4.8 (0.7)		103	4.8 (0.6)	
Glucose (mmol/L)	Week 8 (EOS)	97	4.9 (0.6)	0.2 (0.9)	81	4.9 (0.9)	0 (1.1)	92	4.8 (0.6)	0 (0.9)
Hematocrit (fraction of 1)	Baseline	106	0.4 (0)		100	0.4 (0)		102	0.4 (0)	
Hematocrit (fraction of 1)	Week 8 (EOS)	98	0.4 (0)	0 (0)	81	0.4 (0)	0 (0)	92	0.4 (0)	0 (0)
Hemoglobin (g/L)	Baseline	106	129.2 (9.7)		100	130.6 (8.4)		102	131.1 (8.1)	
Hemoglobin (g/L)	Week 8 (EOS)	98	127.7 (9.4)	-1.8 (6.9)	81	131.5 (9.9)	0.8 (9.9)	92	129.4 (9.1)	-1.7 (6)
Leukocytes (10^9/L)	Baseline	106	6.2 (1.8)		100	6.7 (2.1)		102	6.3 (2)	
Leukocytes (10^9/L)	Week 8 (EOS)	98	6.4 (2.1)	0.1 (2)	81	6.1 (1.9)	-0.5 (1.6)	92	6.3 (2.1)	-0.1 (2)
Neutrophils (10^9/L)	Baseline	106	2.9 (1.3)		100	3.2 (1.3)		102	3 (1.6)	
Neutrophils (10^9/L)	Week 8 (EOS)	98	3 (1.7)	0.1 (1.8)	81	2.8 (1.2)	-0.4 (1.3)	92	3 (1.6)	0 (1.8)
Platelets (10^9/L)	Baseline	106	311.6 (67.3)		100	312.5 (67)		102	314.8 (67.1)	
Platelets (10^9/L)	Week 8 (EOS)	98	288.6 (67.1)	-21.3 (54.1)	81	287.9 (63.9)	-23.6 (54.8)	92	303.2 (60.6)	-12 (53.3)
Potassium (mmol/L)	Baseline	107	4.5 (0.4)		100	4.4 (0.4)		103	4.5 (0.4)	
Potassium (mmol/L)	Week 8 (EOS)	97	4.4 (0.4)	-0.1 (0.5)	81	4.3 (0.4)	-0.1 (0.4)	92	4.4 (0.4)	-0.1 (0.4)

Reference ID: 4698714

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Sodium (mmol/L)	Baseline	107	140.1 (1.9)		100	140 (1.9)		103	139.9 (1.9)	
Sodium (mmol/L)	Week 8 (EOS)	97	140.1 (2.2)	0.1 (2.5)	81	140.1 (2)	0.2 (2.2)	92	140.2 (2.1)	0.4 (2.4)

Source: ad b.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Abbreviations: EOS = end of study; SPN = viloxazine

Table 180. Laboratory Values[1] (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Alanine Aminotransferase (U/L)	Baseline	100	15.1 (8.1)		99	14.6 (5.6)		97	14.2 (7.9)	
Alanine Aminotransferase (U/L)	Week 7 (EOS)	86	20.2 (16.5)	5 (16.2)	88	16.9 (9.6)	2.3 (9.6)	88	13.9 (6.6)	-0.5 (5.2)
Alkaline Phosphatase (U/L)	Baseline	100	206.8 (116.5)		99	223.3 (106.3)		97	204.1 (114.4)	
Alkaline Phosphatase (U/L)	Week 7 (EOS)	86	207.2 (118.3)	3.1 (36.6)	88	219.5 (109.1)	2.6 (28.8)	88	194.1 (108.6)	-8.6 (31.9)
Aspartate Aminotransferase (U/L)	Baseline	100	21.1 (6.2)		99	21.4 (5.4)		97	20.2 (5.5)	
Aspartate Aminotransferase (U/L)	Week 7 (EOS)	86	23.1 (8.8)	2.3 (9)	88	20.9 (6.5)	-0.1 (5.6)	88	19.5 (5.4)	-0.5 (4)
Bilirubin (µmol/L)	Baseline	100	7.6 (4.3)		99	8.3 (4.6)		97	8 (5.3)	
Bilirubin (µmol/L)	Week 7 (EOS)	86	6.2 (3.6)	-1.4 (3.4)	88	6.6 (3.7)	-1.8 (3.5)	88	7.7 (4.5)	-0.2 (3.8)
Blood Urea Nitrogen (mmol/L)	Baseline	100	3.9 (1)		99	4 (1.1)		97	3.9 (1)	
Blood Urea Nitrogen (mmol/L)	Week 7 (EOS)	86	3.8 (1.2)	0 (1.1)	88	3.9 (1.1)	-0.2 (1.2)	88	4.2 (1.2)	0.3 (1.2)
Calcium (mmol/L)	Baseline	100	2.4 (0.1)		99	2.4 (0.1)		97	2.4 (0.1)	
Calcium (mmol/L)	Week 7 (EOS)	86	2.4 (0.1)	0 (0.1)	88	2.4 (0.1)	0 (0.1)	88	2.4 (0.1)	0 (0.1)
Chloride (mmol/L)	Baseline	100	100.7 (2)		99	100.6 (2.2)		97	100.5 (2.5)	
Chloride (mmol/L)	Week 7 (EOS)	86	101 (2.2)	0.3 (2.5)	88	100.6 (2.1)	0.1 (2.7)	88	100.8 (2.2)	0.1 (2.7)

Reference ID: 4698714

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Creatinine (µmol/L)	Baseline	100	59.4 (13.7)		99	58.7 (11.9)		97	58.9 (12.2)	
Creatinine (µmol/L)	Week 7 (EOS)	86	61 (13.7)	1.6 (8.6)	88	61.3 (13.2)	2.6 (9.6)	88	59.4 (12.8)	0.5 (8.7)
Direct Bilirubin (µmol/L)	Baseline	100	3.1 (0.6)		99	3.2 (0.6)		97	3.2 (0.6)	
Direct Bilirubin (µmol/L)	Week 7 (EOS)	86	3.8 (7.1)	0.7 (7)	88	3.1 (0.3)	-0.1 (0.4)	88	3.2 (0.6)	0 (0.5)
Eosinophils (10^9/L)	Baseline	100	0.3 (0.2)		99	0.2 (0.2)		96	0.2 (0.2)	
Eosinophils (10^9/L)	Week 7 (EOS)	88	0.2 (0.2)	0 (0.1)	88	0.2 (0.2)	0 (0.2)	86	0.2 (0.2)	0 (0.2)
Glucose (mmol/L)	Baseline	100	4.9 (0.6)		99	5 (0.7)		97	4.8 (0.7)	
Glucose (mmol/L)	Week 7 (EOS)	86	4.8 (1)	0 (1.1)	88	4.9 (0.8)	-0.1 (1.1)	88	5 (0.7)	0.1 (0.8)
Hematocrit (fraction of 1)	Baseline	100	0.4 (0)		99	0.4 (0)		96	0.4 (0)	
Hematocrit (fraction of 1)	Week 7 (EOS)	88	0.4 (0)	0 (0)	88	0.4 (0)	0 (0)	86	0.4 (0)	0 (0)
Hemoglobin (g/L)	Baseline	100	136.4 (13.9)		99	138.9 (10.5)		96	136.8 (11.8)	
Hemoglobin (g/L)	Week 7 (EOS)	88	137.2 (15.5)	0.6 (7.7)	88	140.2 (12.1)	0.9 (6.6)	86	134 (12.2)	-2.3 (7)
Leukocytes (10^9/L)	Baseline	100	6.4 (1.9)		99	6.5 (1.9)		96	6.4 (1.8)	
Leukocytes (10^9/L)	Week 7 (EOS)	88	6.2 (1.7)	-0.3 (1.8)	88	6.1 (1.5)	-0.5 (1.9)	86	6.2 (1.6)	-0.3 (1.6)
Lymphocytes (10^9/L)	Baseline	100	2.3 (0.7)		99	2.3 (0.7)		96	2.2 (0.6)	
Lymphocytes (10^9/L)	Week 7 (EOS)	88	2.3 (0.8)	-0.1 (0.6)	88	2.2 (0.7)	-0.1 (0.7)	86	2.1 (0.5)	-0.1 (0.5)
Neutrophils (10^9/L)	Baseline	100	3.3 (1.6)		99	3.5 (1.7)		96	3.5 (1.6)	
Neutrophils (10^9/L)	Week 7 (EOS)	88	3.1 (1.3)	-0.2 (1.5)	88	3.2 (1.2)	-0.4 (1.7)	86	3.4 (1.3)	-0.2 (1.4)
Platelets (10^9/L)	Baseline	100	285.4 (71.7)		99	277.6 (57.7)		96	282.1 (68.1)	
Platelets (10^9/L)	Week 7 (EOS)	88	269.9 (59.5)	-10.9 (37.6)	88	269.1 (51.5)	-8.3 (36.1)	86	282.4 (65.5)	-2.5 (35.5)
Potassium (mmol/L)	Baseline	100	4.4 (0.4)		99	4.4 (0.4)		97	4.5 (0.4)	
Potassium (mmol/L)	Week 7 (EOS)	86	4.4 (0.4)	0 (0.4)	88	4.4 (0.4)	0 (0.5)	88	4.4 (0.4)	0 (0.5)

Reference ID: 4698714

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Sodium (mmol/L)	Baseline	100	140.3 (1.8)		99	140.7 (2)		97	140.8 (2.1)	
Sodium (mmol/L)	Week 7 (EOS)	86	140.4 (1.7)	0.1 (2.3)	88	140.6 (2.1)	-0.2 (2.7)	88	140.3 (1.9)	-0.6 (2.5)

Source: ad b.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Abbreviations: EOS = end of study; SPN = viloxazine

The review team also conducted an analysis of the percentage of patients in each treatment group with out-of-range laboratory values and the percentage of patients whose laboratory values shifted from within to below or above the normal range. Patients receiving viloxazine ER in the controlled phase 3 clinical studies were more likely to experience a shift in liver transaminases from within to greater than the upper limit of the reference range (Table 37). Otherwise, no clinically meaningful effect on laboratory parameters was evident with viloxazine ER exposure.

The mean changes in laboratory parameters over the course of the long-term safety extension study (812P310) were small. Table 181 lists the mean changes from baseline in laboratory parameters at month 12.

Table 181. Laboratory Parameters by Visit, Safety Population (Study 812P310)

Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
Alanine aminotransferase (U/L)	Month 12	71	17.4 (7.3)	16 (7, 44)	-0.7 (5.9)	-1 (-17, 12)
Albumin (g/L)	Month 12	71	45.8 (2.5)	46 (40, 51)	-1 (3.3)	-1 (-11, 7)
Alkaline Phosphatase (U/L)	Month 12	71	247.5 (85.4)	237 (78, 468)	7.9 (56.9)	11 (-171, 198)
Aspartate aminotransferase (U/L)	Month 12	71	24.9 (6.2)	25 (12, 44)	0.1 (6.1)	0 (-13, 24)
Basophils (10^9/L)	Month 12	71	0.1 (0.1)	0.1 (0, 0.1)	0 (0.1)	0 (-0.3, 0.1)
Bicarbonate (mmol/L)	Month 12	11	20.4 (2.4)	20 (17, 25)	-1.1 (2.6)	-1 (-6, 2)
Bilirubin (µmol/L)	Month 12	71	4.7 (2.2)	4 (3, 14)	-0.2 (1.9)	0 (-6, 5)
Blood Urea Nitrogen (mmol/L)	Month 12	71	4 (1)	3.9 (2, 6.8)	-0.5 (1.2)	-0.5 (-2.7, 2.3)
Calcium (mmol/L)	Month 12	71	2.4 (0.1)	2.4 (2.2, 2.7)	-0.1 (0.1)	-0.1 (-0.4, 0.2)
Creatinine (µmol/L)	Month 12	71	49.6 (10.4)	49 (32, 84)	-0.7 (8.2)	1 (-37, 19)
Direct bilirubin (µmol/L)	Month 12	71	3 (0)	3 (3, 3)	0.6 (1.3)	1 (-7, 1)
Eosinophils (10^9/L)	Month 12	71	0.2 (0.2)	0.1 (0, 0.9)	0 (0.2)	0 (-0.6, 0.6)

Reference ID: 4698714

Parameter	Visit[1]	Sample Size	Mean (SD)	Median (Min, Max)	Mean Change from Baseline (SD)	Median Change from Baseline (Min, Max)
Erythrocytes (10^{12}/L)	Month 12	71	4.6 (0.4)	4.6 (3.7, 5.4)	-0.1 (0.3)	-0.1 (-0.7, 0.6)
Glucose (mmol/L)	Month 12	71	5 (0.9)	4.8 (1.7, 7.1)	-0.1 (1.2)	-0.2 (-3.5, 3.8)
Hematocrit (%)	Month 12	71	42.3 (3.8)	42 (33, 52)	0.6 (3.1)	1 (-6, 8)
Hemoglobin (g/L)	Month 12	71	133.4 (11.2)	132 (104, 161)	2.2 (7.9)	3 (-16, 25)
Leukocytes (10^9/L)	Month 12	71	6.2 (2)	6 (2.8, 12.9)	0.4 (1.8)	0.3 (-3.3, 6.4)
Lymphocytes (10^9/L)	Month 12	71	2.3 (0.7)	2.2 (1.1, 3.9)	0 (0.5)	0.1 (-1.2, 1.9)
Monocytes (10^9/L)	Month 12	71	0.4 (0.2)	0.4 (0, 1.3)	0.1 (0.2)	0.1 (-0.2, 0.9)
Neutrophils (10^9/L)	Month 12	71	3.3 (1.7)	3 (1, 9.7)	0.3 (1.6)	0.1 (-3.7, 7.1)
Phosphate (mmol/L)	Month 12	59	1.6 (0.2)	1.6 (1, 2.1)	0.1 (0.2)	0 (-0.4, 0.5)
Platelets (10^9/L)	Month 12	71	264.5 (61.4)	257 (140, 456)	-3.4 (50.7)	-7.5 (-143, 157)
Potassium (mmol/L)	Month 12	71	4.5 (0.4)	4.4 (3.8, 5.4)	0.1 (0.5)	0.1 (-1.2, 1.3)
Protein (g/L)	Month 12	71	69 (3.7)	69 (62, 79)	-1.5 (4.8)	-1 (-14, 9)
Sodium (mmol/L)	Month 12	71	141 (2.4)	141 (136, 149)	1.4 (2.8)	1 (-4, 11)

Source: ad b.xpt; Software, Reviewer modified.
[1] Unscheduled visits were not included

Electrocardiograms

The mean increases in heart rate with viloxazine ER exposure as measured by ECG were similar to those in vital signs. Viloxazine ER was not associated with clinically meaningful changes in corrected QT interval or other ECG parameters (Table 182, Table 183, Table 184, and Table 185).

Table 182. Electrocardiogram Values[1] (Study 812P301)

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Heart Rate (bpm)	Baseline	154	79 (11.2)		161	77.7 (11.5)		159	78.5 (10.3)	
Heart Rate (bpm)	Week 6 (EOS)	139	81 (11.8)	2.2 (10.6)	146	81.8 (13)	4.5 (11.9)	142	78.5 (10.1)	0.4 (9.2)
PR Interval (msec)	Baseline	154	137.8 (17.2)		161	137.4 (20.4)		158	138.3 (20.2)	
PR Interval (msec)	Week 6 (EOS)	138	136.2 (16.2)	-0.9 (10.3)	146	136.8 (16.9)	-0.8 (13.6)	142	139.6 (21.3)	1.4 (12.5)

Reference ID: 4698714

		SPN-812 100 mg (N=154)			SPN-812 200 mg (N=161)			SPN-812 Placebo (N=159)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
QRS Duration (msec)	Baseline	154	82.2 (8.7)		161	80.3 (8.9)		159	81.2 (9.9)	
QRS Duration (msec)	Week 6 (EOS)	139	82.5 (9.6)	-0.2 (6.5)	146	81.9 (8.9)	0.8 (6.7)	142	81.6 (9.2)	0.1 (7.3)
QT Interval (msec)	Baseline	154	363.3 (23.2)		161	365.3 (28.8)		159	363.1 (21.4)	
QT Interval (msec)	Week 6 (EOS)	139	359.7 (26.9)	-4.1 (19.2)	146	357.5 (27.6)	-9 (22)	142	363.5 (22.2)	0 (16.3)
QTcF Interval (msec)	Baseline	154	396.5 (15.5)		161	396 (19.1)		159	395.5 (14.1)	
QTcF Interval (msec)	Week 6 (EOS)	139	395.4 (17.4)	-1.3 (12.9)	146	394.2 (18.9)	-2.4 (15.9)	142	396.2 (15.4)	0.7 (12.2)

Source: adeg.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Reference ranges: Heart rate, 60 to 140 bpm; PR interval, 90 to 170 msec; QRS duration, 40 to 90 msec
Abbreviations: EOS = end of study; SPN = viloxazine

Table 183. Electrocardiogram Values[1] (Study 812P302)

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
Heart Rate (bpm)	Baseline	99	71 (10.3)		105	67.5 (10.2)		104	71.5 (11.5)	
Heart Rate (bpm)	Week 6 (EOS)	89	75.9 (13.1)	4.5 (12.6)	97	74.9 (12.2)	7.4 (11.4)	102	71.2 (10.9)	-0.5 (11.1)
PR Interval (ms)	Baseline	98	142.5 (17)		105	146.3 (21.5)		103	145.1 (17.5)	
PR Interval (ms)	Week 6 (EOS)	89	142.4 (18.4)	0.2 (13.1)	97	144.5 (18.3)	-1.9 (11.9)	102	144.8 (18.5)	-0.4 (13.5)
QRS Duration (msec)	Baseline	99	89 (9.3)		105	87.2 (8.9)		104	86 (8.5)	
QRS Duration (msec)	Week 6 (EOS)	89	90 (8.2)	1.1 (7)	97	88.1 (9.3)	0.9 (8.1)	102	87.1 (10.1)	1.2 (7.1)
QT Interval (msec)	Baseline	99	379.3 (26.9)		105	386.1 (27.7)		104	380 (28.7)	
QT Interval (msec)	Week 6 (EOS)	89	370.7 (28.1)	-8.4 (23.4)	97	369.2 (28.4)	-16.9 (24.6)	102	378 (27.4)	-1.4 (24.9)

Reference ID: 4698714

		SPN-812 200 mg (N=99)			SPN-812 400 mg (N=105)			SPN-812 Placebo (N=104)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)	N	Mean (SD)	Mean Change (SD)
QTcF Interval (msec)	Baseline	99	399.5 (19.9)		105	399.8 (20.2)		104	400.8 (17.7)	
QTcF Interval (msec)	Week 6 (EOS)	89	398.5 (17.8)	-1.7 (14.3)	97	395.3 (17.4)	-4.5 (15.4)	102	398.4 (18.3)	-2.1 (15.4)

Source: adeg.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Reference ranges: Heart rate, 50 to 130 bpm; PR interval, 90 to 200 msec; QRS duration, 40 to 100 msec
Abbreviations: EOS = end of study; SPN = viloxazine

Table 184. Electrocardiogram Values[1] (Study 812P303)

		SPN-812 200 mg (N=107)			SPN-812 400 mg (N=100)			SPN-812 Placebo (N=103)		
Parameter	Visit	N	Mean (SD)	Mean Change (SD)	N	Mean	Mean Change	N	Mean (SD)	Mean Change (SD)
Heart Rate (bpm)	Baseline	107	76 (11.7)		100	77.5 (11.5)		103	77.8 (12.4)	
Heart Rate (bpm)	Week 8 (EOS)	99	79.3 (12.5)	3.8 (11.1)	83	82.5 (14.8)	4.9 (14.3)	93	79 (10)	0.2 (12.6)
PR Interval (msec)	Baseline	106	135.2 (17.4)		99	138.2 (18.4)		101	138.4 (17.1)	
PR Interval (msec)	Week 8 (EOS)	99	135.5 (16.4)	0.3 (11.2)	83	136.5 (18.5)	-2.6 (14.3)	93	138.7 (17.3)	1 (12.4)
QRS Duration (msec)	Baseline	107	82.2 (8.9)		100	83.4 (9.4)		103	81.9 (8.3)	
QRS Duration (msec)	Week 8 (EOS)	99	83.4 (8.8)	0.9 (5.9)	83	83.7 (8.1)	0.5 (6.6)	93	82.4 (8.1)	0.9 (5.2)
QT Interval (msec)	Baseline	107	374 (28.9)		100	370.5 (27.6)		103	369 (26)	
QT Interval (msec)	Week 8 (EOS)	99	367.2 (31.3)	-7.9 (24.8)	83	361.7 (32.3)	-8.2 (30.3)	93	365.9 (25.6)	-1.7 (26.4)
QTcF Interval (msec)	Baseline	107	402.4 (18.5)		100	401.4 (18.8)		103	400.3 (18)	
QTcF Interval (msec)	Week 8 (EOS)	99	400.4 (20.3)	-2.3 (15.3)	83	399 (18.2)	-1.8 (16.8)	93	399.4 (17.2)	-1 (16.5)

Source: adeg.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Reference ranges: Heart rate, 60 to 140 bpm; PR interval, 90 to 170 msec; QRS duration, 40 to 90 msec
Abbreviations: EOS = end of study; SPN = viloxazine

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Table 185. Electrocardiogram Values[1] (Study 812P304)

		SPN-812 400 mg (N=100)			SPN-812 600 mg (N=99)			SPN-812 Placebo (N=97)		
Parameter	**Visit**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**	**N**	**Mean (SD)**	**Mean Change (SD)**
Heart Rate (bpm)	Baseline	100	70.8 (12.1)		99	69.9 (11.5)		97	69.1 (10.9)	
Heart Rate (bpm)	Week 7 (EOS)	91	76.7 (14.3)	5.7 (10.9)	90	78.1 (12.7)	7 (11.8)	89	69.1 (12)	-0.4 (11.8)
PR Interval (msec)	Baseline	99	143.8 (18.5)		99	140.1 (19.2)		97	145.1 (21.4)	
PR Interval (msec)	Week 7 (EOS)	91	142.5 (20.2)	-0.8 (13.2)	89	141 (17)	0.3 (14.9)	89	144.6 (20.5)	0.3 (12.8)
QRS Duration (msec)	Baseline	100	89.8 (8)		99	89.5 (8.4)		97	88.6 (9.3)	
QRS Duration (msec)	Week 7 (EOS)	91	89.1 (7.9)	-0.8 (6.9)	90	89.1 (8.3)	-0.2 (6.2)	89	89.6 (10.9)	1 (6.4)
QT Interval (msec)	Baseline	100	382.9 (25.4)		99	385.3 (29.3)		97	387.1 (27.8)	
QT Interval (msec)	Week 7 (EOS)	91	372.3 (29.4)	-10 (23.7)	90	367.8 (27.9)	-14.7 (25.6)	89	387 (27.9)	1 (25.3)
QTcF Interval (msec)	Baseline	100	402.2 (17.6)		99	402.8 (16.7)		97	403.6 (18)	
QTcF Interval (msec)	Week 7 (EOS)	91	401 (18.5)	-1.1 (16.1)	90	398.9 (16.5)	-3.6 (16.9)	89	403.3 (21.1)	-0.1 (15.8)

Source: adeg.xpt. Created by the Clinical Data Scientist.
[1] Does not include unscheduled visits
Reference ranges: Heart rate, 50 to 130 bpm; PR interval, 90 to 200 msec; QRS duration, 40 to 100 msec
Abbreviations: EOS = end of study; SPN = viloxazine

Table 186 lists the QTcF values for patients in the phase 3 controlled trials whose QTcF increased from normal to >440 msec by EOS. No patient receiving viloxazine ER had a >60 msec increase in QTcF and no patient had a QTc value of >500 msec. The observed changes are unlikely to be clinically meaningful. Of note, the total QT study did not find evidence that

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viloxazine ER prolongs the QT interval. Please see the QT-IRT consultative review for a full discussion of studies evaluating the effect of viloxazine ER on the QT interval.

Table 186. Shift from Normal to Prolonged QTcF (> 440) in Viloxazine ER–Exposed Patients (Studies 812P301, 812P302, 812P303, and 812P304)

Patient ID	Treatment Arm	Study Visit	QTcF (msec)
303 (b) (6)	SPN-812 ER 200 mg	Week 8 (EOS)	452
304	SPN-812 ER 400 mg	Week 7 (EOS)	441
304	SPN-812 ER 400 mg	Week 7 (EOS)	453
304	SPN-812 ER 400 mg	Week 7 (EOS)	442

Source: adeg.xpt. Created by the Clinical Data Scientist.
Abbreviations: EOS = end of study; ER = extended release

Additional Safety Data—Studies 812P202 and 812P310

Table 187 lists the AEs reported by ≥2% of patients treated with viloxazine ER and that occurred more frequently than in the placebo group in Study 812P202. The AE profile in this phase 2 dose-ranging study was comparable to that in the phase 3 safety and efficacy studies.

Table 187. Treatment-Emergent Adverse Events Occurring in ≥2% of Viloxazine-Treated Patients and More Frequently than Placebo (Study 812P202)

Adverse Event	Total Viloxazine (N=193) n (%)	Placebo (N=24) n (%)
Somnolence	41 (21)	1 (4)
Headache	27 (14)	1 (4)
Decreased appetite	24 (12)	2 (8)
Vomiting	14 (7)	0
Insomnia	12 (6)	0
Abdominal pain	12 (6)	1 (4)
Fatigue	10 (5)	0
Nausea	10 (5)	0
Gastroenteritis	9 (5)	1 (4)
Irritability	8 (4)	0
Tachycardia	7 (4)	0
Weight decreased	5 (3)	0
Rash	5 (3)	0
Agitation	5 (3)	0
Dyspepsia	4 (2)	0
Suicidal ideation	4 (2)	0
Sedation	4 (2)	0
Diarrhea	4 (2)	0
Tearfulness	4 (2)	0

Source: adae.xpt. Created by the Clinical Reviewer.
Somnolence: somnolence, hypersomnia
Headache: headache, migraine, tension headache
Vomiting: vomiting, procedural vomiting
Abdominal pain: abdominal pain, abdominal pain upper, abdominal discomfort
Insomnia: insomnia, initial insomnia, middle insomnia, terminal insomnia,
Gastroenteritis: viral gastroenteritis, gastroenteritis, gastrointestinal viral infection
Tachycardia: tachycardia, increased heart rate
Rash: contact dermatitis, rash, skin exfoliation, urticaria
Agitation: agitation, anger

The most common AEs in Study 812P310 were upper respiratory infection (12.3%), somnolence/sedation (12.1%), headache (8.8%), decreased appetite (5.8%), fatigue (5.5%), and

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abdominal pain (4.6%), irritability (3.6%), insomnia/poor quality sleep (3.2%), vomiting (2.7%), tachycardia/increased heart rate (2.6%), nausea (2.4%), and suicidal ideation/behavior (2.1%).

Subgroup Analysis of Safety Signals

Table 188 summarizes the adverse event profile in demographic subgroups. The proportion of patients who experienced adverse events was comparable in males and females and across age groups. The proportion of patients experiencing an adverse event was also similar in non-Hispanic and Hispanic patients as well as in white and black patients. AE data in patients from other racial groups are difficult to interpret because of the small number included.

Table 188. Adverse Events by Demographic Subgroup, Safety Population (Studies 812P301, 812P302, 812P303, and 812P304)

Characteristic	Treatment N=925 [n/N_s (%)]	Placebo N=463 [n/N_s (%)]
Sex, n (%)		
Male	322/611 (53)	93/285 (33)
Female	155/314 (49)	78/178 (44)
Age group, years, n (%)		
6-9	187/356 (53)	59/175 (34)
10-11	78/166 (47)	35/87 (40)
12-14	139/267 (52)	49/134 (37)
15-17	73/136 (54)	28/67 (42)
Race, n (%)		
American Indian or Alaska Native	6/6 (100)	4/4 (100)
Black or African American	180/368 (49)	51/175 (29)
Multiple	21/33 (64)	9/19 (47)
White	267/515 (52)	105/263 (40)
Asian	2/2 (100)	2/2 (100)
Native Hawaiian or other Pacific Islander	1/1 (100)	0
Ethnicity, n (%)		
Hispanic or Latino	129/277 (47)	39/131 (30)
Not Hispanic or Latino	347/647 (54)	132/331 (40)
Not allowed to ask as per local regulations	0	0/1 (0)
Missing	1/1 (100)	0

Source: ad b.xpt, adae.xpt; Software: R
Abbreviations: N = number of subjects in the treatment group; n = number of subjects with a given characteristic; N_s = number of subjects in the subgroup

Consultative Review, Interdisciplinary Review Team for Cardiac Safety Studies

Viloxazine ER is not associated with prolongation of the corrected QT interval, but it inhibits the cardiac sodium and potassium channels, which may have implications for patients with underlying cardiac disease. The IRT for Cardiac Safety Studies Consultative Review is excerpted below:

> The effect of viloxazine was evaluated in two separate studies—1) thorough QT study (Study #812P117) and 2) a single- and multiple- ascending dose study (812P120) by concentration-QT analysis. Although no significant QTc prolongation effect of viloxazine

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was detected, the QTc interval was shortened in a dose- and concentration-dependent manner.

The results of nonclinical studies indicate that viloxazine inhibits the cardiac sodium and hERG potassium channels (see Section 3.1.2 of our previous review for details). We have concerns about the sodium channel blocking potential as other drugs that block the cardiac sodium channel have been observed to increase mortality in patients with structural heart disease in the CAST trials (i.e., encainide, flecainide, and moricizine) and IMPACT study (i.e., mexiletine). Whether or not viloxazine carries the same risk is unknown. Additionally, some sodium channel-blocking drugs have a potential for unmasking Brugada syndrome. We have previously recommended that the sponsor conducts additional nonclinical experiments to determine the anti-arrhythmic class of viloxazine, as this information would be useful to better characterize the potential risk for viloxazine.

We propose to add a description of the nonclinical findings for the cardiac sodium channel to Section 12.2 of the label to clarify that the lack of QRS duration changes in healthy volunteers does not necessarily mean that the viloxazine does not inhibit cardiac sodium channels.

Figure 47 shows the IRT for Cardiac Safety Studies recommendations for revision of the Applicant's draft labeling. The Division agreed with these recommendations.

Figure 47. IRT for Cardiac Safety Studies Recommendations for Labeling Revisions

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) At a dose (b) (4) times (b) (4) the maximum recommended dose (b) (4) TRADENAME does not prolong the QT interval to any clinically relevant extent. There was no effect of TRADENAME on the PR interval or QRS duration in healthy volunteers. However, nonclinical studies suggest a potential for TRADENAME to inhibit cardiac sodium channels. (b) (4)

(b) (4)

Abbreviations: IRT = interdisciplinary review team

Consultative Review, Controlled Substances Staff

Consultative Review, Controlled Substances Staff

The Controlled Substances Staff (CSS) completed a consultative review evaluating data related to the abuse liability of viloxazine ER. The CSS has concluded that viloxazine ER does not have clinically relevant abuse liability. The CSS will recommend that viloxazine ER is not controlled by the Controlled Substances Act (CSA). The Executive Summary of the CSS review is included below (refer to the complete review for additional details).

Background

This memorandum responds to a consult request by the Division of Psychiatry (DP) to evaluate abuse-related preclinical and clinical data submitted by Supernus Pharmaceuticals, INC., (Sponsor) under NDA 211964 and IND 108864 for viloxazine

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(SPN-812). The Sponsor is seeking an indication for attention-deficit hyperactivity disorder (ADHD) in pediatric patients 6 – 17 years of age. The Sponsor also holds (b) (4) IND (b) (4) for ADHD in adults for the same substance. CSS was first consulted on April 18, 2017, during the IND phase, at which time the Sponsor was informed that it was not necessary to conduct animal or human abuse-related studies, however, they should continue to monitor for adverse events (AEs) related to abuse potential (DARRTS; IND 108864; Hawkins, Edward; 07/05/2017).

Viloxazine was first marketed Europe as an immediate-release formulation for the treatment of depression. It was removed from the market for business reasons and there were no indications any individuals were of abusing the drug during its marketing cycle. The Sponsor is proposing an extended- release formulation with single oral doses of (b) (4) mg in a 24-hour period in patients aged 6 through 11 years old and doses of (b) (4) mg in a 24-hour period in ages 12 through 17 years old.

In vitro binding studies indicate that viloxazine functions through several mechanisms of action, the most predominant of which are norepinephrine (NE) release and modulation of serotonin (5-HT) receptors. Viloxazine is a potent antagonist of the NE transporter (NET), an antagonist of the 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C} receptors, and a weak agonist of the 5-HT_{7} receptor.

In animal behavior studies, viloxazine did not produce behaviors that are indicative of abuse potential. In a modified Irwin Screen the only viloxazine-induced measures that were statistically different from control animals were a decrease in approach response, mydriasis, and decreased body temperature.

There were no significant behavioral effects in multiple dose toxicity studies in rats given doses of 20 to 500 mg/kg. Doses above 500 mg/kg resulted in death from convulsions.

Animal studies produced no signs of tolerance or physical dependence. The results from these studies are consistent with human data published in the literature from when the drug was marketed in Europe. There were also no signals of tolerance or dependence in the clinical adverse event (AE) profile.

The AE profile in phase 1 studies in healthy adult volunteers (N = 321) indicate that the most common AEs from oral doses of viloxazine (200 to 2100 mg) were dizziness 30 (9.35%), headache 26 (8.1%), and somnolence 22 (6.85%). Out of 30 adult subjects given 3-fold the highest therapeutic dose of 1800 mg, there was one report of euphoric mood (3.33%) and one report of a visual hallucination (3.33%). In phase 2 and 3 studies, conducted in children aged 6 - 17, the most common AEs were somnolence, with a frequency of 360 (16.68%), headache, 218 (10.10%), decreased appetite, 167 (7.74%), and fatigue, 120 (5.56%). In these studies, viloxazine did produce affect lability 32 (1.48%), auditory hallucination 1 (0.05%), and visual hallucination 2 (0.10%).

In the NDA submission, the Sponsor proposes to not control viloxazine in the Controlled Substances Act (CSA). After evaluating the nonclinical and clinical data in the NDA, CSS concludes that viloxazine should not be controlled in the CSA. (b) (4)

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(b) (4)

Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 211964 for viloxazine and concludes that the drug does not have a concerning level of abuse potential and should not be controlled in the CSA. This conclusion is based on the following data:

- In receptor binding and functional studies, viloxazine causes release of NE through blockade of the NET. It also functions as an antagonist at specific 5-HT receptors.
- In animal general behavior tests, viloxazine did not produce behaviors consistent with drugs that have abuse potential.
- In animal physical dependence studies, chronic administration of viloxazine did not produce signs of withdrawal following drug discontinuation.
- Phase 1 multiple ascending dose studies in healthy subjects indicate that the drug produced dizziness, headache, and somnolence. Abuse-related AEs did occur at supratherapeutic doses, (euphoric mood (1) and visual hallucination (1)) in these studies. There was no increase in abuse-related AEs in subjects given Vyvanse or Concerta in conjunction with viloxazine. In Phase 2 and 3 studies, abuse-related AEs occurred at low rates in viloxazine treated subjects (0.05 – 1.48%). These results indicate that abuse-related AEs occur at low rates in healthy and viloxazine-treated subjects.
- Viloxazine did not produce abuse potential, tolerance, or a withdrawal syndrome in previous use of the drug when it was approved and marketed in Europe as an antidepressant. The formulation in Europe was for an immediate-release product which one might expect to have increased abuse potential based on the PK data [in Table 189]:

Table 189. PK Parameters of Single Oral Doses of 200mg ER and IR Formulations of SPN812

	Treatment (200 mg Viloxazine)	
PK Parameter	**SPN812 ER**	**SPN812 IR**
C_{max} (µg/mL)	1.33	3.42
t_{max} (h)	5.25	1.96
AUC_{last} (µg*h/mL)	26	30.9
$t_{1/2}$ (h)	7.02	4.26

Recommendations

Based on the CSS determinations that viloxazine does not have abuse potential and does not appear to produce physical dependence, CSS concludes that:

1. Viloxazine should not be recommended for control in the CSA.
2. Section 9 (Drug Abuse and Dependence) should not be included in the drug label.

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18. Mechanism of Action/Drug Resistance Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations Additional Information

Not applicable.

20. Data Integrity-Related Consults (OSI, Other Inspections)

The Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (OSI) conducted site inspections as described in **Section** II.10. Please refer to the OSI clinical inspection summary for full details.

21. Labeling Summary of Considerations and Key Additional Information

Overview of Major Labeling Changes

The information below represents significant changes made to the full prescribing information from the Applicant's proposed label for QELBREE (viloxazine ER).

HIGHLIGHTS and **TABLE OF CONTENTS** were revised for consistency with the full Prescribing Information and to reflect the appropriate established pharmacologic class

BOXED WARNING

The Applicant's draft labeling contained a warning about an increased risk of suicidal ideation and advised healthcare professionals to monitor for suicidality, clinical worsening, and unusual changes in behavior. As described in **Section** II.7.6.2, patients exposed to viloxazine ER were more likely to report suicidal ideation and behavior than patients on placebo. We considered whether viloxazine ER should also carry a boxed warning for suicidal ideation and behavior. Although viloxazine ER does not function as a serotonin reuptake inhibitor, it does have activity at serotonin receptors and has previously been marketed as an antidepressant in Europe. Suicidal ideation and behavior in pediatric patients have been associated with use of serotonergic medications including the serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRI). Of note, all antidepressant medications approved by FDA carry a class warning for increased risk of suicidal ideation and behavior in patients ages 24 years or younger. In addition, atomoxetine, which has a similar mechanism of action as viloxazine ER, also has a boxed warning for increased risk of suicidal ideation in children and adolescents. Given the imbalance of suicidal ideation and behavior events in the viloxazine ER clinical trials;

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the occurrence of suicidal ideation in patients receiving viloxazine who did not necessarily have a prior history of suicidal ideation or behavior or mood disorders; and the fact that an increased risk of suicidal ideation and behaviors has been observed with other medications that have activity at the serotonin and norepinephrine receptors, we determined that a boxed warning was appropriate to alert healthcare professionals to this potential risk.

INDICATIONS AND USAGE

Labeling indicates that viloxazine ER is indicated for the treatment of ADHD in pediatric patients ages 6 to 17 years. The indication statement is appropriate because it reflects the patient population that was included in the registration trials. The mechanism of action (selective norepinephrine reuptake inhibitor) was added.

DOSAGE AND ADMINISTRATION

The recommended starting dose and titration schedule were included for clarity. Revisions to the label specify that the recommended dose for pediatric patients ages 6 to 11 years is 100 mg once daily and that the dosage may be titrated weekly, in increments of 100 mg, up to a dosage of 400 mg once daily. For patients ages 12 to 17 years, the recommended starting dose is 200 mg once daily. The dosage may be titrated, in increments of 200 mg, up to a dosage of 400 mg once daily. (b) (4) . Healthcare professionals are advised to measure heart rate and blood pressure prior to initiating treatment with viloxazine ER. Healthcare professionals should also screen patients for risk factors for bipolar disorder.

Section 2.4. Dose Modification in Patients with Renal Impairment

A maximum recommended dose of 200 mg for severely renal impaired patients was included due to a ~90% increase in the viloxazine AUC when viloxazine ER is administered to these patients.

CONTRAINDICATIONS

The review team agreed with the Applicant's proposal to contraindicate viloxazine ER in patients who are concomitantly prescribed monoamine oxidase inhibitors (MAOIs). Use with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range is also contraindicated. (b) (4)

WARNINGS AND PRECAUTIONS

The Applicant listed warnings regarding the risk of (b) (4) and the risk of suicidal ideation in the draft labeling submitted with the NDA. The review team determined that a warning regarding the risk of somnolence, including the advice that patients should use caution when driving or operating (b) (4) machinery, would more appropriately describe the potential risk to patients. As described in **Section 7.5**, somnolence and sedation were frequently occurring adverse events in the development program. Although the risk of driving impairment with viloxazine ER exposure has not been evaluated in a separate study, somnolence and sedation could plausibly impact patients' ability to drive. This information will be relevant to adolescent

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patients who are prescribed viloxazine ER for the treatment of ADHD who drive or operate machinery.

The review team also recommended retaining the warning regarding suicidal ideation and, as noted above, recommended adding a boxed warning about this risk.

Warnings regarding effects on blood pressure and heart rate and effects on weight were included for reasons described in **Section 7.6**, Review Issues Relevant to the Evaluation of Risk.

In addition, a warning about the need to screen patients for bipolar disorder was added because of the possible risk of induction of a mixed or manic episode. Viloxazine ER acts on adrenergic receptors; other medications with activity at adrenergic receptors have been associated with the emergence of manic symptoms. Patients with bipolar disorder were specifically excluded from the viloxazine ER studies, so the effects of viloxazine ER in pediatric patients with bipolar disorder are unknown. Co-occurring depressive symptoms are common in patients with ADHD, and pediatric patients with bipolar disorder may present first with depression rather than mania or hypomania. Healthcare professionals should screen patients for risk factors for bipolar disorder, including a positive family history.

ADVERSE REACTIONS

The Applicant initially presented a table of adverse reactions that included (b) (4) data from the phase 2 dose-finding study. The Applicant included adverse reactions that occurred in (b) (4)% of patients who received viloxazine ER. The table was revised to include adverse reaction data from the four phase 3 placebo-controlled studies that were used to establish evidence of effectiveness. (b) (4) As discussed in **Section 17**, preferred terms representing similar adverse reactions were grouped to prevent dilution of safety signals. In accordance with Division requirements, adverse reactions occurring in ≥2% of patients and at a greater rate than in placebo-treated patients are listed.

DRUG INTERACTIONS

As described above, viloxazine ER is contraindicated in patients who are prescribed sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range. Viloxazine is a potent (greater than 5-fold increase in AUC) inhibitor of CYP1A2 and a weak inhibitor (< 2-fold increase in AUC) of CYP2D6 and CYP3A4.

USE IN SPECIFIC POPULATIONS

The prescribing information has been revised to include information about the possible risk of maternal harm during pregnancy (based on animal studies). Viloxazine ER should be discontinued when pregnancy is recognized. Healthcare professionals should report pregnancies to (b) (4).

Renal Impairment

Section 8.6. Total exposure to viloxazine is increased by about 90% when administered to severe renal function compared to normal renal function patients. (b) (4) . No dose adjustment is recommended for patients with mild to moderate renal impairment.

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CLINICAL PHARMACOLOGY

Section 12.1 was revised to describe the mechanism of action of viloxazine and the Highlights section was revised to align with the established pharmacological class of viloxazine—a selective norepinephrine reuptake inhibitor.

NONCLINICAL TOXICOLOGY

Section 13.1 was revised to include the findings from fertility studies with the corresponding NOAELs and exposure multiples for male and female fertility. Section 13.2 was revised to describe the doses at which convulsions were observed in the animal studies and the corresponding exposure multiples relative to the maximal recommended human dose.

CLINICAL STUDIES

Section 14 describes the phase 3, placebo-controlled studies (Studies 812P301, 302, 303, and 304) submitted as evidence of efficacy.

In addition to information about the effects of viloxazine ER on the primary efficacy endpoint, the ADHD-RS-5, the Applicant has described the effect on the Clinical Global Impression-Improvement, which was a prespecified key secondary endpoint in the statistical analysis plans. The Applicant and Division reached agreement on the ADHD-RS-5 as the primary endpoint prior to the conduct of the study, but the Division did not endorse the use of the CGI-I because of concerns that it is vulnerable to recall bias. The Division communicated its concerns about the use of the CGI-I in the pre-NDA meeting. The use of the CGI-I as a secondary endpoint intended for inclusion in labeling therefore became a review issue.

In Studies 812P301, 812P302, and 812P300, a greater reduction (more improvement) was observed in the CGI-I score at EOS in all dose groups as compared to placebo. Study 812P304 did not demonstrate statistical significance on the primary efficacy endpoint, so the statistical significance of the key secondary endpoints was not formally tested. Although concerns about the possibility of recall bias remain, the fact that the positive findings on the CGI-I were replicated in multiple studies suggests that it is a reliable finding. The CGI-I results also provide information on how clinically meaningful the treatment effect was in the judgment of clinicians. Therefore, the review team determined that the Applicant's proposal to include the CGI-I results in labeling was acceptable.

(b) (4)

22. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) are recommended by the review team:

- **Single-arm pregnancy study:** The pharmacology/toxicology team reviewed the available nonclinical data related to exposure during pregnancy. The Division of Pediatric and Maternal Health also provided a consultative review of the application. Maternal deaths occurred when both rats and mice were exposed to viloxazine in later pregnancy. Limited data regarding the safety of viloxazine in pregnancy are available in postmarketing databases

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or in the literature. The review team recommends a PMR for a single-arm pregnancy study to evaluate the effect of viloxazine ER on pregnancy outcomes.

- **Milk-only lactation study:** No data are available regarding the presence of viloxazine in animal or human milk, the effect of viloxazine ER on lactation, or the effect of viloxazine ER on breast-fed infants. The review team recommends a PMR for a milk-only lactation study in lactating patients to determine if viloxazine ER is present in breast milk and to assess the milk: plasma ratio and the relative infant dose.

- **Safety and efficacy study in patients ages 4 to <6 years:** See Section 8.3 for discussion of the agreed Pediatric Study Plan (PSP). The review team recommends a PMR for one safety and efficacy study in patients ages 4 to <6 years.

- **Long-term, open-label safety study in patients ages 4 to <6 years**: As described in the agreed PSP, the Applicant should conduct a 6-month, open-label safety and tolerability study in patients ages 4 to <6 years who completed the short-term safety and efficacy study.

- **Hepatic impairment study:** The effect of hepatic impairment on viloxazine ER exposure has not been evaluated. The Applicant has previously indicated that a hepatic impairment study will be conducted in parallel with the adult development program. The review team recommends a PMR to complete this study.

23. Financial Disclosure

Table 190. Covered Clinical Studies: 812P301, 812P302, 812P303, 812P304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study 812P301, 34; Study 812P302, 33: Study 812P303, 28; Study 812P304, 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: N/A		
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): N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 4698714

24. References

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Reference ID: 4698714

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25. Review Team

Table 191. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Kofi Ansah, PharmD
Nonclinical Reviewer	Jia Yao, Ph.D.
Nonclinical Team Leader	Aisar Atrakchi, Ph.D.
Office of Clinical Pharmacology Reviewer(s)	Kofi A. Kumi, Ph.D., Vishnu Sharma, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Atul Bhattaram, Ph.D., Luning (Ada) Zhuang, Ph.D.
Clinical Reviewer	Martine Solages, MD
Clinical Team Leader	Bernard Fischer, MD
Statistical Reviewer	Semhar Ogbagaber, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Bernard Fischer, MD
Division Director (DP)	Tiffany R. Farchione, MD
Division Director (OCP)	Mehul Mehta, Ph.D.
Division Director (OB)	Hsien Ming J Hung, PhD
Office Director (or designated signatory authority)	Eric Bastings, MD

DHOT = Division of Hematology Oncology Toxicology
OCP = Office of Clinical Pharmacology
OB = Office of Biostatistics
OHOP = Office of Hematology and Oncology Products

Reference ID: 4698714

Table 192. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
Drug Product	Grace Chiou (primary) and Julia Pinto (secondary)
Drug Substance	Friedrich Burnett (primary) and Donna Christner (secondary)
Process & Facilities	Yongming Lu (primary) and Jonathan Swoboda (secondary)
Biopharmaceutics	Leah Falade (primary) and Ta-Chen Wu (secondary)
DPMH	
Peds	Ethan Hausman and Shetarra Walker (TL)
MHT	Catherine Roca and Miriam Dinatale (TL)
OPDP	Nima Ossareh and Aline Moukhtara (TL)
OSI	Jenn Sellers and Phillip Kronstein (TL)
OSE/DEPI	Andrew Mosholder and Kira Leishear (TL)
OSE/DMEPA	Loretta Holmes and Sevan Kolejian (TL)
OSE/DRISK	Sangeeta Tandon, Victoria Sammarco and Selena Ready (TL)
Other	
CDS	Jen Ginsberg, Salman Hosain and Jinzhong (Jin) Liu
CSS	Edward (Greg) Hawkins and Chad Reissig
DMPP-PLT	Susan Redwood and Barbara Fuller (TL)
OSE/DPV	Jonn Bailey, Robert Levin and Vicky Chan (TL)
QT-IRT	Girish Bende, Lars Johannesen and Christine Garnett

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

Table 193. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Eric Bastings, MD	CDER/OND/ON	Entire Review ☐ Authored ☒ Approved
Signatory Authority	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA = interdisciplinary assessment; ES, Executive Summary

Reference ID: 4698714

Table 193 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Martine Solages	OND/ON - DP	☒ Authored – Sections 2, 3, 4, 7.2, 7.3, 7.4, 7.5, 10, 12, 15, 17, 21, 22, 23 ☒ Contributed – Sections 6, 7.6, 24 ☐ Approved
Reviewer	**Signature:** Martine M. Solages -S Digitally signed by Martine M. Solages -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002523371, cn=Martine M. Solages -S Date: 2020.11.05 13:49:00 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Statistical	Peiling Yang	OB/DBI	Sections 2, 3, 6, 16 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Pharmacology/Toxicology	Aisar Atrakchi	OND/DPT-N	IA5.1, 7.1, 7.6, 8.3, 8.4; Appendix 13.1, 13.2, and 21 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Jia Yao	OND/DPT-N	IA5.1, 7.1, 7.6, 8.3, 8.4; Appendix 13.1, 13.2, and 21 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Jia Yao -S	Digitally signed by Jia Yao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jia Yao -S, 0.9.2342.19200300.100.1.1=2001626953 Date: 2020.11.05 13:34:10 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Mehul Mehta	OTS/OCP	5, 8.1, 8.2, Appendix 14.1, 14.2, and 14.3 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Luning Zhuang	OTS/OCP	5, 8.1, 8.2, Appendix 14.1, 14.2, and 14.3 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
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Clinical Pharmacology/Pharmacometrics	Atul Bhattaram	OTS/OCP	6.3, 14.4 ☒ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Venkatesh A. Bhattaram -S Digitally signed by Venkatesh A. Bhattaram -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300212823, cn=Venkatesh A. Bhattaram -S Date: 2020.11.06 10:27:57 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Vishnu Sharma	OTS/OCP	6.3, 14.4 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Vishnu D. Sharma -S Digitally signed by Vishnu D. Sharma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002769265, cn=Vishnu D. Sharma -S Date: 2020.11.06 09:52:46 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Kofi Ansah	OND/ORO-DRON	Appendix 12 ☐ Authored ☒ Contributed ☐ Approved
Project Manager	**Signature:** Kofi B. Ansah -S3 Digitally signed by Kofi B Ansah S3 DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Kofi B Ansah S3 0 9 2342 19200300 100 1 1=1300437219 Date: 2020 11 05 13:29:00 05'00'		

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11/06/2020 07:28:22 PM

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 211964
Drug Name:	Viloxazine Hydrochloride (SPN-812V)
Indication(s):	Treatment of attention deficit/hyperactivity disorder (ADHD) in pediatric patients ages 6 to 17 years.
Studies	One Two Year Oral Gavage Carcinogenicity Study in Wistar Rats and One Six-Month Oral Gavage Carcinogenicity Study in rasH2 Transgenic Mice.
Applicant:	Sponsor: SUPERNUS PHARMACEUTICALS, INC 1550 East Gude Drive Rockville, Md 20850, USA Test facility: [redacted] (b) (4) (b) (4)
Documents Reviewed:	Electronic submission, dated: December 20, 2019 via SN0005 Electronic data submitted on January 20, 2020 via SN0014.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	Jia Yao, PhD
Project Manager:	Kofi Ansah, PharmD
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in Wistar rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Viloxazine Hydrochloride (SPN-812V) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Yao.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Wistar rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 1. The dose levels for the three treated groups were 30, 87, and 217 mg/kg/day at study initiation, for both male and female rats. Mortality and adverse clinical signs such as tremors and convulsions were observed at 217 mg/kg/day from Day 123. Following these observations, the top two doses of 87 and 217 mg/kg/day were reduced to 65 and 130 mg/kg/day, respectively, beginning Day 130. Recurrence of adverse signs (including tremors and convulsions) was noted from Day 187 and mortality was observed from Day 191 necessitating further dose reduction. To ensure adequate survival, the dose levels were reduced to 22, 43 and 87 mg/kg/day, in consultation with the FDA, beginning Day 197. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle only (Milli-Q water), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	65	65
Low[#]	2	30/22	30/22	65	65
Medium[##]	3	87/65/43	87/65/43	65	65
High[##]	4	217/130/87	217/130/87	65	65

[##]: The doses of 87 and 217 mg/kg/day were reduced to 65 and 130 mg/kg/day, respectively, from Day 130

[#]: The doses of 30, 65, and 130 mg/kg/day were reduced to 22, 43 and 87 mg/kg/day, respectively from Day 197.

During the study period all animals were observed for general health/mortality and moribundity twice daily i.e. once during pre-dose and once during post dose during treatment period. On the days of detailed clinical examination, these observations will replace the daily observations for the post-dose observations except on Day 1, where the pre-dose observations will replace detailed clinical examination. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. During detailed clinical examination, all rats will be observed for changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lacrimation, piloerection, pupil size, unusual respiratory pattern), changes in gait, posture and response to handling as well as the

presence of clonic or tonic movements, stereotypes (e.g. excessive grooming, repetitive circling or bizarre behavior [e.g. self-mutilation, walking backwards]). Detailed examinations for palpable masses were done at least once every 2 weeks (± 2 day) for the first 12 months and thereafter at weekly intervals (± 2 day) for all external grossly visible, palpable tumors or tumor-prone tissues. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Individual body weights will be recorded at the beginning of the treatment and once weekly (± 2 days) during treatment period.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the survival for each sex was analyzed using life table techniques incorporating Kaplan-Meier product limit estimate graphs of proportions surviving over time and the Cox-Tarone binary regression and Gehan-Breslow tests for trend and control versus treated group comparisons of censored survival data. The Cox-Tarone statistic is weighted heavier for late deaths ("geriatric effect") and the Gehan-Breslow test is weighted heavier for early deaths ("pediatric effect"). As a result, both tests are useful tools for evaluating survival and other incidence data incorporating time-to-event information. All the probabilities reported were one sided. The tests were implemented using Proc LIFETEST in SAS. The time to death or sacrifice (in weeks) was the dependent variable.

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals with a death or sacrifice status recorded as a scheduled sacrifice (interim or terminal) or accidental death were censored in the analysis. All hypothesis testing will be done at two-sided $p \leq 0.01$ level.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy, including animals that died during the necropsy period (week 105-106), were 54 (83.08%), 50 (76.92%), 48 (73.85%), and 42 (64.62%), in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 51 (78.46%), 47 (72.31%), 50 (76.92%), and 44 (67.69%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report showed a statistically significant dose response relationship in the mortality in male rats (p=0.0026, using Wilcoxon tests, p=0.0034 using Cox-Tarone). The pairwise comparisons showed statistically significant increase in mortality in the high dose group when compared the vehicle control group in male rats (p=0.0036, using Wilcoxon tests, p=0.0043 using Cox-Tarone).

2.1.2. Tumor data analysis

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for each dosed group against the vehicle control group. Occult occult neoplastic lesions for incidental and fatal or combined were analyzed by the IARC asymptotic fixed interval-based test (Peto et al., 1980). The cut-off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79-92, 93-before terminal sacrifice, and terminal sacrifice (the NTP intervals). Actual dose levels were used as the scores. Fatal and non-fatal tumors were analyzed together, with separate stratum for each using the death-

rate method and the prevalence methods, respectively. Tumors of uncertain context were included in the analysis as non-fatal. The test was implemented using PROC MULTTEST in the SAS system (SAS, 2008). In the case of sparse tables (total <5 in all groups combined), the exact form of the test was used. Otherwise, the asymptotic version of the test was used. Skin and mammary tumors were analyzed using the Cox-Tarone binary regression/Gehan-Breslow using the death time or first palpation time as a surrogate for onset time., statistical analysis was performed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group.

Site or tumor combinations were statistically analyzed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data and were not assigned based on the day/week of necropsy. All tests will be evaluated at $p \leq 0.01$ level, one-sided.

Adjustment for the multiplicity:

For multiplicity adjustment testing, no detailed information was provided in the sponsor's report.

Sponsor's findings:

The sponsor's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased viloxazine hydrochloride (SPN-812V) dose. The pairwise comparison test presented in the sponsor's report showed statistically significant increases in the low dose group for the incidences of glandular hyperplasia, in the mammary glands, when compared to the vehicle control group in male rats with (p-value =0.0016).

No significant findings were noted in female rats.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on January 20, 2020 via SN0014.

It was noticed that in this rat study, the initial top two doses of 87 and 217 mg/kg/day were reduced to 65 and 130 mg/kg/day, respectively, beginning Day 130. Beginning Day 197, further dose reduction was observed, the dose levels were reduced to 22, 43 and 87 mg/kg/day, in consultation with the FDA. Therefore, an adjusted dose level of 24.15, 52.94 and 114.47 mg/kg/day was calculated and used in the analysis, for males and females respectively.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy, including two males in the vehicle control group and three females (one animal in the vehicle control, in the medium dose and high dose group) that died during the necropsy period (week 105-106), were 54 (83.08%), 50 (76.92%), 48 (73.85%), and 42 (64.62%), in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 51 (78.46%), 47 (72.31%), 50 (76.92%), and 44 (67.69%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed a statistically significant dose response relationship in the mortality of male rats (p=0.0106). The pairwise comparisons showed statistically significant increase in mortality in the high dose group when compared the vehicle control group in male rats (p=0.0110)

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with (0, 2778, 6154 and 13221 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons Treated Groups and Control Group in Rats

sex	Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	24.15 mg Low (N=65) P - C vs. L	52.94 mg Med (N=65) P - C vs. M	114.47 mg High (N=65) P - C vs. H
Male	Brain, Cerebrum	Glioma, Malignant	0/65 (62) 0.3765	0/65 (59) NC	4/65 (57) 0.0497*	0/65 (53) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
*: Statistically significant at 0.05 for rare tumor in pairwise comparison.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female mice. The pairwise comparisons test showed a statistically significant increases in the medium dose group for the incidences of malignant glioma, in the brain cerebrum, when compared to the vehicle control group in male rats with (p-value =0.0497).

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and twenty Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 20 animals. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, for up to 26 weeks, as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with three intra-peritoneal injections of 1000 mg/kg/day of urethane dissolved in 0.9% (w/v) sodium chloride at 1000 mg/kg/day, on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [Milli-Q water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 133 when the clinical signs of carcinogenicity became evident in the lung and spleen and the survival rate decreased to 50%.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	25	25
Low	2	5	5	25	25
Medium	3	15	15	25	25
High	4	50	50	25	25
Positive control	5	1000(urethane)	1000(urethane)	20	20

The positive control was administered with 3 intraperitoneal (i.p.) injections of urethane in saline on Days 1, 3 and 5.

During the study period, all animals were observed for general health/mortality and moribundity twice daily (i.e., morning and afternoon). For cage side only, positive control animals were observed on Days 1, 3, and 5. Also for the Main Cohort, detailed hands-on examination was performed on Day 1 and weekly thereafter for the duration of the study. Observations included, but not limited to, evaluation for reaction to treatment. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, were recorded at the same intervals as detailed observations, particular attention being paid to the animals during and for the first hour after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights of individual animals were recorded pre-dose on Day 1, weekly through Week 13, and biweekly thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

For the analysis of the survival data of the mouse study, the sponsor used similar methodologies that were used for the analyses of the survival data of the rat study.

Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 24 (96%), and 24 (96%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), and 24 (96%), in female mice, respectively. The sponsor's report concluded that there were no statistically significant findings in survival rate in either sex of mice.

3.1.2 Tumor data analysis

For the analysis of the tumor data of the mouse study, the sponsor used similar methodologies that were used for the analyses of tumor data of the rat study.

Multiple testing adjustment:

For multiplicity adjustment testing, no detailed information was provided in the sponsor's report.

Sponsor's findings:

For both males and females, there were no statistically significant tumor findings.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 24 (96%), and 24 (96%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), and 24 (96%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Also following the same FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for mouse study the significance levels were 0.05 for all dose response relationship tests and pairwise comparisons, regardless of common or rare tumors.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any non-positive control treated groups, when compare to the vehicle control group in both male and female mice.

Also the pairwise comparisons showed statistically significant increases in the positive control group for

the incidences of benign adenoma, malignant carcinoma in lungs/bronchus, benign hemangioma and malignant hemangiosarcoma in the spleen, when compared to the vehicle control group in both male and female mice (p-values <0.0001, 0.0004, <0.0001, <0.0001, and <0.0001, <0.0001, 0.0003, <0.0001, respectively).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Viloxazine Hydrochloride (SPN-812V) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals. The dose levels for the three treated groups were 30, 87, and 217 mg/kg/day at study initiation, for both male and female rats. Mortality and adverse clinical signs such as tremors and convulsions were observed at 217 mg/kg/day from Day 123. Following these observations, the top two doses of 87 and 217 mg/kg/day were reduced to 65 and 130 mg/kg/day, respectively, beginning Day 130. Recurrence of adverse signs (including tremors and convulsions) was noted from Day 187 and mortality was observed from Day 191 necessitating further dose reduction. To ensure adequate survival, the dose levels were reduced to 22, 43 and 87 mg/kg/day, in consultation with the FDA, beginning Day 197. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle only (Milli-Q water), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

It was noticed that in this rat study, the top two doses of 87 and 217 mg/kg/day were reduced to 65 and 130 mg/kg/day, respectively, beginning Day 130. Also beginning Day 197, the dose levels were reduced to 22, 43 and 87 mg/kg/day, in consultation with the FDA. Therefore, an adjusted dose level of 24.15, 52.94 and 114.47 mg/kg/day was calculated and used in the analysis, for males and females respectively.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy, including two males in the vehicle control group and three females (one animal in the vehicle control, in the medium dose and high dose group) that died during the necropsy period (week 105-106), were 54 (83.08%), 50 (76.92%), 48 (73.85%), and 42 (64.62%), in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 51 (78.46%), 47 (72.31%), 50 (76.92%), and 44 (67.69%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed a statistically significant dose response relationship in the mortality of male rats (p=0.0106). The pairwise comparisons showed statistically significant increase in mortality in the high dose group when compared the vehicle control group in male rats (p=0.0110)

For tumor data, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female mice. The pairwise comparisons test showed a statistically significant increases in the medium dose group for the incidences of malignant glioma, in the brain cerebrum, when compared to the vehicle control group in male rats with (p-value =0.0497).

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and twenty Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 20 animals. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, for up to 26 weeks. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with three intra-peritoneal injections of 1000 mg/kg/day of urethane dissolved in 0.9% (w/v) sodium chloride at 1000 mg/kg/day, on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [Milli-Q water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 133 when the clinical signs of carcinogenicity became evident in the lung and spleen and the survival rate decreased to 50%.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 24 (96%), and 24 (96%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), and 24 (96%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased SPN-812V dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any non-positive control treated groups, when compare to the vehicle control group in both male and female mice.

Also the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of benign adenoma, malignant carcinoma in lungs/bronchus, benign hemangioma, malignant hemangiosarcoma in the spleen, when compared to the vehicle control group in both male and female mice (p-values <0.0001, <0.001, 0.0004, <0.001, and <0.0001, <0.0001, 0.0003, <0.0001, respectively).

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA (b) (4) - SPN-812V
Dr. Tsong Dr. Lin
Kofi Ansah, Dr. Yao
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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0mg|kg|day Vehicle Control		24.15 mg|kg|day Low		52.94 mg|kg|day Med		114.47 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	.	.	.	.	.	.	2	3.08
53 - 78	.	.	5	7.69	9	13.85	7	13.85
79 - 92	5	7.69	4	13.85	5	21.54	6	23.08
93 - 106	6	16.92	6	23.08	3	26.15	8	35.38
Ter. Sac.	54	83.08	50	76.92	48	73.85	42	64.62
Total	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table1B: Intercurrent Mortality Rate
Female Rats

	0mg|kg|day Vehicle Control		24.15 mg|kg|day Low		52.94 mg|kg|day Med		114.47 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	.	.	.	.	.	.	4	6.15
53 - 78	.	.	3	4.62	1	1.54	2	9.23
79 - 92	6	9.23	7	15.38	4	7.69	1	10.77
92-106	8	21.54	8	27.69	10	23.08	14	32.31
Ter. Sac.	51	78.46	47	72.31	50	76.92	44	67.69
Total	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.0106*	0.3545	0.1396	0.0110*
Homogeneity (Log-Rank)	0.0722	0.3541	0.1387	0.0111*

* = statistically significant at the 0.05 significance level

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.2576	0.3781	0.8831	0.1945
Homogeneity (Log-Rank)	0.4997	0.3765	0.8826	0.1938

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3 test

Organ Name	Tumor Name	0mgVeh. Cont. (N=65) P - Trend	24.15 mg Low (N=65) P -VC vs. L	52.94 mg Med (N=65) P -VC vs. M	114.47 mg High (N=65) P -VC vs. H
Adipose Tissue, White	Lipoma, Benign	0/65 (62) 0.7874	2/65 (59) 0.2357	0/65 (55) NC	0/65 (53) NC
	Liposarcoma, Malignant	0/65 (62) 0.7293	1/65 (59) 0.4876	0/65 (55) NC	0/65 (53) NC
Brain, Cerebellum	Granular Cell Tumor, Malignant	1/65 (62) 1.0000	0/65 (59) 1.0000	0/65 (55) 1.0000	0/65 (53) 1.0000
	Meningioma, Malignant	1/65 (62) 1.0000	0/65 (59) 1.0000	0/65 (55) 1.0000	0/65 (53) 1.0000
Brain, Cerebrum	Glioma, Malignant	0/65 (62) 0.3765	0/65 (59) NC	4/65 (57) 0.0497*	0/65 (53) NC
	Granular Cell Tumor, Benign	0/65 (62) 0.2314	0/65 (59) NC	0/65 (55) NC	1/65 (53) 0.4609
	Granular Cell Tumor, Malignant	1/65 (62) 0.9282	1/65 (60) 0.7438	0/65 (55) 1.0000	0/65 (53) 1.0000
	Granular Cell Tumor Benigm/Malignant	1/65 (62) 0.5091	1/65 (60) 0.7438	0/65 (55) 1.0000	1/65 (53) 0.7115
Epididymis	Mesothelioma, Benign	0/65 (62) 0.7281	1/64 (58) 0.4833	0/65 (55) NC	0/65 (53) NC
Gland, Adrenal	Adenoma, Benign	1/65 (62) 0.7219	0/65 (59) 1.0000	1/64 (55) 0.7213	0/65 (53) 1.0000
	Pheochromocytoma, Benign	0/65 (62) 0.3155	4/65 (59) 0.0536	0/64 (55) NC	2/65 (53) 0.2102
	Pheochromocytoma, Malignant	1/65 (62) 1.0000	0/65 (59) 1.0000	0/64 (55) 1.0000	0/65 (53) 1.0000
	Pheochromocytoma Benign/Malignant	1/65 (62) 0.4702	4/65 (59) 0.1671	0/65 (55) 1.0000	2/65 (53) 0.4409
Gland, Parathyroid	Adenoma, Benign	0/65 (62) 0.3939	2/61 (55) 0.2188	0/60 (51) NC	1/62 (51) 0.4513
Gland, Pituitary	Adenoma, Benign	24/65 (64) 0.9428	22/65 (64) 0.7096	17/65 (60) 0.8991	14/65 (56) 0.9527
Gland, Prostate	Adenocarcinoma, Malignant	0/65 (62) 0.2314	0/65 (59) NC	0/64 (55) NC	1/65 (53) 0.4609
Gland, Seminal Vesicle	Adenocarcinoma, Malignant	0/65 (62) 0.5913	1/65 (59) 0.4876	1/65 (55) 0.4701	0/65 (53) NC
Gland, Thyroid	Adenoma, Benign	6/65 (62) 0.6898	6/64 (59) 0.5833	5/65 (55) 0.6623	4/65 (54) 0.7764

Male Rats Poly-3 test

Organ Name	Tumor Name	0mgVeh. Cont. (N=65) P - Trend	24.15 mg Low (N=65) P -VC vs. L	52.94 mg Med (N=65) P -VC vs. M	114.47 mg High (N=65) P -VC vs. H
	Adenoma, C-Cell, Benign	5/65 (62) 0.3793	4/64 (59) 0.7292	2/65 (55) 0.9219	5/65 (53) 0.5256
	Carcinoma, C-Cell, Malignant	0/65 (62) 0.1644	0/64 (59) NC	1/65 (55) 0.4701	1/65 (53) 0.4609
	Adenoma/Carcinoma, C-Cell, Benign/Malignant	5/65 (62) 0.2361	4/65 (59) 0.7292	3/65 (55) 0.8215	6/65 (53) 0.3903
	Carcinoma, Malignant	1/65 (62) 0.3530	0/64 (59) 1.0000	1/65 (55) 0.7213	1/65 (53) 0.7115
	Adenoma, Benign / Carcinoma, Malignant	7/65 (62) 0.6215	6/65 (59) 0.6875	6/65 (55) 0.6384	5/65 (54) 0.7447
Hemolymphoreticular Tissue	Lymphoma, Malignant	2/65 (62) 0.7985	3/65 (59) 0.4764	0/65 (55) 1.0000	1/65 (53) 0.8468
	Sarcoma, Histiocytic, Malignant	0/65 (62) 0.4739	0/65 (59) NC	1/65 (56) 0.4746	0/65 (53) NC
Large Intestine, Colon	Leiomyoma, Benign	1/64 (61) 1.0000	0/64 (58) 1.0000	0/63 (55) 1.0000	0/59 (50) 1.0000
Liver	Carcinoma, Hepatocellular, Malignant	1/65 (62) 0.9276	1/65 (59) 0.7395	0/65 (55) 1.0000	0/65 (53) 1.0000
Lung/Bronchus	Carcinoma, Islet Cell, Malignant	0/65 (62) 0.2314	0/65 (59) NC	0/65 (55) NC	1/65 (53) 0.4609
Lymph Node, Mesenteric	Hemangioma, Benign	4/65 (62) 0.5613	3/64 (58) 0.7520	2/65 (55) 0.8665	3/65 (53) 0.7109
	Hemangiosarcoma, Malignant	0/65 (62) 0.4737	0/64 (58) NC	1/65 (55) 0.4701	0/65 (53) NC
Mesentery	Fibrosarcoma, Malignant	1/65 (62) 1.0000	0/65 (59) 1.0000	0/65 (55) 1.0000	0/65 (53) 1.0000
	Schwannoma, Malignant	1/65 (62) 0.7243	0/65 (59) 1.0000	1/65 (56) 0.7261	0/65 (53) 1.0000
Muscle, Biceps Femoris	Granular Cell Tumor, Benign	0/65 (62) 0.7293	1/65 (59) 0.4876	0/65 (55) NC	0/65 (53) NC
Pancreas	Adenoma, Islet Cell, Benign	1/65 (62) 0.3530	0/65 (59) 1.0000	1/64 (55) 0.7213	1/65 (53) 0.7115
	Carcinoma, Islet Cell, Malignant	0/65 (62) 0.2314	0/65 (59) NC	0/64 (55) NC	1/65 (53) 0.4609
Skin	Adenoma/Carcinoma Islet Cell	1/65 (62) 0.1401	0/65 (59) 1.0000	1/65 (55) 0.7213	2/65 (53) 0.4409
	Carcinoma, Basal Cell, Malignant	0/65 (62) 0.4739	0/65 (59) NC	1/65 (56) 0.4746	0/65 (53) NC

Male Rats Poly-3 test

Organ Name	Tumor Name	0mgVeh. Cont. (N=65) P - Trend	24.15 mg Low (N=65) P -VC vs. L	52.94 mg Med (N=65) P -VC vs. M	114.47 mg High (N=65) P -VC vs. H
	Carcinoma, Malignant	1/65 (62) 1.0000	0/65 (59) 1.0000	0/65 (55) 1.0000	0/65 (53) 1.0000
	Fibroma, Benign	0/65 (62) 0.0939	1/65 (59) 0.4876	0/65 (55) NC	2/65 (54) 0.2145
	Fibrosarcoma, Malignant	0/65 (62) 0.4716	0/65 (59) NC	1/65 (55) 0.4701	0/65 (53) NC
	Hemangiosarcoma, Malignant	1/65 (62) 0.7219	0/65 (59) 1.0000	1/65 (55) 0.7213	0/65 (53) 1.0000
	Keratoacanthoma, Benign	1/65 (62) 0.3275	0/65 (59) 1.0000	2/65 (55) 0.4548	1/65 (53) 0.7115
	Schwannoma, Malignant	1/65 (62) 0.2239	1/65 (59) 0.7395	0/65 (55) 1.0000	2/65 (54) 0.4479
Small Intestine, Jejunum	Adenocarcinoma, Malignant	1/63 (61) 1.0000	0/62 (58) 1.0000	0/61 (54) 1.0000	0/51 (46) 1.0000
	Sarcoma, Malignant	0/63 (60) 0.4587	0/62 (58) NC	1/61 (54) 0.4737	0/51 (46) NC
Stomach	Fibrosarcoma, Malignant	0/64 (61) 0.4714	0/64 (59) NC	1/64 (56) 0.4786	0/60 (51) NC
Testis	Leydig Cell Adenoma, Benign	4/65 (62) 0.9442	1/65 (59) 0.9674	3/65 (55) 0.7281	0/65 (53) 1.0000
	Mesothelioma, Benign	0/65 (62) 0.1644	0/65 (59) NC	1/65 (55) 0.4701	1/65 (53) 0.4609
	Teratoma, Malignant	0/65 (62) 0.4716	0/65 (59) NC	1/65 (55) 0.4701	0/65 (53) NC
Thymus	Carcinoma, Malignant	0/62 (59) 0.2374	0/61 (57) NC	0/58 (51) NC	1/61 (52) 0.4685
	Thymoma, Benign	0/62 (59) 0.2908	1/61 (57) 0.4914	0/58 (51) NC	1/61 (52) 0.4685
Whole Body	Hemangioma/Hemangiosarcoma	5/65 (62) 0.6265	3/65 (59) 0.8471	4/65 (55) 0.6913	3/65 (53) 0.8070

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
*: Statistically significant at 0.05 for rare tumor in pairwise comparison.

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Veh.Cont (N=65) P - Trend	24.15 mg Low (N=65) P - C vs. L	52.94 mg Med (N=65) P - C vs. M	114.47 mg High (N=65) P - C vs. H
Adipose Tissue, White	Lipoma, Benign	1/65 (61) 0.9351	1/65 (59) 0.7437	0/65 (61) 1.0000	0/65 (57) 1.0000
Brain, Cerebellum	Granular Cell Tumor, Malignant	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
Brain, Cerebrum	Carcinoma, Malignant	0/65 (61) 0.2395	0/65 (59) NC	0/65 (61) NC	1/65 (57) 0.4831
	Ependymoma, Malignant	0/65 (61) 0.7437	1/65 (59) 0.4917	0/65 (61) NC	0/65 (57) NC
	Granular Cell Tumor, Benign	0/65 (61) 0.4873	0/65 (59) NC	2/65 (61) 0.2479	0/65 (57) NC
	Granular Cell Tumor, Malignant	3/65 (61) 0.9695	1/65 (59) 0.9365	1/65 (62) 0.9425	0/65 (57) 1.0000
	Granular Cell Tumor Benign/Malignant	3/65 (61) 0.9139	1/65 (59) 0.9365	3/65 (62) 0.6679	0/65 (57) 1.0000
Gland, Adrenal	Adenoma, Benign	1/65 (61) 1.0000	0/65 (59) 1.0000	0/65 (61) 1.0000	0/65 (57) 1.0000
	Pheochromocytoma, Benign	0/65 (61) 0.2589	3/65 (59) 0.1158	1/65 (62) 0.5041	2/65 (57) 0.2312
	Pheochromocytoma, Malignant	1/65 (61) 1.0000	0/65 (59) 1.0000	0/65 (61) 1.0000	0/65 (57) 1.0000
	Pheochromocytoma Benign/Malignant	1/65 (61) 0.4174	3/65 (59) 0.2968	1/65 (62) 0.7561	2/65 (57) 0.4744
Gland, Mammary	Adenocarcinoma, Malignant	5/65 (61) 0.9690	1/65 (59) 0.9848	4/65 (62) 0.7625	0/65 (57) 1.0000
	Adenoma, Benign	2/65 (61) 0.9842	6/65 (59) 0.1255	0/65 (61) 1.0000	0/65 (57) 1.0000
	Fibroadenoma, Benign	8/65 (61) 0.9737	8/65 (59) 0.5773	2/65 (61) 0.9917	3/65 (58) 0.9675
Gland, Pituitary	Adenoma, Benign	43/65 (65) 0.9493	45/65 (62) 0.2771	33/65 (65) 0.9751	35/65 (60) 0.8986
	Carcinoma, Malignant	0/65 (61) 0.2395	0/65 (59) NC	0/65 (61) NC	1/65 (57) 0.4831
	Adenoma / Carcinoma C-Cell	43/65 (65) 0.9245	45/65 (62) 0.2771	33/65 (65) 0.9751	35/65 (60) 0.8614
Gland, Thyroid	Adenoma, Benign	1/65 (61) 0.6973	3/64 (58) 0.2905	0/65 (61) 1.0000	1/65 (57) 0.7349

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Veh.Cont (N=65) P - Trend	24.15 mg Low (N=65) P - C vs. L	52.94 mg Med (N=65) P - C vs. M	114.47 mg High (N=65) P - C vs. H
	Adenoma, C-Cell, Benign	4/65 (61) 0.4673	4/64 (58) 0.6129	4/65 (61) 0.6414	4/65 (57) 0.6029
	Carcinoma, Malignant	1/65 (61) 0.8704	2/64 (58) 0.4809	1/65 (61) 0.7521	0/65 (57) 1.0000
	Adenoma/Carcinoma	2/65 (61) 0.8665	5/65 (59) 0.2059	1/65 (61) 0.8781	1/65 (57) 0.8652
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/65 (61) 0.7437	1/65 (59) 0.4917	0/65 (61) NC	0/65 (57) NC
	Sarcoma, Histiocytic, Malignant	0/65 (61) 0.2427	0/65 (59) NC	0/65 (61) NC	1/65 (58) 0.4874
Ileum with Peyers Patch	Leiomyoma, Benign	0/63 (60) 0.4957	0/63 (57) NC	1/62 (59) 0.4958	0/62 (56) NC
Kidney	Adenoma, Renal Cell, Benign	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
	Nephroblastoma, Malignant	0/65 (61) 0.2427	0/65 (59) NC	0/65 (61) NC	1/65 (58) 0.4874
Liver	Adenoma, Hepatocellular, Benign	0/65 (61) 0.4873	0/65 (59) NC	2/65 (61) 0.2479	0/65 (57) NC
Mesentery	Adenocarcinoma, Malignant	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
	Schwannoma, Malignant	0/65 (61) 0.7437	1/65 (59) 0.4917	0/65 (61) NC	0/65 (57) NC
Nose	Hemangioma, Benign	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
Ovary/Oviduct	Adenoma, Tubulostromal, Benign	2/65 (61) 0.8881	0/65 (59) 1.0000	1/65 (61) 0.8781	0/65 (57) 1.0000
	Granulosa Cell Tumor, Benign	1/65 (61) 0.2365	1/65 (59) 0.7437	0/65 (61) 1.0000	2/65 (57) 0.4744
	Sex Cord Stromal Adenoma, Benign	2/65 (61) 1.0000	0/65 (59) 1.0000	0/65 (61) 1.0000	0/65 (57) 1.0000
	Teratoma, Benign	1/65 (61) 1.0000	0/65 (59) 1.0000	0/65 (61) 1.0000	0/65 (57) 1.0000
Pancreas	Adenoma, Islet Cell, Benign	0/65 (61) 0.4979	0/64 (58) NC	1/65 (61) 0.5000	0/65 (57) NC
Skin	Carcinoma, Basal Cell, Malignant	1/65 (61) 0.1469	0/65 (59) 1.0000	0/65 (61) 1.0000	2/65 (58) 0.4809
	Carcinoma, Malignant	0/65 (61) 0.7437	1/65 (59) 0.4917	0/65 (61) NC	0/65 (57) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Veh.Cont (N=65) P - Trend	24.15 mg Low (N=65) P - C vs. L	52.94 mg Med (N=65) P - C vs. M	114.47 mg High (N=65) P - C vs. H
	Fibroma, Benign	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
	Schwannoma, Malignant	0/65 (61) 0.4958	0/65 (59) NC	1/65 (61) 0.5000	0/65 (57) NC
Uterus/Cervix	Adenocarcinoma, Malignant	3/65 (61) 0.4091	5/65 (59) 0.3400	4/65 (62) 0.5091	4/65 (57) 0.4620
	Polyp, Benign	3/65 (61) 0.1722	5/65 (59) 0.3400	3/65 (61) 0.6602	6/65 (58) 0.2207
	Schwannoma, Malignant	0/65 (61) 0.2829	1/65 (59) 0.4917	1/65 (61) 0.5000	1/65 (57) 0.4831
	Stromal Sarcoma, Endometrial, Malignant	0/65 (61) 0.8075	2/65 (59) 0.2396	0/65 (61) NC	0/65 (57) NC
Vagina	Schwannoma, Malignant	0/65 (61) 0.2383	0/63 (57) NC	0/65 (61) NC	1/63 (56) 0.4786

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

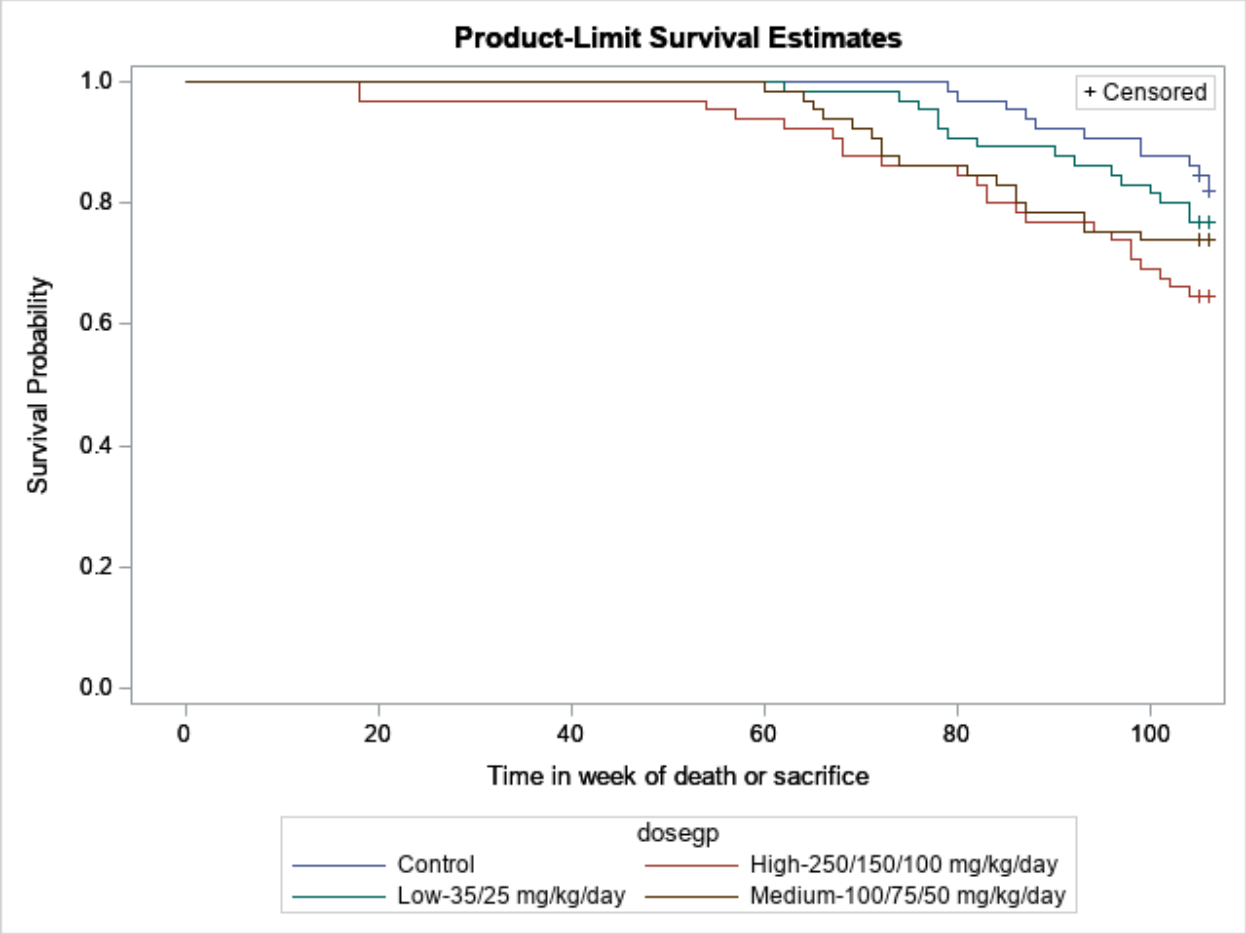

Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

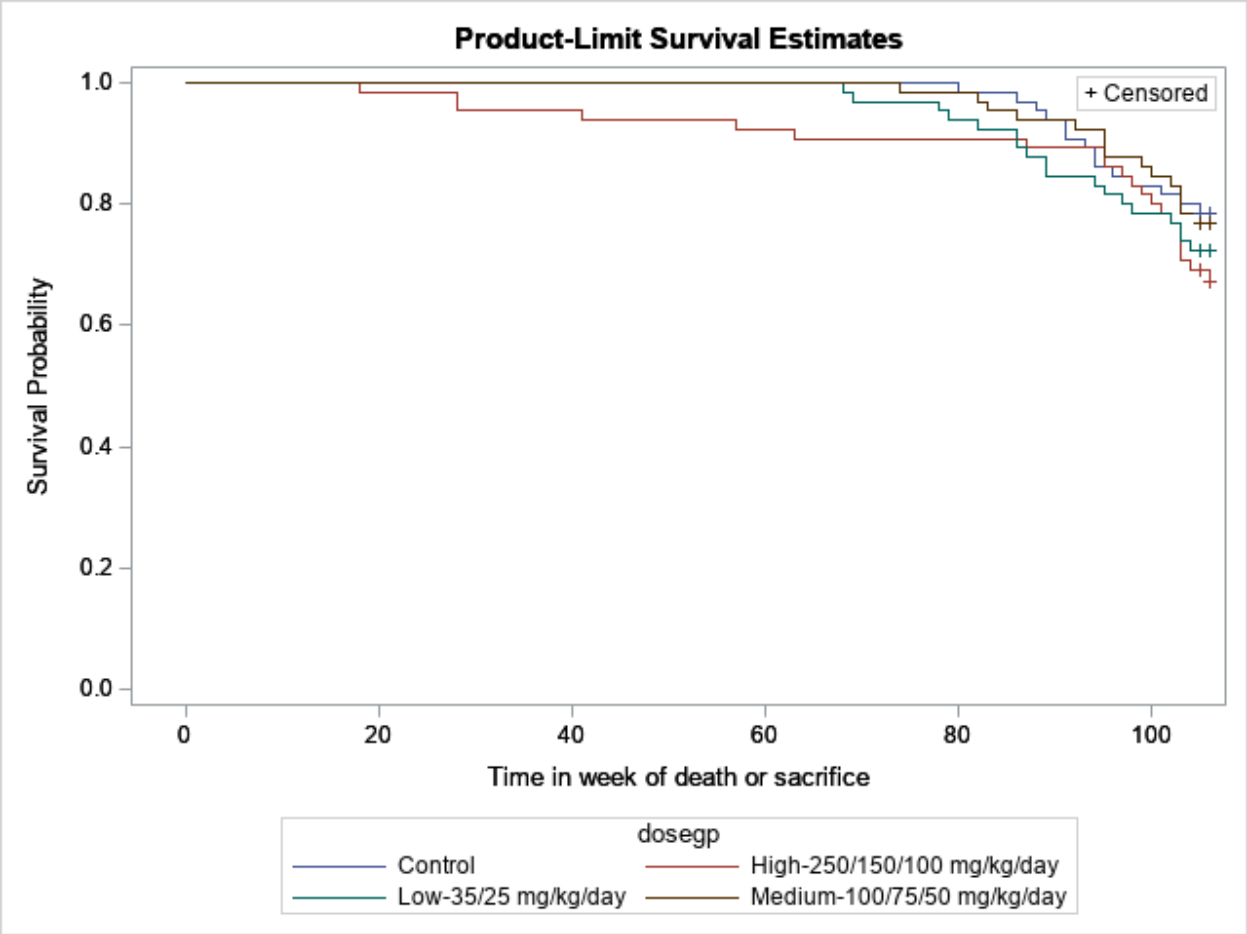

Table4A: Intercurrent Mortality Rate
Male Mice

	0mg|kg|day Vehicle Cont.		5mg|kg|day Low		15mg|kg|day Med		50mg|kg|day High		1000 mg|kg|day Positive Cont.	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	1	5.00
14 - 25			2	8.00	1	4.00	1	4.00	9	50.00
ADD	1	4.00	.	.	.	.	.	.	.	.
IS	.	.	.	.	.	.	.	.	10	100.00
Ter. Sac.	24	96.00	23	92.00	24	96.00	24	96.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	20	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded
IS: Interim sacrifice on week 19

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg|kg|day Vehicle Cont.		5mg|kg|day Low		15mg|kg|day Med		50mg|kg|day High		1000 mg|kg|day Positive Cont.	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 26	1	4.00	1	4.00	.	.	1	4.00	8	40.00
IS	.	.	.	.	.	.	.	.	12	100.00
Ter. Sac.	24	96.00	24	96.00	25	100.00	24	96.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	20	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded
IS: Interim sacrifice on week 19

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.9049	0.0983	0.2460	0.2460	NC
Homogeneity (Log-Rank)	0.5722	0.1615	0.3272	0.3272	NC

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.9258	1.0000	0.2390	0.9885	NC
Homogeneity (Log-Rank)	0.7972	1.0000	0.3173	0.9885	NC

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Veh. Cont (N=25) P - Trend	5 mg Low (N=25) P - C vs. L	15 mg Med (N=25) P - C vs. M	50 mg High (N=25) P - C vs. H	1000 mg Posi (N=20) P - VC vs. C
Gland, Thyroid	Carcinoma, Malignant	1/25 (23) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/20 (6) 1.0000
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (23) NC NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	1/20 (7) 0.2333
	Sarcoma, Histiocytic, Malignant	0/25 (23) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	1/20 (7) 0.2333
Lung/Bronchus	Adenoma, Benign	0/25 (23) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	20/20 (20) <0.0001*
	Carcinoma, Malignant	1/25 (23) 0.7632	0/25 (23) 1.0000	1/25 (24) 0.7660	0/25 (24) 1.0000	7/20 (11) 0.0004*
Skin	Hemangiosarcoma, Malignant	0/25 (23) 0.7553	1/25 (23) 0.5000	0/25 (24) NC	0/25 (24) NC	0/20 (6) NC
	Keratoacanthoma, Benign	1/25 (23) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/20 (6) 1.0000
Spleen	Hemangioma, Benign	0/25 (23) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	7/20 (11) 0.0001*
	Hemangiosarcoma, Malignant	0/25 (23) 0.5106	0/25 (23) NC	1/25 (24) 0.5106	0/25 (24) NC	12/20 (14) <0.0001*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable *: Statistically significant at 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons
Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Veh. Cont (N=25) P - Trend	5 mg Low (N=25) P - C vs. L	15 mg Med (N=25) P - C vs. M	50 mg High (N=25) P - C vs. H	1000 mg Posi (N=20) P - VC vs. C
Brain, Cerebrum	Hemangioma, Benign	0/25 (24) 0.2500	0/25 (24) NC	0/25 (24) NC	1/25 (24) 0.5000	0/20 (6) NC
Lung/Bronchus	Adenoma, Benign	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	20/20 (20) <0.0001*
	Carcinoma, Malignant	0/25 (24) 0.8132	2/25 (24) 0.2447	0/25 (24) NC	0/25 (24) NC	15/20 (17) <0.0001*
Skin	Hemangiosarcoma, Malignant	1/25 (24) 0.9395	1/25 (24) 0.7553	0/25 (24) 1.0000	0/25 (24) 1.0000	0/20 (6) 1.0000
Spleen	Hemangioma, Benign	1/25 (24) 0.3931	0/25 (24) 1.0000	1/25 (24) 0.7553	1/25 (24) 0.7553	7/20 (11) 0.0003*
	Hemangiosarcoma, Malignant	0/25 (24) 0.0605	0/25 (24) NC	1/25 (24) 0.5000	2/25 (24) 0.2447	8/20 (12) <0.0001*
Uterus/Cervix	Polyp, Benign	1/25 (24) 0.4395	0/25 (24) 1.0000	0/25 (24) 1.0000	1/25 (24) 0.7553	0/20 (6) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;
NC = Not calculable;
*: Statistically significant at 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons

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Figure 2A: Kaplan-Meier Survival Curves for

Male Mice

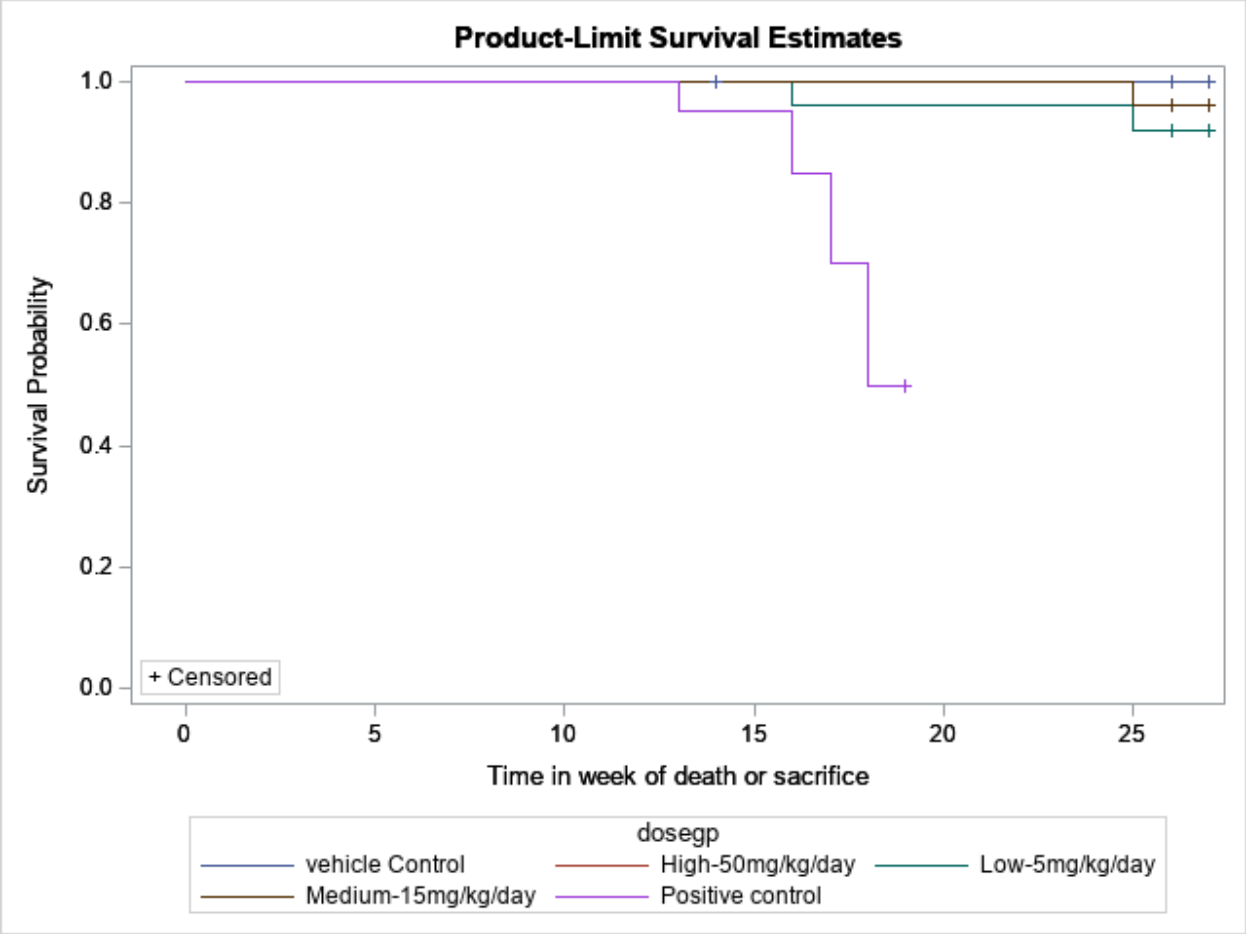
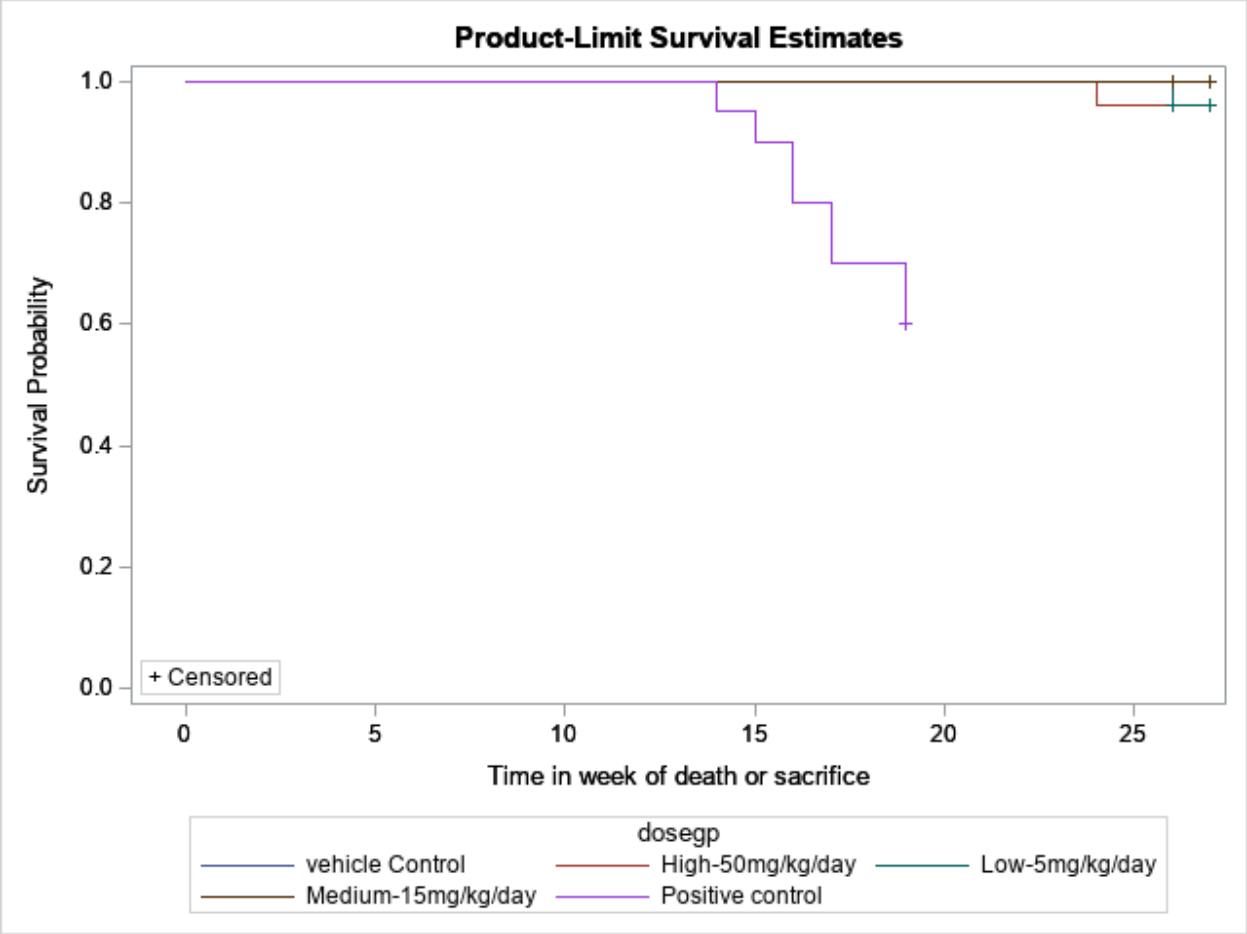


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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