TITLE PAGE

Protocol Number:	812P418
Title:	Evaluation of the Excretion of Viloxazine and Its Metabolite 5-Hydroxy-viloxazine Glucuronide into Breast Milk Following Multiple Doses of SPN-812 (600mg, QD) in Healthy Lactating Women
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Ave Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
IND number:	108,864
Investigational Medicinal Product:	Viloxazine extended-release capsule
Clinical Contract Research Organization (CRO):	PPD, part of Thermo Fisher Scientific 929 North Front Street Wilmington, NC, 28401-3331 Phone: +1 910 251 0081
Bioanalytical Facility	Supernus Pharmaceuticals, Inc. (Supernus) 9715 Key West Ave Rockville, MD 20850 Phone: (240) 403-5644
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Sponsor Medical Advisor	[redacted]
Phase:	4
Protocol Version:	2.0 (Final)
Version Date:	02 September 2022
Good Clinical Practice (GCP) Statement:	This study will be performed in full compliance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP) and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principle Investigator's Signature	Date

Print Name

SUPERNUS PHARMACEUTICALS, INC. PROTOCOL APPROVAL PAGE

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CLINICAL PROTOCOL SYNOPSIS

Name of Product: SPN-812 (viloxazine extended-release capsule)	**Name of Active Ingredient:** Viloxazine Hydrochloride

Full Title of Study: Evaluation of the Excretion of Viloxazine and Its Metabolite 5-Hydroxy-viloxazine Glucuronide into Breast Milk Following Multiple Doses of SPN-812 (600mg, QD) in Healthy Lactating Women

Phase of Development: 4

Investigator(s) / Center(s): Up to 2 study sites in the US

Objective:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of viloxazine and its major metabolite 5-hydroxy-viloxazine glucuronide (5-HVLX-gluc) in breast milk in healthy lactating women following multiple oral doses of SPN-812.

Secondary Objectives:

- To evaluate the PK of viloxazine and 5-HVLX-gluc in plasma in healthy lactating women following multiple oral doses of SPN-812.
- To evaluate the overall exposure between breast milk and plasma in healthy lactating women following multiple oral doses of SPN-812.
- To estimate daily infant dose of SPN-812 via breast milk.

Safety Objective:

- To evaluate the safety and tolerability of multiple doses of SPN-812 in healthy lactating women.

Endpoints

Primary Endpoints:

Breast milk PK parameters when SPN-812 reaches plasma steady-state:

- $AUC_{tau,milk}$, $C_{max,milk}$, $T_{max,milk}$, $C_{trough,milk}$, $C_{ave,milk}$ for viloxazine and 5-HVLX-gluc
- Total amount of drug in breast milk (Am_{milk}, mg/day) over a period of 24 hours for viloxazine and 5-HVLX-gluc

Secondary Endpoints:

- Plasma $AUC_{tau,ss}$, $C_{max,ss}$, $T_{max,ss}$, CL/F_{ss}, $C_{ave,ss}$ and $C_{trough,ss}$ for viloxazine and 5-HVLX-gluc at plasma steady-state, if applicable
- Breast milk-plasma ratio (ML/PL) based on AUC over 24 hours for viloxazine and 5-HVLX-gluc at plasma steady-state
- Estimated daily infant dosage (EDID, mg/kg/day) and relative infant dose (RID, %) at plasma steady-state (Table 2)

Safety Endpoints:

- Adverse Events (AEs)
- Clinical laboratory test results (clinical chemistry, hematology and urinalysis)
- 12-lead Electrocardiogram (ECG)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital signs
- Physical examination
- Concomitant medications

Study Design:

This is an open label, single treatment, lactation study of repeated doses of 600mg SPN-812, QD, in healthy lactating women.

Number of Subjects:

Up to 15 healthy, lactating women will be enrolled in the study.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Healthy lactating females, 18 to 45 years of age, who are actively breastfeeding (including baby to breast, bottle feeding mother's expressed breast milk) and are at least 12 weeks postpartum of a healthy term newborn infant (no medical complications) and not more than 2 years postpartum. Lactation must be well established and the mother is exclusively breast feeding her baby (not providing supplemental formula) prior to the day of admission to inpatient unit.
2. Has a body mass index between 18 to 35 kg/m^2, included.
3. Is considered medically healthy by the Investigator via assessment of physical examination (neurological examinations included), medical history, clinical laboratory tests, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) and electrocardiogram (ECG).
4. Is willing to temporarily discontinue breastfeeding their infant and discard all their breast milk for 7 consecutive days, including day of admission to inpatient unit (Day -1), 3 consecutive days of dosing SM while in the inpatient unit (Days 1 to 3), and 3 consecutive days after last dose of SM (including day of discharge from the inpatient unit and 2 days at home; Days 4 to 6); and willing to store sufficient amount of breastmilk (e.g., breast milk pumped and stored in freezer before the day of admission), and/or infant formula to feed infant during these 7 consecutive days.
5. Is either sexually inactive (abstinent) or, if sexually active, must agree to use/practice one of the following acceptable birth control methods beginning during the screening period prior to the first dose of SM, throughout the inpatient study, and for 3 days following the last dose of SM (Day 3):
   - intra-uterine contraceptive device;
   - barrier method: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;

- is surgically sterile or male partner is surgically sterile;
- established use of a patch, vaginal ring, oral, injected or implanted hormonal methods of contraception that can be used in lactating women;
- Essure® procedure performed at least 6 months prior to Screening and had hysterosalpingogram after the Essure procedure to document tubal occlusion prior to screening.

6. Must not be in the process of weaning before admission and have maintained an adequate breast milk supply with regularly pumping or routine breastfeeding (e.g., pumping or feeding 3-4 times a day) at admission.
7. Is currently a non-smoker who has not used tobacco or nicotine-containing products (chewed or smoked) or replacement products, including electronic cigarettes, within 3 months prior to screening and a negative cotinine test result at Screening.
8. Agrees to use only the emollient or nipple cream recommended by the investigator for use during the sampling period, if needed.
9. Able to voluntarily provide written informed consent to participate in the study.
10. Able to understand and willing to comply with all study requirements.
11. Able and willing to swallow capsules whole, without crushing, chewing or cutting.

Exclusion Criteria:

1. Participation in any other investigational study drug trial in which receipt of an investigational study drug within 30 days or 5 half-lives before Screening, whichever is longer.
2. Is unwilling or unable to comply with the Lifestyle guidelines presented in the protocol during the study period.
3. Has history or presence of clinically significant systemic disease (including psychological and psychiatric disorders).
4. Is currently using, or tests positive at Screening for cotinine, alcohol or drugs (opiates, methadone, cocaine, amphetamines [including ecstasy], barbiturates, PCP, benzodiazepines, and THC/cannabis).
5. Is pregnant (has positive serum pregnancy test at Screening) or becomes pregnant during study (has positive urine pregnancy test).
6. Has history of breast implants, breast augmentation, or breast reduction surgery.
7. Has history of mastitis within 30 days, breast cancer and/or has had a mastectomy or lumpectomy with the exception of a benign fibroma or lipoma removal at the investigator's discretion; and/or a clinically significant abnormality observed in either breast during a clinical breast exam at Screening or Admission (Day -1).
8. Has a history of alcohol use disorder within 1 year of Screening; or assessed by the PI as having regularly consumed alcohol exceeding 14 units per week (1 unit equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within 1 year of Screening.

9. Is using recreational or illicit drug(s) (e.g., cannabis /tetrahydrocannabinol (THC), opiates, methadone, cocaine, amphetamines [including ecstasy], barbiturates, and benzodiazepines) within 1 year of Screening.
10. Has clinically significant vital signs abnormalities (systolic blood pressure less than 90 or greater than 140 mmHg, diastolic blood pressure less than 60 or greater than 90 mmHg, or pulse rate (PR) less than 50 or greater than 100 bpm at Screening.
11. Has a clinical laboratory test values outside the reference range at Screening that, in the opinion of the investigator, are clinically significant, or any of the following:
    - Serum creatinine >1.5 times the upper limit of normal (ULN)
    - Serum total bilirubin >1.5 times ULN
    - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times ULN
12. Has a clinically significant ECG abnormalities at Screening, including:
    - PR interval >220 ms
    - QRS interval >130 ms
    - QTcF interval >470 ms
13. Has any disease or medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or interfere with the conduct or interpretation of the study.
14. Has evidence of infection with hepatitis B and C, and human immunodeficiency virus HIV-1 and HIV-2, as determined by results of testing at Screening.
15. Has a condition or planned procedure that may interfere with the absorption, metabolism, or elimination of the study drug (e.g., cholecystectomy).
16. Is using prescription medication within 14 days prior to administration of SM or 5 half-lives, whichever is longer, with the exception of hormonal contraceptives.
17. Is using over-the-counter products (including vitamins, herbal products and natural food supplements) within 14 days prior to administration of SM or 5 half-lives, whichever is longer. Exceptions include postnatal vitamins, topical products without systemic absorption and acetaminophen (< 2 g/day).
18. Has an allergy to viloxazine.
19. Has an Edinburgh Postnatal Depression Scale score >13.
20. Has attempted suicide within the 6 months prior to Screening or is at significant risk of suicide (either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the 12 months prior to screening).
21. In the investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Treatment, Dose, and Mode of Administration:

Study medication, SPN-812 (QELBREE®, viloxazine extended-release capsule) 600 mg (3 x 200 mg capsule), will be administered orally once daily with or without food.

Duration of Treatment and Study Duration:

Up to 32 days including up to 28 days for Screening Period and 4 days for Treatment Period.

Treatment Schedule:

Screening Period

Subjects will be screened within 28 days prior to dosing. After informed consent is obtained, information (including demographics, medical history and maternal-related information) from subjects will be collected, and subjects will undergo screening evaluations. Inclusion/exclusion criteria will be reviewed to determine the subject's eligibility at Screening.

Inpatient Admission

Eligible subjects will be admitted to inpatient unit on Day -1. Inclusion/exclusion criteria will be reviewed to confirm eligibility. Breast milk (non-PK samples) will be collected per subject's pumping routine prior to first dose on Day 1. Subjects will remain in the inpatient unit for 5 consecutive days; including the day of admission to inpatient unit (Day -1), 3 days of dosing SM (Day 1-3), and the day of discharge from inpatient unit (Day 4).

Treatment Period

Subjects will receive 600 mg SPN-812 in the morning on Days 1, 2, and 3 after the completion of safety assessments. On Day 2 and Day 3, SM will be administered at the same time in the morning (±30 min) relative to the time that SM administration occurred on Day 1. On Days 1-4, breast milk will be pumped/collected from each breast per the PK breast milk sampling schedule or subject's pumping routine. For each breast milk collection period, the start and end times of the collection will be recorded, and the total volume (mL) of breast milk collected will be measured and recorded.

Serial breast milk and blood samples will be collected on Day 3 to 4 for PK analysis. Breast milk samples collected out of the PK sampling period (non-PK breast milk sample) will not be analyzed for drug concentrations. The end of study (EOS) procedures will be conducted prior to discharge on Day 4 following the last breast milk and blood sample collection. If subject discontinues early, all EOS procedures will be conducted.

Pharmacokinetic Sampling:

Breast Milk:

A total of 9 expressed breast milk samples will be collected on Day 3 at the following time intervals:

Day 1: -4 to <0 hours pre-dose;

Day 3: -4 to <0 hours pre-dose, and '0 to 4', '4 to 6', '6 to 8', '8 to 10', '10 to 12', '12 to 16' and '16 to 24' hours post-dose.

Breast milk from each breast will be emptied as thoroughly as possible at each session using an electric breast pump at the planned time intervals. To ensure that the pump completely removes milk from the breasts, double pump for no less than 10 minutes until milk flow ceases. The length of each expressing session should be no longer than 30 minutes.

Non-PK breast milk samples (not to be analyzed for drug concentrations but volume will be recorded) will be collected at the following time intervals:

- Day -1: store milk as pumped per subject's pumping routine
- Day 1: 0 to 24 hours post-dose per subject's pumping routine
- Day 2: 0 to 20 hours post-dose per subject's pumping routine

Blood:

A total of 13 blood draws (4 mL each) for PK will be collected on Day 1 pre-dose, Day 3 pre-dose, and Day 3 at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 16.0 and 24.0 hours post-dose. The following windows are permitted relative to the protocol-specified PK sample collection times:

Pre-dose:	-15 minutes
< 1 hour post-dose:	± 3 minute
1 to 8 hours post-dose:	± 5 minutes
> 8 to 24 hours post-dose:	± 10 minutes

Bioanalytical Methods

Concentrations of viloxazine and 5-HVLX-gluc in plasma and breast milk will be determined using validated achiral chromatographic tandem mass spectrometry methods.

Safety Monitoring:

See Table 1 for safety monitoring procedures. Adverse event (AE) and concomitant medication monitoring will be performed throughout the study.

Statistical Methods

Analysis Populations

- The **Safety Population** will include all subjects who receive at least one dose of SM.
- The **PK Population** will include all subjects in the safety population who have a sufficient PK profile to derive at least 1 PK parameter without major events that could impact the PK data (e.g., emesis).

Pharmacokinetic Analyses

The PK Population will be used to generate breast milk and plasma PK parameters of viloxazine and 5-HVLX-gluc for all subjects.

Descriptive statistics (number of subjects, mean, standard deviation [SD], and coefficient of variation [CV], minimum, median, and maximum) will be used to summarize breast milk and plasma concentration data at each planned sampling time point for each analyte in breast milk and plasma. The midpoint time for breast milk expressions will be used as the milk sampling time. Breast milk and plasma PK parameters calculated from the concentrations and actual times will be summarized by analyte using descriptive statistics (including geometric mean and geometric CV). Individual and mean breast milk and plasma concentration-time profiles for viloxazine and 5-HVLX-gluc will be presented graphically on linear and semi-logarithmic scales. All PK parameters will be derived using a non-compartmental analysis method.

Sample Size Determination

The sample size selected is not based on statistical power considerations. Up to 15 healthy lactating women volunteers will be enrolled in the study, with the expectation that 12 subjects will complete the study. A sample size of 12 subjects is considered sufficient to achieve the primary objective of this study.

Safety Analysis:

AEs coded by system organ class and preferred term will be listed and summarized. Vital signs, ECG, C-SSRS, physical examination and clinical laboratory values will be summarized and listed with abnormal values flagged.

TABLE OF CONTENTS

TITLE PAGE **1**
SUPERNUS PHARMACEUTICALS, INC. PROTOCOL APPROVAL PAGE **3**
Endpoints **4**
LIST OF ABBREVIATIONS **15**
1 INTRODUCTION **16**
1.1 Background **16**
1.2 Clinical Information **16**
1.2.1 Phase 1 Studies 16
1.2.2 Phase 2 Studies 18
1.2.3 Phase 3 Studies 18
2 STUDY OBJECTIVES AND ENDPOINTS **19**
2.1 Study Objectives **19**
2.1.1 Primary Objective 19
2.1.2 Secondary Objectives 19
2.1.3 Safety Objective: 19
2.2 Study Endpoints **19**
2.2.1 Primary Endpoints 19
2.2.2 Secondary Endpoints 19
2.2.3 Safety Endpoints: 19
3 STUDY DESIGN **20**
3.1 Overall Study Design and Plan **20**
3.2 Rationale of Study Design **21**
4 STUDY POPULATION **22**
4.1 Number of Subjects **22**
4.2 Inclusion Criteria **22**
4.3 Exclusion Criteria **23**
4.4 Subject Withdrawal **24**
5 STUDY TREATMENT **26**
5.1 Study Medication Identity, Packaging, and Labeling **26**
5.2 Treatment Assignment and Administration **26**
5.3 Blinding **26**

5.4 Study Medication Handling and Accountability 26
5.5 Prior and Concomitant Medications 26
6 STUDY SCHEDULE AND PROCEDURES 28
6.1 Study Schedule 28
6.1.1 Screening Period (Study Days -28 to -1) 28
6.1.2 Inpatient Admission (Study Day -1) 28
6.1.3 Treatment Period (Study Days 1, 2, and 3) 28
6.1.4 Inpatient Discharge (Study Day 4); End of Study (EOS)/Early Termination (ET) 28
6.1.5 Follow-up Phone Call (FPC) 28
6.1.6 Repeat Safety Assessments (Unscheduled Visits) 28
6.2 Study Procedures 30
6.2.1 Screening Period (Study Day -28 to Study Day -1) 30
6.2.2 Inpatient Admission (Study Day-1) 30
6.2.3 Treatment Period (Study Days 1 to 3; Inpatient) 31
6.2.3.1 Study Days 1 and 2 31
6.2.3.2 Study Day 3 31
6.2.4 Inpatient Discharge (Study Day 4); EOS/ET 31
6.2.5 Follow-up Phone Call (Study Day 11 [±2 days]) 31
6.3 Study Restrictions 32
6.3.1 Meals and Water Consumption 32
6.3.2 Physical Activity Restrictions 32
6.3.3 Prohibitions 32
7 STUDY ASSESSMENTS 33
7.1 Baseline Characteristics 33
7.2 Pharmacokinetic Assessments 33
7.2.1 Pharmacokinetic Sample Collection 33
7.2.1.1 Breast Milk 33
7.2.1.2 Blood 33
7.2.2 Drug Concentration Measurements 34
7.2.3 Pharmacokinetic Parameters 34
7.3 Pharmacodynamic Assessments 36
7.4 Safety Assessment 36
7.4.1 Clinical Laboratory Measurements 36

7.4.2 Vital Signs 37
7.4.3 Physical Examinations 37
7.4.4 Clinical Breast Examination 37
7.4.5 Electrocardiograms (ECGs) 37
7.4.6 Prospective Assessment of Suicidality via C-SSRS 38
7.4.6.1 C-SSRS findings 38
7.4.7 Adverse Event 39
7.4.7.1 Causality 39
7.4.7.2 Recording and Evaluation of Adverse Events 39
7.4.7.3 Criteria for Assessing Severity 40
7.4.7.4 Criteria for Assessing Causality 40
7.4.7.5 Serious Adverse Events (SAE) 41
7.5 Screening Scales and Assessment Tools 41
7.5.1 Edinburgh Postnatal Depression Scale (EPDS) 41
8 STATISTICAL METHODS 43
8.1 Statistical and Analytical Plans 43
8.1.1 Analysis Populations 43
8.1.2 Demographics/Baseline Analysis 43
8.1.2.1 Protocol Deviations 43
8.1.2.2 Study Medication 43
8.1.2.3 Prior and Concomitant Medications 43
8.1.3 Pharmacokinetics Analysis 44
8.1.3.1 Pharmacokinetic Concentrations 44
8.1.3.2 Pharmacokinetic Parameters 44
8.1.4 Efficacy Analysis 44
8.1.5 Safety Analysis 44
8.1.5.1 Adverse Events 45
8.1.5.2 Laboratory Values 45
8.1.5.3 Vital Signs, Physical Examination, and Clinical Breast Examination 45
8.1.5.4 ECG Results 45
8.1.5.5 Prospective Suicidality Monitoring (C-SSRS) 45
8.2 Sample Size and Power Considerations 46
8.3 Interim Analyses 46
9 REPORTING OF ADVERSE EVENTS 47

9.1 Investigator Responsibilities for Reporting SAEs 47
9.2 Other Events Requiring Immediate Reporting 47
9.3 Sponsor Responsibilities for Expedited Reporting of SAEs 47
10 DOCUMENTATION 49
10.1 Adherence to the Protocol 49
10.2 Changes to the Protocol 49
10.3 Protocol Deviations 49
10.4 Data Quality Assurance 50
10.4.1 Data Collection 50
10.4.2 Clinical Data Management 50
10.4.3 Database Quality Assurance 50
10.4.4 Bioanalytical Sample Handling 50
10.5 Retention of Records 51
10.6 Auditing Procedures 51
10.7 Publication of Results 51
10.8 Financing and Insurance 51
10.9 Disclosure and Confidentiality 52
10.10 Discontinuation of Study 52
11 Final Report 53
12 ETHICS 54
12.1 Institutional Review Boards / Independent Ethics Committees 54
12.2 Ethical Conduct of the Study 54
12.3 Investigators and Study Personnel 54
12.4 Subject Information and Consent 55
13 REFERENCES 56
14 APPENDIX 57
14.1 Screening/Safety Assessment Scales 57
14.1.1 EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS) 58
14.1.2 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) 59
14.1.2.1 C-SSRS “Baseline/Screening” Version 59
14.1.2.2 C-SSRS “Since Last Visit” version 62

LIST OF TABLES AND FIGURES

Table 1: Schedule of Events and Assessments....29
Table 2. Pharmacokinetic Parameter for Plasma/Breast Milk....35
Table 3: Clinical Laboratory Tests....36

Figure 1: Study Schematic....21

LIST OF ABBREVIATIONS

5-HVLX-gluc	5-hydroxy-viloxaine glucuronide, the major metabolite of viloxazine
ADHD	Attention-Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
ECG	Electrocardiogram
EPDS	Edinburgh Postnatal Depression Scale
EOS	End of Study
ER	Extended-Release
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
PR	Interval between the P and R waves on the electrocardiogram tracing
QD	Once Daily
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTc	Corrected value of the interval between the Q and T waves on the
QTcF	QT interval corrected using Fridericia's method
RR	Interval between successive R waves on the electrocardiogram
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard deviation
SOP	Standard Operating Procedure
SM	Study Medication
RR	Respiratory Rate
TEAE	Treatment Emergent Adverse Event

NOTE: Pharmacokinetic parameters are defined in Section 7.2.3

1 INTRODUCTION

To distinguish between data in the public domain and that generated by Supernus, historical data will be associated with the term “viloxazine” and data generated by Supernus will be associated with the term “SPN-809V [IR], SPN-812, SPN-812 IR, or SPN-812 ER.

1.1 Background

SPN-812 (viloxazine extended-release capsules; QELBREE®) is a structurally distinct, bicyclic, norepinephrine reuptake inhibitor. The active substance in SPN-812 is viloxazine, whose mechanism of action is multimodal with antagonistic activity observed at 5-HT2B and agonistic activity at 5-HT2C receptors, as well as weaker antagonistic effects at ADRα1B, ADRβ2 and 5-HT7 receptors. Additionally, SPN-812 acts as a modulator with inhibitory effects at the norepinephrine reuptake transporter. Viloxazine was previously marketed in several European countries as an antidepressant as an immediate-release (IR) product. An extended-release (ER) formulation of viloxazine, SPN-812, has been developed by Supernus to prolong the release and absorption of viloxazine post-administration, thereby allowing longer dosing intervals for a drug with a relatively short half-life. As of April 2022, SPN-812 (QELBREE PI) is FDA-approved for the treatment of ADHD in persons 6 years of age and older based on clinical trials described below.

1.2 Clinical Information

Thirteen Phase 1 studies in adults, one Phase 2 and one Phase 3 studies in adults with ADHD, one Phase 2 in children with ADHD and four Phase 3 studies in children and adolescents with ADHD have been conducted with SPN-812. Data collection in two open-label extension studies evaluating long-term safety and efficacy of SPN-812 in ADHD patients, one inchildren and adolescents (6 to 17 years of age) with ADHD and one in adults (18-65 years of age) with ADHD, has concluded; final results are pending.

1.2.1 Phase 1 Studies

Phase 1 studies include comparison of various ER formulations to an equivalent daily dose of IR viloxazine (812P101), comparison of single- and two-bead SPN-812 ER formulations to an IR formulation at single and multiple doses (812P102 and 812P103, respectively), an evaluation of maximum tolerable doses in a single- and multiple-ascending dose study (812P120), as well as an evaluation of food and sprinkling effects (812P105) and alcohol (812P115). In addition, a [14C]-labelled oral solution was used to examine absorption, metabolism, and excretion (812P111). Drug-drug interaction of SPN-812 on cytochrome P450 (CYP) 1A2, 2D6, and 3A4 isoenzymes was evaluated in study 812P113.1. Drug-drug interaction studies with stimulants were performed with d-amphetamine and methylphenidate in the 812P113.2 and 812P113.3 studies, respectively. A study evaluating the DDI potential of paroxetine (strong inhibitor of CYP2D6) as a perpetrator of SPN-812 metabolism (812P113.4) was conducted. The effect of a multiple supratherapeutic dose of SPN-812 on QT interval has also been evaluated (812P117). Further, the effect of renal and hepatic impairment on the pharmacokinetics (PK) of SPN-812 has also been evaluated in 812P112.1 and 812P112.2, respectively.

Results from these studies demonstrated that 200 mg single dose of an extended release SPN-812 formulation resulted in a mean maximum plasma concentration (C_{max}) of 1.33 µg/mL, area

under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}) of 27.3 hr*µg/mL, median time to maximum concentration (T_{max}) of 5 hours, and a half-life of approximately 7 hours (812P103). Lower mean C_{max} was observed for SPN-812 as compared to SPN-812 IR and by 48 hours overall viloxazine exposure was comparable between the two formulations. The rate of absorption of viloxazine was formulation dependent; SPN-812 exhibited a slower absorption rate than SPN-812 IR. Following multiple-dose administration of SPN-812 on consecutive days, steady-state was achieved by the second day of multiple dosing. Little systemic accumulation of viloxazine was observed as no major increase in PK parameters was observed following multiple administration of SPN-812 compared to single dose administration, during the same time interval.

Food and sprinkling did not affect the relative bioavailability of viloxazine following administration of SPN-812 capsules (812P105). SPN-812 interacted as a strong inhibitor of CYP1A2, a weak inhibitor of CYP2D6, a weak inhibitor of CYP3A4; and displayed no significant differences in metabolism within CYP2D6 poor metabolizers and CYP2D6 extensive metabolizers (812P113.1). There was no DDI between SPN-812 and d-amphetamine (812P113.2) nor between SPN-812 and methylphenidate (812P113.3). There was no clinically relevant impact of paroxetine on SPN-812 (812P113.4). In addition, there was no dose dumping observed with co-administration of alcohol with SPN-812 (812P115). Renal impairment resulted in a 1.09-fold, 1.3-fold, and 1.9-fold increase in AUC for mild, moderate, and severe renal impairment subjects receiving 400 mg SPN-812 as compared to healthy subjects (812P112.1). Hepatic impairment (HI) resulted in approximately 21% increase and up to 6% decrease in AUC of viloxazine for mild and moderate HI subject receiving SPN-812 400mg compared to matched healthy subjects; severe HI subjects receiving 200mg of SPN-812 had a 25% increase in AUC of viloxazine compared to matched healthy subjects (812P112.2). Multiple doses of 1800 mg (supra-therapeutic) SPN-812 did not affect cardiac repolarization as measured by QTcI and QTcF or other electrocardiographic parameters (812P117). In the single ascending/multiple ascending dose study (812P120), SPN-812 was well tolerated up to 2100 mg/day as a single dose and up to 1800 mg/day as multiple doses given once daily for 5 consecutive days. Intolerable adverse events (AEs) were not observed at doses of up to 1800 mg/day. SPN-812 at a single supratherapeutic dose had no effect on cardiac repolarization or other electrocardiographic parameters, other than slight increase in heart rate consistent with the known anticholinergic effect of viloxazine (812P120).

In the human absorption, metabolism, and excretion study (812P111), absorption of the isomers, R- and S-viloxazine, was rapid with a median T_{max} of 1.0 hour and showed a 2:1 concentration ratio, respectively. Nearly 100% of the radioactive dose was recovered with approximately 90% being recovered within 24 hours of administration, demonstrating complete absorption of the drug followed by rapid elimination. The primary circulating form was SPN-812; the only metabolite found above 10% total radioactivity was 5-hydroxyviloxazine-glucuronide (5-HVLX-gluc).

The most common AEs in the Phase 1 studies in healthy adults were somnolence and headache. Most AEs were mild; none were severe or serious. No clinically significant, study medication-related findings were observed for laboratory or electrocardiogram (ECG) tests in any study. In general, SPN-812 is considered to be well-tolerated with no safety events observed that would be unexpected for viloxazine.

1.2.2 Phase 2 Studies

Study 812P201, conducted in adults with ADHD using an earlier, IR formulation of viloxazine, was a randomized, blinded, proof-of-concept study. Subjects received either placebo or IR formulation of viloxazine three times a day in a dose range of 150 to 300 mg/day (26 subjects per treatment). The most common AEs the treatment group were nausea, decreased appetite, headache, and insomnia. No serious adverse events (SAEs) or deaths occurred during the study.

In the Phase 2 dose finding study, 812P202, children 6-12 years old with ADHD were randomized in a 1:2:2:2:2 ratio to received placebo or 100, 200, 300, or 400 mg SPN-812 ER once daily for 5-8 weeks (titration and 5 weeks of maintenance). SPN-812 ER at 200-400 mg was shown to be efficacious on the primary objective, reduction of ADHD-RS-IV Total Score. All doses of SPN-812 were well tolerated with no serious or severe AEs.

1.2.3 Phase 3 Studies

Four pediatric pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter, 3-arm, parallel-group clinical trials evaluating the efficacy and safety of SPN-812 for the treatment of ADHD in children and adolescents have been conducted, including two clinical trials in children 6 to 11 years of age with ADHD (Studies 812P301 and 812P303; evaluated 100 mg, 200 mg, and 400 mg) and two clinical trials in adolescents 12 to 17 years of age with ADHD (Studies 812P302 and 812P304; evaluated 200 mg, 400 mg, and 600 mg). In April 2021, the Food and Drug Administration (FDA) approved SPN-812 (Qelbree®; viloxazine extended-release capsules) 100-400mg for the treatment of ADHD in pediatric patients 6 to 17 years of age. The most common adverse events (100-400mg) for were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

A single pivotal Phase 3, randomized, double-blind, placebo-controlled, multicenter, 2-arm, parallel-group clinical trial evaluating the efficacy and safety of SPN-812 (200-600mg) for the treatment of ADHD in adults 18 to 65 years of age with ADHD (Study 812P306) was also conducted. Subjects were randomized in a 1:1 ratio to placebo or SPN-812 (200 to 600mg/day) for a total of 6 weeks of treatment. In total, 374 subjects were randomized and 372 subjects were treated: 183 subjects with placebo and 189 subjects with SPN-812. SPN-812 was well tolerated in all dose levels, with no deaths, and 2 SAEs were reported in 2 subjects receiving placebo (cardiac failure congestive and pancreatitis), and no SAE occurred in any subject receiving SPN-812. No safety concerns were identified in this study. The most frequently reported treatment-emergent adverse events (≥5%) were insomnia, nausea, dry mouth, constipation, headache, fatigue and decreased appetite.

As of July 2022, data collection in two open-label extension studies evaluating the long-term safety and efficacy of SPN-812 has concluded, including one in children and adolescents (6 to 17 years of age) with ADHD (Study 812P310) and one in adults (18 to 65 years of age) with ADHD (Study 812P311); final results for both are pending.

Information and data from clinical studies are available in greater detail in the current SPN-812 Investigator Brochure.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the pharmacokinetics (PK) of viloxazine and its major metabolite 5-hydroxy-viloxazine glucuronide (5-HVLX-gluc) in breast milk in healthy lactating women following multiple oral doses of SPN-812.

2.1.2 Secondary Objectives

- To evaluate the PK of viloxazine and 5-HVLX-gluc in plasma in healthy lactating women following multiple oral doses of SPN-812.
- To evaluate the overall exposure between breast milk and plasma in healthy lactating women following multiple oral doses of SPN-812.
- To estimate daily infant dose of SPN-812 via breast milk.

2.1.3 Safety Objective:

- To evaluate the safety and tolerability of multiple doses of SPN-812 in healthy lactating women.

2.2 Study Endpoints

2.2.1 Primary Endpoints

Breast milk PK parameters when SPN-812 reaches plasma steady-state:

- $AUC_{tau,milk}$, $C_{max,milk}$, $T_{max,milk}$, $C_{trough,milk}$, $C_{ave,milk}$ for viloxazine and 5-HVLX-gluc
- Total amount of drug in breast milk (Am_{milk}, mg/day) over a period of 24 hours for viloxazine and 5-HVLX-gluc

2.2.2 Secondary Endpoints

- Plasma $AUC_{tau,ss}$, $C_{max,ss}$, $T_{max,ss}$, CL/F_{ss}, $C_{ave,ss}$ and $C_{trough,ss}$ for viloxazine and 5-HVLX-gluc at plasma steady-state, if applicable
- Breast milk-plasma ratio (ML/PL) based on AUC over 24 hours for viloxazine and 5-HVLX-gluc at plasma steady-state
- Estimated daily infant dosage (EDID, mg/kg/day) and relative infant dose (RID, %) at plasma steady-state (Table 2)

2.2.3 Safety Endpoints:

- Adverse Events (AEs)
- Clinical laboratory test results (clinical chemistry, hematology and urinalysis)
- 12-lead Electrocardiogram (ECG)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital signs
- Physical examination
- Concomitant medications

3 STUDY DESIGN

3.1 Overall Study Design and Plan

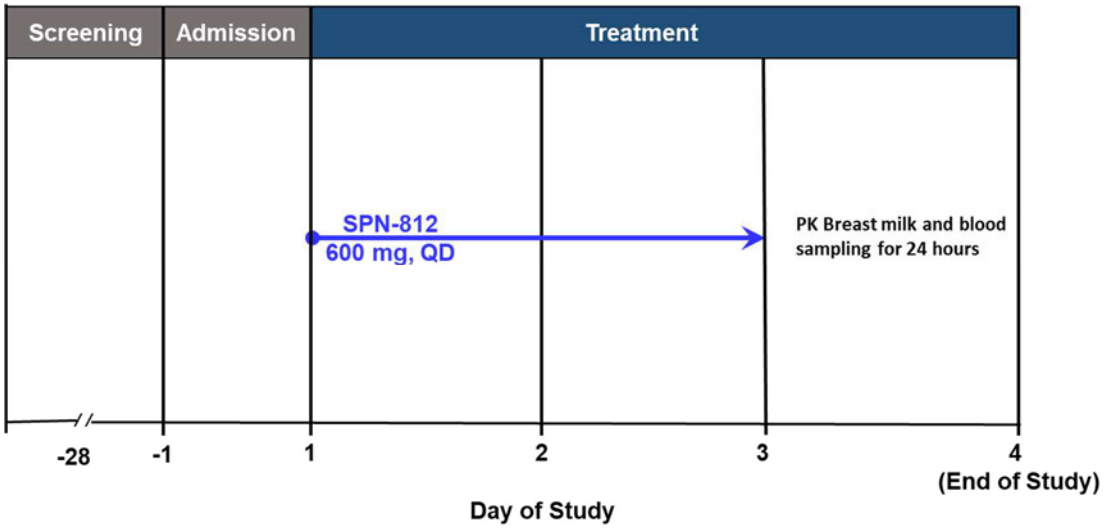
This is an open label, single treatment, lactation study of SPN-812 in healthy lactating women. The study is designed to assess the excretion of viloxazine and its major metabolite 5-HVLX-gluc into breast milk following repeated administration of SPN-812 600 mg, QD.

This study is comprised of Screening, Inpatient Admission, Treatment Period and End of Study (EOS). The total duration of the study is up to 1 month including Screening up to 28 days and 4 days of Treatment Period. Subjects will remain in the inpatient unit for 5 days, including the day of admission to the inpatient unit (Day -1), 3 days of dosing SM (Days 1-3), and the day of discharge (Day 4).

Subjects will be screened within 28 days prior to dosing. After informed consent is obtained, information from subjects will be collected (including maternal-related information) and subjects will undergo screening evaluations (see Table 1). Inclusion/exclusion criteria will be reviewed to determine the subject's eligibility at Screening. A lactation consultant will be available to provide lactation support to subjects once they are enrolled.

Subjects will be admitted to inpatient unit on Day -1 to confirm eligibility. Subjects will receive 600 mg SPN-812 on the morning of Days 1, 2 and 3 after completion of safety assessments. SM should be administered at the same time in the morning (±30 min) of dosing days. Breast milk and blood sample for PK analysis will then be collected on Day 3 per schedule in Section 7.2.1.1 and Section 7.2.1.2, respectively. Non-PK breast milk expressed on Days -1, 1, and 2 will be collected over the time intervals in Section 7.2.1.1, and these samples will not be analyzed for drug concentrations. The volume and the start and end times of the collection of each non-PK and PK breast milk sample will be recorded. The end of study (EOS) procedures will be conducted prior to discharge on Day 4 following the last breast milk and blood sample collection. If subject discontinues early, all EOS procedures will be conducted. Study schematic is shown in Figure 1, and Schedule of Events and Procedures is presented in Table 1.

Figure 1: Study Schematic



3.2 Rationale of Study Design

SPN-812, an extended-release oral capsule formulation of viloxazine, has been approved for the treatment of ADHD in pediatric patients 6 to 17 years of age. A Phase 3 clinical trial for the treatment of ADHD in adults has been completed and is under FDA review. Per FDA request, a post-marketing lactation study needs to be conducted "*in lactating women who have received therapeutic doses of viloxazine extended-release capsules to assess concentrations of viloxazine in breast milk"*. This study will be conducted in healthy lactating women, and drug concentration in breast milk and estimated infant dose via breastfeeding will be assessed following the FDA guidance (FDA guidance for clinical lactation studies, May 2019); the mother-infant pair will not be enrolled in this study, since there is no information available about the extent of drug transfer into breast milk, including evidence that the drug accumulates in breast milk and if the drug is likely to be absorbed by the breastfed infant. In this study, a multiple-dose design will be used since SPN-812 is administered chronically to treat patients with ADHD. The plasma steady-state will be reached after two days of once-daily administration without obvious accumulation (QELBREE PI). In this study, the dose of SPN-812 will not be titrated up in incremental doses since a previous multiple ascending dose study of up to 2100 mg/day SPN-812 (812P120) has been conducted and no safety concerns were reported. The dose to be administered in the study, 600 mg SPN-812 once daily, is the highest dose administered in pivotal Phase 3 studies conducted/completed in adolescents (812P304) and adults (812P306) with ADHD.

4 STUDY POPULATION

4.1 Number of Subjects

Up to 15 healthy, lactating women will be enrolled in the study.

4.2 Inclusion Criteria

1. Healthy lactating females, 18 to 45 years of age, who are actively breastfeeding (including baby to breast, bottle feeding mother's expressed breast milk) and are at least 12 weeks postpartum of a healthy term newborn infant (no medical complications) and not more than 2 years postpartum. Lactation must be well established and the mother is exclusively breast feeding her baby (not providing supplemental formula) prior to the day of admission to inpatient unit.
2. Has a body mass index between 18 to 35 kg/m^2, included.
3. Is considered medically healthy by the Investigator via assessment of physical examination (neurological examinations included), medical history, clinical laboratory tests, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) and electrocardiogram (ECG).
4. Is willing to temporarily discontinue breastfeeding their infant and discard all their breast milk for 7 consecutive days, including (day of admission to inpatient unit (Day -1), 3 consecutive days of dosing SM while in the inpatient unit (Days 1 to 3), and 3 consecutive days after last dose of SM (including the day of discharge from the inpatient unit and 2 days at home; Days 4 to 6); and willing to store sufficient amount of breastmilk (e.g., breast milk pumped and stored in freezer before the day of admission), and/or infant formula to feed infant during these 7 consecutive days.
5. Is either sexually inactive (abstinent) or, if sexually active, must agree to use/practice one of the following acceptable birth control methods beginning during the screening period prior to the first dose of SM, throughout the inpatient stay, and for 3 days following the last dose of SM (Day 3):
    - intra-uterine contraceptive device;
    - barrier method: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
    - is surgically sterile or male partner is surgically sterile;
    - established use of a patch, vaginal ring, oral, injected or implanted hormonal methods of contraception that can be used in lactating women;
    - Essure® procedure performed at least 6 months prior to Screening and had hysterosalpingogram after the Essure procedure to document tubal occlusion prior to screening.
6. Must not be in the process of weaning before admission to inpatient unit and have maintained an adequate breast milk supply with regularly pumping or routine breastfeeding (e.g., pumping or feeding 3-4 times a day) at admission.

7. Is currently a non-smoker who has not used tobacco or nicotine-containing products (chewed or smoked) or replacement products, including electronic cigarettes, within 3 months prior to screening and a negative cotinine test result at Screening.
8. Agrees to use only the emollient or nipple cream recommended by the investigator for use during the sampling period, if needed.
9. Able to voluntarily provide written informed consent to participate in the study.
10. Able to understand and willing to comply with all study requirements.
11. Able and willing to swallow capsules whole, without crushing, chewing or cutting.

4.3 Exclusion Criteria

1. Participation in any other investigational study drug trial in which receipt of an investigational study drug within 30 days or 5 half-lives before Screening, whichever is longer.
2. Is unwilling or unable to comply with the Lifestyle guidelines presented in the protocol during the study period.
3. Has history or presence of clinically significant systemic disease (including psychological and psychiatric disorders).
4. Is currently using, or tests positive at Screening for cotinine, alcohol or drugs (opiates, methadone, cocaine, amphetamines [including ecstasy], barbiturates, PCP, benzodiazepines, and THC/cannabis).
5. Is pregnant (has positive serum pregnancy test at Screening) or becomes pregnant during study (has positive urine pregnancy test).
6. Has history of breast implants, breast augmentation, or breast reduction surgery.
7. Has history of mastitis within 30 days, breast cancer and/or has had a mastectomy or lumpectomy with the exception of a benign fibroma or lipoma removal at the investigator's discretion; and/or a clinically significant abnormality observed in either breast during a clinical breast exam at Screening or Admission (Day -1).
8. Has a history of alcohol use disorder within 1 year of Screening; or assessed by the PI as having regularly consumed alcohol exceeding 14 units per week (1 unit equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within 1 year of Screening.
9. Is using recreational or illicit drug(s) (e.g., cannabis /tetrahydrocannabinol (THC), opiates, methadone, cocaine, amphetamines [including ecstasy], barbiturates, benzodiazepines) within 1 year of Screening.
10. Has clinically significant vital sign abnormalities (systolic blood pressure less than 90 or greater than 140 mmHg, diastolic blood pressure less than 60 or greater than 90 mmHg, or pulse rate (PR) less than 50 or greater than 100 bpm at Screening.

11. Has a clinical laboratory test values outside the reference range at Screening that, in the opinion of the investigator, are clinically significant, or any of the following:
    - Serum creatinine >1.5 times the upper limit of normal (ULN)
    - Serum total bilirubin >1.5 times ULN
    - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times ULN
12. Has a clinically significant ECG abnormalities at Screening, including:
    - PR interval >220 ms
    - QRS interval >130 ms
    - QTcF interval >470 ms
13. Has any disease or medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or interfere with the conduct or interpretation of the study.
14. Has evidence of infection with hepatitis B and C, and human immunodeficiency virus HIV-1 and HIV-2, as determined by results of testing at Screening.
15. Has a condition or planned procedure that may interfere with the absorption, metabolism, or elimination of the study drug (e.g., cholecystectomy).
16. Is using prescription medication within 14 days prior to administration of SM or 5 half-lives, whichever is longer, with the exception of hormonal contraceptives.
17. Is using -over-the-counter products (including vitamins, herbal products and natural food supplements) within 14 days prior to administration of SM or 5 half-lives, whichever is longer. Exceptions include postnatal vitamins, topical products without systemic absorption and acetaminophen (< 2 g/day).
18. Has an allergy to viloxazine.
19. Has an Edinburgh Postnatal Depression Scale score >13.
20. Has attempted suicide within the 6 months prior to Screening or is at significant risk of suicide (either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the 12 months prior to screening).
21. In the investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

4.4 Subject Withdrawal

A subject is free to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Subjects who withdraw from the study will undergo the EOS procedures prior to exit from the unit. The primary reason for withdrawal will be recorded. If a subject is withdrawn for more than one reason, each reason will be documented. Subjects who discontinue due to an AE will be followed until resolution of the AE

or until, in the medical judgment of the Principal/Site Investigator, the event has stabilized or resolved. A subject removed from the study for any reason will not be replaced.

Subject withdrawal will be done in accordance with the clinical site's SOP. Over the course of the study, the Sponsor and the Principal/Site Investigator or designee may withdraw any subject from the study for reasons including but not limited to the following:

- Safety reason
- Non-compliance with protocol requirements
- Significant protocol deviation

Withdrawal of subjects experiencing emesis should be considered on a case-by-case basis. PK samples collected from the subject withdrawn will be analyzed.

5 STUDY TREATMENT

5.1 Study Medication Identity, Packaging, and Labeling

Study medication, SPN-812 (QELBREE®, viloxazine extended-release capsule), will be provided at a strength of 200 mg. The 200 mg capsule is formulated to deliver viloxazine hydrochloride in the quantity of 200 mg viloxazine freebase.

5.2 Treatment Assignment and Administration

Each subject will receive 600 mg (3 x 200 mg) SPN-812 capsules. SM will be orally administered to subjects in the morning with water and with or without food. Subject will receive SPN-812 capsules at approximately the same time each day (Day 1, 2, and 3).

5.3 Blinding

Not applicable as this is an open-label study.

5.4 Study Medication Handling and Accountability

All SM will be supplied to the Investigator by the Sponsor. SM supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM labels. Following Sponsor instructions and in compliance with ICH E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log. A copy will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used in a manner other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or a representative of the FDA. The assigned CRA will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies, including empty containers, are to be returned to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site.

5.5 Prior and Concomitant Medications

Prior medications are defined as those taken up to 30 days prior to dosing and concomitant medications are those starting or ongoing while the subject is on study drug. All prior and

concomitant medications will be recorded in the document source. No concomitant medications except for the following will be allowed during the study:

- Hormonal birth control or hormone replacement
- Medical management of an AE (e.g., acetaminophen, ≤2 g/day)
- Postnatal vitamins
- Topical products without significant systemic absorption

The use of any concomitant medication, including acetaminophen, will be evaluated on a case-by-case basis by the Investigator and Medical Monitor.

6 STUDY SCHEDULE AND PROCEDURES

6.1 Study Schedule

The study consists of Screening, Inpatient Admission, Treatment and End of Study (EOS). All subjects who consent to be in this study are required to follow the study protocol events and procedures as described in Table 1. Blood/breast milk sample collections and safety variables are described in detail in Section 7.2.1 and Section 7.4, respectively.

6.1.1 Screening Period (Study Days -28 to -1)

Subjects will complete the screening visit, after informed consent is obtained, within 28 days prior to dose initiation. Since the mother's infant cannot receive breast milk for 7 consecutive days (Day -1 to Day 6), the mother will be reminded at Screening to make plans to have their infant fed 7 consecutive days with either (a) formula or (b) stored breast milk (e.g., breast milk pumped and stored in freezer during screening period between screening visit and day of admission to inpatient unit).

6.1.2 Inpatient Admission (Study Day -1)

Subjects will be admitted to the inpatient unit on Day -1 to confirm eligibility. A subject must meet all of the Inclusion Criteria and none of the Exclusion Criteria to remain eligible for enrollment in the study. Non-PK breast milk samples will be collected according to the schedule described in Section 7.2.1.1. Subject will remain in the inpatient unit for 5 consecutive days, including day of admission to inpatient unit (Day -1), 3 days of dosing SM (Days 1 to 3) and day of discharge from inpatient unit (Day 4).

6.1.3 Treatment Period (Study Days 1, 2, and 3)

All eligible subjects will receive 600 mg SPN-812 on Days 1, 2, and 3. Subjects will remain in the inpatient unit during this time. The Treatment Period includes collections of blood and breast milk samples, according to the schedule described in Section 7.2.1.1 and Section 7.2.1.2.

6.1.4 Inpatient Discharge (Study Day 4); End of Study (EOS)/Early Termination (ET)

EOS procedures will be completed and subject will be discharged from the inpatient unit on Day 4, 24 hours after the final dose has been administered and the breast milk and plasma PK sampling is completed (Section 6.2.4), or if the subject is discontinued during the inpatient before Day 4.

6.1.5 Follow-up Phone Call (FPC)

Subjects will be contacted via telephone 7 (± 2) days after discharge or final dose of SM for safety follow-up.

6.1.6 Repeat Safety Assessments (Unscheduled Visits)

At discretion of investigator, repeat assessments, including ECG, measure vital signs/weight, draw blood sample for hematology and/or serum chemistry and/or urine for urinalysis/drug screen, administer C-SSRS (Since Last Visit version), physical examination can be performed before, during and after inpatient study. AEs and concomitant medications should also be assessed at all unscheduled visits. The investigator should notify the medical monitor that they are planning to perform or have performed one of the above assessments again and provide the reason/rationale for repeating one of these assessments.

Table 1: Schedule of Events and Assessments

Study Visit	**Visit 1**	**Visit 2**					**FPC**
Study Period	**Screening**	**Admission**	**Treatment**			**EOS/ET**	
Study Day (window)	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**11 (±2)**
Signed informed consent	X						
Medical/Psychiatric/Maternal history[a]	X	X					
Demographics	X						
Height (BMI)	X						
Physical examination	X					X	
Clinical Breast Exam	X	X				X	
Serum pregnancy test	X	X					
Urine pregnancy test						X	
Serology	X						
Serum chemistry	X	X				X	
Hematology	X	X				X	
Urinalysis	X	X				X	
Urine drug screen[b]	X	X					
Vital signs and weight[c]	X	X	X	X	X	X	
12-lead ECG	X					X	
C-SSRS; Baseline/Screening	X						
C-SSRS; Since Last Visit		X				X	
Review eligibility criteria	X	X[d]					
Review adverse events[e]			X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X
SM administration[f]			X	X	X		
PK blood sampling[g]			X		X	X	
PK breast milk sampling[h]			X		X	X	
Non-PK breast milk sampling[h]		X	X	X			
Confinement		X	X	X	X		

Abbreviations: BMI = body mass index; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = Early Termination; FCP = follow-up phone call; PK = pharmacokinetics; SM = study medication

a. Psychiatric (including Edinburgh Postnatal Depression Scale) and maternal (gestational age at delivery, stage of lactation, and length of time postpartum) information should be included. Medical/psychiatric history will be reviewed and updated as needed at Admission.
b. Cotinine and urine or breath alcohol tests should be included.
c. Vital signs include orthostatic blood pressure, pulse rate, respiratory rate, and oral temperature. Perform vital signs prior to each dose on Day 1, 2, and 3. Weight will not be recorded on Day 4.
d. Inclusion/exclusion criteria should be reviewed prior to breast milk sampling on Day -1.
e. Adverse event should be monitored throughout the study via safety assessments, observation, and unsolicited reporting. Any events that occur prior to SM dosing should be captured as medical history.
f. SM should be administered at the same time in the morning (±30 min) of study Days 1, 2, and 3.
g. See Section 7.2.1.2 for full PK blood sample collection schedule.
h. PK and Non-PK breast milk samples will be collect following the collection schedule in Section 7.2.1.1. The volume and the start and end times of each breast milk sample will be recorded.

6.2 Study Procedures

6.2.1 Screening Period (Study Day -28 to Study Day -1)

A voluntary, written study-specific informed consent will be obtained from the participant before enrollment and before any study-related procedures are performed. The following procedures will be performed during Screening on subjects choosing to participate in this study and may be performed on more than one day. Abnormal results on screening laboratory tests and vital signs may be repeated at the discretion of the Investigator.

- Obtain written Informed Consent
- Confirm Inclusion/Exclusion criteria
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity)
- Obtain medical history
- Obtain psychiatric history (including the Edinburgh Postnatal Depression Scale)
- Obtain maternal-related information/history (gestational age at delivery, stage of lactation, and length of time postpartum)
- Record concomitant medications
- Measure and record vital signs and weight
- Measure and record height (calculate baseline BMI)
- Perform physical examination
- Perform clinical breast examination (see Section 7.4.4)
- Administer C-SSRS (Baseline/Screening version)
- Perform 12-lead ECG
- Collect blood sample for:
  - Serum chemistry and hematology
  - Serum pregnancy test
  - Serology
- Collect urine sample for:
  - Urinalysis
  - Urine drug screen (including urine or breath alcohol and cotinine)

6.2.2 Inpatient Admission (Study Day-1)

Subjects will be admitted to the clinical study inpatient facility and will remain in the unit until completion of the study. The procedures that will be performed on this day are listed below:

- Admitted to the inpatient unit on Day – 1; begin inpatient stay
- Confirm eligibility status (inclusion/exclusion criteria)
- Administer C-SSRS (Since Last Visit version)
- Review/update Medical history
- Review concomitant medications
- Perform clinical breast examination
- Measure and record vital signs and weight
- Collect blood sample for:
  - Serum chemistry and hematology
  - Serum pregnancy test
- Collect urine sample for:
  - Urinalysis
  - Urine drug screen (including urine or breath alcohol and cotinine)
- Collect non-PK breast milk samples per schedule in Section 7.2.1.1

6.2.3 Treatment Period (Study Days 1 to 3; Inpatient)

Treatment period is comprised of repeated doses of SPN-812 and collections of PK blood and breast milk samples on Day 3. The procedures to be performed are:

6.2.3.1 Study Days 1 and 2

- Measure and record vital signs and weight before morning dose
- Administer of 600 mg SPN-812
- Review concomitant medications
- Assess and record adverse events
- Collect non-PK breast milk samples per schedule in Section 7.2.1.1
- Collect pre-dose PK breast milk sample on Day 1
- Collect pre-dose PK blood sample on Day 1

6.2.3.2 Study Day 3

- Measure and record vital signs and weight before morning dose
- Administer 600 mg SPN-812
- Collect breast milk PK samples per Section 7.2.1.1
- Collect PK blood samples per Section 7.2.1.2
- Review concomitant medications
- Assess and record adverse events

6.2.4 Inpatient Discharge (Study Day 4); EOS/ET

The following procedures will be performed at study completion (EOS) or early termination (ET):

- Collect '16-24' h post-dose breast milk sample (breast milk sample not required at ET)
- Collect 24-h post-dose PK blood sample (PK blood draw not required at ET)
- Measure and record vital signs
- Perform 12-lead ECG
- Perform physical examination and note any changes from baseline
- Perform clinical breast examination and note any changes from baseline
- Administer C-SSRS (Since Last Visit version)
- Collect blood sample for chemistry and hematology
- Collect urine sample for urinalysis and pregnancy test
- Assess and record adverse events
- Review concomitant medications
- Remind mother: no breast feeding, discard all breast milk for the next 2 consecutive days.
- Discharge from inpatient unit

6.2.5 Follow-up Phone Call (Study Day 11 [±2 days])

The following procedures will be performed:

- Assess and record adverse events
- Review concomitant medications

6.3 Study Restrictions

6.3.1 Meals and Water Consumption

Subjects may consume only the food given to them while in the unit. Coffee or caffeine containing drinks will not be supplied.

6.3.2 Physical Activity Restrictions

For safety reasons, subjects will be required to remain seated or in a semi-supine position and avoid lying down or sleeping for the first two hours after drug administration. However, failure of subjects to comply with these requirements does not constitute a deviation from the protocol if it is medically necessary, procedurally required, or to go to the bathroom. Vigorous activity will be prohibited at all times during the confinement.

Outings will be permitted at the discretion of the Principal/Site Investigator and under supervision by clinical site staff to ensure compliance with protocol and will be limited to the grounds surrounding the clinical site as per appropriate SOP.

6.3.3 Prohibitions

No subject may take prescription medication (other than topical products without systemic absorption and hormonal contraception) within 14 days of the first dose or at any time while on study. Herbal products, natural food supplements, and vitamins (except postnatal vitamins) will not be permitted within 14 days prior to the first dose until the end of the study.

Smoking, alcohol, and illicit drugs are prohibited at any time while on study.

Consumption of foods, beverages or products containing the following substances will be prohibited while on study as indicated:

- Alcohol-based products from 48 hours prior to the first dosing until after the last study day.
- Food containing poppy seeds within 24 hours prior to admission until after the last study day.
- Food or beverages containing xanthine derivatives or xanthine-related compounds (e.g. caffeine) or energy drinks from 72 hours prior to the first dosing until after the last study day.
- Natural health products (including herbal remedies such as homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) from 14 days prior to the first dosing until the last study day.

7 STUDY ASSESSMENTS

7.1 Baseline Characteristics

The following demographic parameters will be captured: date of birth, gender, race, and ethnicity. The following will be assessed as related to the eligibility criteria as listed in Section 4.2 and Section 4.3 and will include the following:

- Medical History
- Medication History (including all medications taken within 30 days before Screening)
- History of drug, tobacco, and alcohol use

7.2 Pharmacokinetic Assessments

7.2.1 Pharmacokinetic Sample Collection

7.2.1.1 Breast Milk

A total of 9 expressed PK breast milk samples will be collected for PK analysis at the following time intervals:

- Day 1: -4 to <0 hours pre-dose;
- Day 3: -4 to <0 hours pre-dose, and '0 to 4', '4 to 6', '6 to 8', '8 to 10', '10 to 12', '12 to 16' and '16 to 24' hours post-dose.

Breast milk from each breast will be emptied as thoroughly as possible at each session using an electric breast pump at the planned time intervals. To ensure that the pump completely removes milk from the breasts, double pump for no less than 10 minutes until milk flow ceases. The length of each expressing session should be no longer than 30 minutes.

Non-PK breast milk samples (not to be analyzed for drug concentrations but volume will be recorded) will be collected at the following time intervals:

- Day -1: store milk as pumped per subject's pumping routine;
- Day 1: 0 to 24 hours post-dose per subject's pumping routine;
- Day 2: 0 to 20 hours post-dose per subject's pumping routine.

The type of breast pump preferred will be determined on an individual basis. Those subjects with their own pumps and sterilizers will be permitted to continue using these. Subjects without their own pumps will be provided with a breast pump by the clinic. For each breast milk collection period, the start and end times of the collection will be recorded, and the total volume (mL) of breast milk collected will be measured and recorded.

7.2.1.2 Blood

A total of 13 blood draws (4 mL each) for PK will be collected on Day 1 pre-dose, Day 3 pre-dose and Days 3 at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 16.0 and 24.0 hours post-dose. The following windows are permitted relative to the specified PK sample collection times:

Pre-dose:	- 15 minutes
< 1 hour post-dose:	± 3 minutes
1 to 8 hours post-dose:	± 5 minutes
> 8 to 24 hours post-dose:	± 10 minutes

The actual time and date of each blood sample collection will be recorded. PK blood samples will be collected in blood collection tubes containing K_2EDTA. As an alternative procedure to multiple blood draws, a catheter may be inserted into the arm to collect blood samples, if judged necessary.

The maximum total volume of blood drawn during the study will be up to 110 mL. This total blood volume includes samples for PK, screening, Day -1, and End of Study safety labs. In addition to repeat tests, additional laboratory tests may be performed to ensure the safety of the subject.

7.2.2 Drug Concentration Measurements

Concentrations of viloxazine and 5-HVLX-gluc in plasma and breast milk will be determined using validated achiral chromatographic tandem mass spectrometry methods.

7.2.3 Pharmacokinetic Parameters

Table 2 shows the PK parameters that will be calculated based on plasma and milk concentration-time data using standard non-compartmental methods:

Table 2. Pharmacokinetic Parameter for Plasma/Breast Milk

Plasma PK Parameter At Plasma Steady-state	**Parameter Description**
$AUC_{tau,ss}$	Area under the plasma concentration-time curve over a 24 h dosing interval.
$C_{ave,ss}$	Average plasma concentration, calculated as the ratio of $AUC_{tau,ss}/24$.
$C_{max,ss}$	Maximum observed plasma concentration.
$C_{trough,ss}$	Observed plasma concentration immediately before the next dose.
CL_{ss}/F*	Apparent clearance.
$T_{max,ss}$	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
Breast Milk PK Parameter	**Parameter Description**
$AUC_{tau,milk}$	Area under the milk concentration-time curve over a 24-hour dosing interval.
Am_{milk}	Total amount of drug excreted in milk, calculated as the sum of the product of milk volumes and concentrations from each time period.
$C_{ave,milk}$	Average drug concentration in milk, calculated as the ratio of $AUC_{tau,milk}/24$.
$C_{max,milk}$	Maximum observed drug concentration in milk.
$C_{trough,milk}$	Observed drug concentration in milk immediately before the next dose
ML/PL	Milk-plasma ratio, calculated as $AUC_{tau,milk}/ AUC_{tau,ss}$.
$T_{max,milk}$	Time of the maximum measured concentration in breast milk. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
DID	Daily infant dosage (mg/day); total drug present in milk and consumed by the infant per day, which is equal to Am_{milk}.
EDID	Estimated daily infant dosage (mg/kg/day) calculated as ML/PL x the average maternal plasma concentration ($C_{ave,ss}$) multiplied by 150 mL/kg/day and 200 mL/kg/day, respectively.
RID	Relative infant dose (%); the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours, calculated as EDID (mg/kg/day)/maternal dosage (mg/kg/day) multiplied by 100 %.

*not calculated for 5-HVLX-gluc

7.3 Pharmacodynamic Assessments

Not Applicable

7.4 Safety Assessment

Safety assessments will consist of ECGs, clinical laboratory tests' results, vital signs, medical history, physical examinations, C-SSRS, concomitant medications, and the monitoring and evaluations of reported or observed AEs.

7.4.1 Clinical Laboratory Measurements

All clinical laboratory tests will be performed either by local laboratory at inpatient unit or by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 1) shows the time points at which blood and urine samples will be collected. Table 3 presents the clinical laboratory tests to be performed.

Table 3: Clinical Laboratory Tests

Category		Parameters
Serology		Human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C
Hematology		Hematocrit, hemoglobin, platelets count, red blood cell count, and white blood cell count (WBC) with differential
Serum Chemistry	***Electrolytes***	Chloride, phosphorus, potassium, sodium, bicarbonate
	Liver function tests	Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin
	Renal function parameters	Blood urea/blood urea nitrogen, creatinine
	Other	Glucose, calcium, albumin, total protein
Urinalysis		Macroscopic examination[1], pH, specific gravity, protein, glucose, ketone, occult blood, leukocyte esterase, nitrites, bilirubin, urobilinogen
Pregnancy test		Blood sample at Screening and Inpatient Admission Urine sample at EOS
Urine Drug Screen		Amphetamines, methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, PCP, 3,4-methylenedioxy-N-methylamphetamine, methadone, cotinine, ethanol[2]

[1] If abnormal findings are found upon macroscopic examination, a microscopic examination will be performed unless otherwise specified.
[2] Breath alcohol test is acceptable.

All laboratory tests will be reviewed in a timely manner by qualified clinic personnel to ensure safety. Abnormal laboratory findings may be confirmed, if necessary, by one repeated testing at the discretion of the Investigator. A laboratory abnormality may qualify as an AE (see Section 7.4.7) if deemed so in the Investigator's judgment.

7.4.2 Vital Signs

Vital signs' measurements, including orthostatic blood pressure, pulse rate, oral temperature and respiratory rate, will be obtained at times (+/- 15 minutes) designated in the Schedule of Events and Assessments (Table 1). Orthostatic blood pressure and pulse rate will be measured after the subject has been seated for a minimum of 5 minutes and within 3 minutes of standing. Vital signs (resting or non-resting) may also be taken at any other time, as deemed necessary by the Principal/Site Investigator.

7.4.3 Physical Examinations

The physical examination conducted at Screening and EOS/ET will include assessments of head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen, lymph nodes, and musculoskeletal. Measurement of height and weight will be performed at Screening. Any clinically significant findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical examination, only changes from Baseline will be noted.

7.4.4 Clinical Breast Examination

The clinical breast examination conducted at Screening, Baseline (day of admission to inpatient unit prior to first dose), and at EOS/ET, is a physical examination of each breast, including visual inspection of the skin and nipples, and an assessment of the underarms and collarbone area. Any clinically significant findings during screening and/or baseline will be recorded as medical history and any clinically significant abnormal findings during or after treatment (after first dose of SM) will be recorded as an AE. Only changes from Baseline will be noted for the clinical breast examination at the EOS.

7.4.5 Electrocardiograms (ECGs)

A single 12-lead ECG will be obtained as per the Schedule of Events and Assessments (Table 1). Additional ECGs may be performed at other times if deemed necessary by the Principal/Site Investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 5 minutes. The ECG will electronically measure the PR, QRS, QT, RR, and QTc intervals, and heart rate.

All ECG tracings will be reviewed within 24 hours by the Principal/Site Investigator or qualified Sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

7.4.6 Prospective Assessment of Suicidality via C-SSRS

Suicidality assessment will be performed using the Columbia Suicide Severity Rating Scale (C-SSRS), which will be administered by a trained professional during Screening**,** Day -1, and at End of Study.

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and behavior using a semi-structured interview to probe subject's responses (Posner et al., 2011). The C-SSRS versions applicable to the current study are the "*Baseline/Screening*" version (Appendix 14.1.2.1) and the "*Since Last Visit*" version (Appendix 14.1.2.2).

- The Baseline/Screening version of the scale assesses suicidal ideation and behavior for lifetime and last 6 months. This version is suitable as part of a subject's first interview and will be used at Screening to identify volunteers who must not participate in the trial due to their suicidal tendencies.
- The Since Last Visit version of the scale assesses any suicidal thoughts or behaviors the subjects may have had since the last administration of the C-SSRS.
- Training will be provided on the administration and interpretation of the C-SSRS.

7.4.6.1 C-SSRS findings

Positive suicidality reports are generated for ANY of the following findings:

- Suicidal ideation with intention to act
- Suicidal ideation with specific plan and intent
- Made suicide attempt
- Interrupted suicide attempt
- Aborted suicide attempt
- Preparatory behaviors for making a suicide attempt

Should the interview reveal that a subject has a positive suicidal ideation, the site staff should take appropriate steps to refer the subject to a psychiatrist for a follow-up evaluation. The subject should not be released from the evaluation site until it is confirmed that the questionnaire answers are reviewed by the Principal/Site Investigator or designee and the subject is not considered to be at risk. Ultimately, the determination of suicidality and risk is up to the Principal/Site Investigator's judgment.

Any confirmed positive findings occurring after initiation of the SM dosing may qualify as treatment-emergent suicidality and should be recorded as an AE on the AE CRF. Positive suicidal findings recorded as an AE should be evaluated by the Principal/Site Investigator, in consultation with the Sponsor Medical Monitor or designee, as a potential important medical event (Section 7.4.7.3). If the suicidal indication has been determined to be an SAE, the subject must be immediately withdrawn from the study and the SAE must be reported to the Sponsor using the SAE Form (See Section 9.1).

7.4.7 Adverse Event

Subjects will be monitored throughout the study by Principal/Site Investigator for AEs. Adequate medical surveillance will be assured during the confinement period and a physician will be available on call at all times. If necessary, a physician, either at the study site or in a nearby hospital, will administer treatment for any AEs. Subjects experiencing AEs will be re-evaluated for eligibility criteria to assess their continuation in the study.
As defined by the ICH Guideline for GCP, an **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.
An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent injuries, or exacerbation of an existing disease.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

7.4.7.1 Causality

Adverse events may be categorized as either Adverse Drug Reactions or Suspected Adverse Drug Reactions based on their relationship to SM and the degree of certainty about causality.
Suspected Adverse Drug Reactions (SADRs) are a subset of adverse events for which there is evidence to suggest a causal relationship between the SM and the AE, i.e., there is a reasonable possibility that the SM caused the adverse event.

Adverse Drug Reactions (ADRs) are a subset of all SADRs for which there is reason to conclude that the SM caused the event.

7.4.7.2 Recording and Evaluation of Adverse Events

All subjects who are enrolled and who receive SM will be monitored and questioned regarding the occurrence of AEs. Adverse events occurring prior to SM administration on Study Day 1 will become part of the subject's medical history. Throughout the study, the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination.

Information on all AEs should be recorded immediately in the source document and also in the appropriate section of the case report form (CRF).

All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they may be grouped under one diagnosis. For

example, fever, elevated WBC, cough, abnormal chest X-ray, etc., can all be reported as "pneumonia".

All AEs occurring after enrollment and receipt of SM and throughout the study period must be recorded. A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of SM, or that worsened following first administration of SM, therefore, all AEs will be treatment-emergent. The clinical course of each AE should be followed until resolution or until, in the medical judgment of the Investigator, the event has stabilized. Subjects that have experienced AE(s) may be re-evaluated for eligibility criteria to assess their continuation in the study as determined by the Investigator and the Sponsor.

The Investigator is responsible for evaluating AEs and determining the following:

- Severity: How pronounced is the incapacity/discomfort caused by an AE?
- Causality: Was AE related or possibly related to the SM?
- Serious vs. Non-serious: Is the event a Serious Adverse Event (SAE)?

7.4.7.3 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

7.4.7.4 Criteria for Assessing Causality

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as **not suspected** or as a **suspected** reaction to SM. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a **causal relationship unlikely**, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- **Not related:** Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- **Unlikely related**: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on medication withdrawal may be lacking or unclear. This will be reported as a **Suspected Adverse Drug Reaction (SADR)**.
- **Definitely related:** Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the medication (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary. This will be reported as an **Adverse Drug Reaction (ADR)**.

7.4.7.5 Serious Adverse Events (SAE)

AEs are classified as serious or non-serious. An AE or **adverse drug reaction** (ADR) is considered **serious** if, in the view of either the investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug dependence or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization, or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

7.5 Screening Scales and Assessment Tools

7.5.1 Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) is a commonly used screening tool developed to assist in identifying possible symptoms of depression in women during pregnancy and during the postnatal period (Cox et al., 1987**;** Wisner et al., 2002; see Appendix 14.1.1). The EPDS is a 10-item self-report questionnaire; items of the scale correspond to various clinical depression symptoms, such as guilt feeling, sleep disturbance, low energy, anhedonia, and suicidal ideation. The individual rates themselves on each item on a 4-point Likert (various response option

equivalent to “not at all” to “all the time”) based on how they have felt in the last 7 days. For items 1, 2, and 4, the four response options are assigned a numeric value of 0-3 top to bottom. For items 3 and 5-10, the four response options are assigned a numeric value of 3-0 top to bottom. A total score is calculated by summating the ratings of all 10 items. The total score ranges between 0 and 30, and a total score of >13 represents presence of depression. It takes approximately 3-5 minutes to complete the EPDS.

8 STATISTICAL METHODS

All statistical analysis will be performed by CRO after the completion of the trial. A statistical analysis plan (SAP) will be written by CRO, reviewed, and approved by the Sponsor prior to database lock.

Summaries for continuous variables will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include the tabulation of frequencies and percentages, except zero (n=0) where percentages will not be displayed. All statistical analysis will be conducted by using SAS Version 9.4 or higher.

8.1 Statistical and Analytical Plans

8.1.1 Analysis Populations

The **Safety Population** will include all subjects who receive at least one dose of study medication.

The **PK Population** will include all subjects in the safety population who have a sufficient PK profile to derive at least 1 PK parameter without major events that could impact the PK data (e.g., emesis).

For subjects experiencing emesis:

PK parameters will be determined and listed for subjects experiencing emesis following the administration of SPN-812, however, parameters for these subjects may be excluded from the affected statistical analysis (i.e., descriptive statistics) per PK scientist's discretion.

Subjects experiencing emesis before study Day 3 may be invited to continue participation in the study if deemed appropriate by the Principal/Site Investigator. The accurate time of emesis should be recorded.

8.1.2 Demographics/Baseline Analysis

For continuous demographic variables, (age, height, weight, and BMI) results for each treatment administered will be summarized using descriptive statistics. For categorical variables (ethnicity, race, and gender), the number and percentage of subjects will be used. All demographic characteristics will be listed by subject.

8.1.2.1 Protocol Deviations

Protocol deviations (both site and individual) will be categorized and listed by subject.

8.1.2.2 Study Medication

The dose administration details (including treatment received, date and time of dose, and dose level administered) will be listed by subject.

8.1.2.3 Prior and Concomitant Medications

Prior and/or concomitant medications will be monitored and coded using the World Health Organization Drug Dictionary and listed by subject. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification and a listing will be provided.

Summary tables will be presented for the reported use of all concomitant medications subsequent to receiving the first administration of the study treatment.

8.1.3 Pharmacokinetics Analysis

The PK Population as defined in Section 8.1.1 will be used to generate breast milk and plasma PK parameters of viloxazine and 5-HVLX-gluc for all subjects. Descriptive statistics (number of subjects, mean, standard deviation [SD], and coefficient of variation [CV], minimum, median, and maximum) will be used to summarize breast milk and plasma concentration data at each planned sampling time point for each analyte in breast milk and plasma. The midpoint of the breast milk collection interval will be used as the milk sampling time. Breast milk and plasma PK parameters calculated from the concentrations and actual times will be summarized by analyte using descriptive statistics (including geometric mean and geometric CV). Individual and mean breast milk and plasma concentration-time profiles for viloxazine and 5-HVLX-gluc will be presented graphically on linear and semi-logarithmic scales. All PK parameters will be derived using a non-compartmental analysis method.

8.1.3.1 Pharmacokinetic Concentrations

Descriptive statistics will be used to summarize evaluable breast milk and plasma concentration data at each planned sampling time point for each treatment. A listing of the actual sampling times and corresponding concentrations will be provided for all PK samples. Generally, concentrations below the lower limit of quantification (BLQ) will be treated as zero in the summary statistics for concentration data. However, if a BLQs value in the profile of Day 3 is between two quantifiable concentrations, then the BLQ value may be treated as missing at PK scientist's discretion.

Viloxazine and 5-HVLX-gluc mean breast milk and plasma concentration versus time profiles will be presented by using the scheduled sampling time on both linear and semi-logarithmic scales. Individual breast milk and plasma concentrations by actual sampling time will be provided on both linear and semi-logarithmic scales.

8.1.3.2 Pharmacokinetic Parameters

Viloxazine and 5-HVLX-gluc PK parameters (see Section 7.2.3) will be calculated from breast milk and plasma concentration-time data by standard non-compartmental methods using Phoenix™ WinNonlin® (Version 8.0 or higher, Certara) and will be summarized using descriptive statistics. All individual subject parameter data will be listed. A list of PK parameters for plasma and breast milk are presented in Table 2.

8.1.4 Efficacy Analysis

There will be no efficacy analysis in this study.

8.1.5 Safety Analysis

Evaluation of safety will be performed on the safety population. Safety analysis will include AEs, clinical laboratory tests' results, vital signs, physical examination, C-SSRS, and ECGs. Safety and tolerability data will be reported using descriptive statistics. A complete description of the

statistical analyses to be performed with the safety and tolerability data will be presented in the SAP.

8.1.5.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by preferred term nested within System Organ Class. All AE data listings will include the verbatim term and MedDRA Preferred Term.

AEs are recorded only after SM has been administered; therefore, all AEs are treatment-emergent.

AEs will be summarized in tables. Listings of all AEs including deaths, SAEs, and AEs resulting in treatment discontinuation.

AEs will be summarized in tables. Listings of all AEs including deaths, SAEs, and AEs leading to treatment discontinuation will be provided.

8.1.5.2 Laboratory Values

Listings of all clinical laboratory results will be provided with the abnormal values flagged and the clinical significance assessment added, when appropriate. Listings will include normal ranges. Descriptive statistics for each clinical laboratory test will be presented. Change from baseline to EOS will also be presented. Laboratory test results will be assigned a low, normal, or high (LNH) classification according to whether the values were below (L), within (N), or above (H) the laboratory parameters' reference ranges provided by the central laboratory. For each laboratory parameter, shift from baseline to end of study visit will be presented in 3 by 3 tables based on LNH classification for each laboratory test, as applicable.

8.1.5.3 Vital Signs, Physical Examination, and Clinical Breast Examination

Vital signs values and physical examination and clinical breast exam assessments will be evaluated on an individual basis, by subject, only for purposes of entry into the study and safety evaluation. Individual subject vital signs will be listed. For vital signs, both actual values and change from Screening values will be summarized.

8.1.5.4 ECG Results

Subject tabular summaries of the quantitative ECG parameters and the overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant) will be presented. QTc will be reported as QTcF (QTcF=QT corrected using Fridericia's method). For the quantitative ECG parameters, both actual values and change from Screening values will be summarized. Individual subject ECGs will be listed.

8.1.5.5 Prospective Suicidality Monitoring (C-SSRS)

Suicidality monitoring data will be evaluated individually by subject and the C-SSRS findings will be presented in data listings.

8.2 Sample Size and Power Considerations

The sample size is not based on statistical power considerations. Based on clinical judgement, up to 15 healthy lactating volunteers will be enrolled in the study, with the expectation that at least 12 subjects will complete the study.

8.3 Interim Analyses

No interim analysis is planned.

9 REPORTING OF ADVERSE EVENTS

9.1 Investigator Responsibilities for Reporting SAEs

The Investigator must report all SAEs to Sponsor within 24 hours of first becoming aware of the SAE, regardless of whether the Investigator believes they are drug related. The Principal/Site Investigator must complete an SAE Form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports, and other relevant documents). The Principal/Site Investigator will keep a copy of this SAE Report Form on file at the study site.

The Principal/Site Investigator, after thorough consideration of all facts that are available, must include an assessment of causality of the SAE to study medication.

Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor as it becomes available using the SAE Report Form.

Principal/Site Investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB including submission of relevant safety information provided by the Sponsor.

The Drug Safety Contact for SAE reporting is:

PPD Medical Monitor
Telephone (24 Hour): 1-888-483-7729
Email: rtpsafety@ppd.com

9.2 Other Events Requiring Immediate Reporting

The Principal/Site Investigator must report a **pregnancy** that occurs in a subject during a clinical study to the Sponsor Medical Monitor within 24 hours of first becoming aware of the event. Pregnancy should be reported on a Pregnancy Report Form. The Investigator must follow-up with any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject or the child after birth must be documented and reported to the Sponsor.

In the case a subject has or manifested any clinical signs characteristic of a reportable disease or condition (e.g., tuberculosis, SARS), it is the responsibility of the Medical Director of CRO to notify the applicable Public Health authorities within 48 hours after becoming aware of the information.

9.3 Sponsor Responsibilities for Expedited Reporting of SAEs

The Sponsor will inform Principal/Site Investigator and regulatory authorities of adverse drug reaction (ADRs) that are both serious and unexpected, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study site submit SAE information to the Sponsor in the manner described above.

Principal/Site Investigator must also submit the safety information provided by the Sponsor to the IRB/IEC unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB/IEC.

It is the responsibility of the Sponsor to notify FDA/regulatory authorities and the Principal/Site Investigator, in a written IND safety report, of any SADR that is both serious and unexpected, as per their applicable SAE reporting guidelines. The Sponsor will also notify Principal/Site Investigator of any findings from other sources (other studies, animal and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

10 DOCUMENTATION

10.1 Adherence to the Protocol

The Principal/Site Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The Principal/Site Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Principal/Site Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Principal/Site Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

10.2 Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor, and IRB must be notified promptly.

Changes to the protocol which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor or CRO will send a letter to the IRB detailing such changes.

10.3 Protocol Deviations

There are to be no Investigator-initiated deviations from the protocol. The date of and reason for deviations must be documented in all cases. Important deviations that significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being must be reported by the Investigator to the IRB immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

Changes to the procedures which may impact the quality of the PK data will be considered important deviations. These changes will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to:

- Sample handling or processing errors that invalidate bioanalytical results
- Inaccurate dosing on the day of PK sampling

In the case of an important deviation, collected blood samples will be analyzed. However, PK concentrations and PK parameters affected by the deviations (per PK scientist's discretion) will be excluded from the study results.

Other changes to the procedures which do not impact the quality of the PK data will not be considered important deviations. If such changes occur, data will be included but the analysis will be adjusted accordingly. A common example of an unimportant deviation is a missed blood sample or deviations from blood collection times. Although these changes are not significant, they are deviations from the protocol and should be documented in the clinical study report.

10.4 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines.

10.4.1 Data Collection

All clinical data will be recorded on site by the clinical staff on source documents and/or recorded electronically using validated software. The Principal/Site Investigator and/or the site staff will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

10.4.2 Clinical Data Management

The clinical database will be populated directly from electronic data as specified in the CRO's data management plan. However, recording of data may be done on raw data sheets (e.g., ECG data) and will be manually transcribed into the validated software. As a result, the CRFs will be populated directly from the validated software database and will be used solely for submission purposes. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

10.4.3 Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail. All data will be verified for quality control and will also be subject to audits from CRO's Quality Assurance Unit.

10.4.4 Bioanalytical Sample Handling

All collected PK breast milk and blood samples will be analyzed. Bioanalytical sample analyses for viloxazine and 5-HVLX-gluc will be performed at Supernus bioanalytical facility and/or a Supernus designated bioanalytical facility. Samples and Sample Inventory Forms/Manifests will be shipped to Supernus bioanalytical facility or the Supernus designated bioanalytical facility, according to instructions provided in a separate document. Primary and secondary (backup) samples will be transported in at least two separate shipments. The samples should be packed

on sufficient dry ice to ensure they will remain and arrive frozen. The bioanalytical reports will be included as appendices to the clinical study report.

10.5 Retention of Records

The Principal/Site Investigator has the responsibility to retain all study "essential documents", as described in ICH E6. Essential documents include but are not limited to the protocol, copies of paper CRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, and regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB/IEC correspondence). The Investigator should take measures to prevent accidental or premature destruction of these documents. Study essential documents should be retained until at least two years after the last approval of a marketing application or after formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Principal/Site Investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

It is requested that at the completion of the required retention period, or should the CRO relocate, the Sponsor should be contacted and give the option of permanently retaining the study records.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

10.6 Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). Any inspections requested by a regulatory authority must be communicated immediately by CRO to the Sponsor.

10.7 Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until any Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

10.8 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between CRO and the Sponsor.

10.9 Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Principal/Site Investigator, the Clinical Trial Site's staff(s), and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

10.10 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Principal/Site Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Principal/Site Investigator reserves the right to discontinue the study should his/her judgment so dictate. The Principal/Site Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

11 Final Report

A final report including clinical and statistical sections will be the responsibility of CRO and will be signed and approved by the Sponsor.

In the event that the study is prematurely terminated, CRO will produce an abbreviated safety report. In such an event, raw data will not be submitted with the abbreviated report but will be archived at CRO, unless requested by the Sponsor.

12 ETHICS

12.1 Institutional Review Boards / Independent Ethics Committees

The Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the informed consent form(s) (ICF) will be reviewed and approved by the appropriate IRB before subjects are enrolled. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at CRO and a copy will be given to the subject. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Principal/Site Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable adverse events (AEs) per International Conference on Harmonization (ICH) guidelines and local IRB standards of practice.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) from both the Sponsor and CRO. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients"), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent and IRB regulations).
- Local, national legal guidelines.

12.3 Investigators and Study Personnel

This study will be conducted by Principal/Site Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor) at CRO.

Contact person(s) at the Sponsor's Medical Monitor and contact information for Serious Adverse Event (SAE) reporting can be found in Section 9.3 of the protocol. Additional details on AE and SAE reporting can be found in Section 9 of the protocol. Contact information for other Sponsor personnel are listed in the Regulatory Binder, maintained by CRO.

The study will be monitored by qualified personnel from Supernus. Data management and statistical analyses will be the responsibility of the CRO data management and biostatistics groups.

12.4 Subject Information and Consent

The Principal/Site Investigator (or designee) will inform the subject of all aspects pertaining to the subject's participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Principal/Site Investigator (or designee) and subject must sign and date the Informed Consent Form(s) (ICF) before the subject can participate in the study. The subject will be given a copy of the signed and dated ICF and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is voluntary. The Principal/Site Investigator (or designee) must emphasize to the subject that consent, regarding study participation, may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICFs are amended during the study, the Principal/Site Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICFs by the IRB and use the amended informed consent form(s) for all subjects (including ongoing subjects).

13 REFERENCES

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782-786.

FDA Guidance for Industry: Clinical Lactation Studies: Considerations for Study Design, May 2019.

QELBREE® Prescribing Information, April 2022; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211964s003lbl.pdf

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011; 168:1266-1277.

14 APPENDIX

14.1 Screening/Safety Assessment Scales

14.1.1 EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

Edinburgh Postnatal Depression Scale (EPDS)

SUBJECT ID #: _____ **DATE COMPLETED:** _____
[Site No] – [Subject No.] DD / MMM / YYYY

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed

I have felt happy:
- ☐ Yes, all the time
- ☒ Yes, most of the time
- ☐ No, not very often
- ☐ No, not at all

This would mean: "I have felt happy most of the time" during the past week
Please complete the other questions in the same way

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - ☐ As much as I always could
   - ☐ Not quite so much now
   - ☐ Definitely not so much now
   - ☐ Not at all

2. I have looked forward with enjoyment to things
   - ☐ As much as I ever did
   - ☐ Rather less than I used to
   - ☐ Definitely less than I used to
   - ☐ Hardly at all

3. I have blamed myself unnecessarily when things
   - ☐ Yes, most of the time
   - ☐ Yes, some of the time
   - ☐ Not very often
   - ☐ No, never

4. I have been anxious or worried for no good reason
   - ☐ No, not at all
   - ☐ Hardly ever
   - ☐ Yes, sometimes
   - ☐ Yes, very often

5. I have felt scared or panicky for no very good reason
   - ☐ Yes, quite a lot
   - ☐ Yes, sometimes
   - ☐ No, not much
   - ☐ No, not at all

6. Things have been getting on top of me
   - ☐ Yes, most of the time I haven't been able to cope at all
   - ☐ Yes, sometimes I haven't been coping as well as usual
   - ☐ No, most of the time I have coped quite well
   - ☐ No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
   - ☐ Yes, most of the time
   - ☐ Yes, sometimes
   - ☐ Not very often
   - ☐ No, not at all

8. have felt sad or miserable
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Not very often
   - ☐ No, not at all

9. I have been so unhappy that I have been crying
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Only occasionally
   - ☐ No, never

10. The thought of harming myself has occurred to me
    - ☐ Yes, quite often
    - ☐ Sometime
    - ☐ Hardly ever
    - ☐ Never

Reviewed by: _____ **Date:** _____

Source:
Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782-786.
Wisner KL, Parry BL, Piontek CM. Clinical practice. Postpartum depression. N Engl J Med. 2002 Jul 18;347(3):194-199.

812P418 Page 1 of 1 v1.0 (14Mar2022)

14.1.2 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

14.1.2.1 C-SSRS "Baseline/Screening" Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _6_ Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

14.1.2.2**C-SSRS "Since Last Visit" version**

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____