Supernus Pharmaceuticals, Inc.

812P418

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

11 August 2023

Final Statistical Analysis Plan

Version 1.0

TABLE OF CONTENTS

List of Abbreviations

5-HVLX-gluc	5-hydroxyviloxazine glucuronide
ADR	adverse drug reaction
AE	adverse event
Am_{milk}	total amount of drug excreted in breast milk
ATC-4	Anatomical Therapeutic Chemical Level 4
AUC	area under the concentration-time curve
$AUC_{tau,milk}$	area under the concentration-time curve over a 24-hour dosing interval in breast milk
$AUC_{tau,ss}$	area under the concentration-time curve over a 24-hour dosing interval in plasma at steady-state
BLQ	below the limit of quantification
BMI	body mass index
$C_{ave,milk}$	average concentration in breast milk
$C_{ave,ss}$	average concentration in plasma at steady-state
CL/F_{ss}	apparent total body clearance in plasma at steady-state
$C_{max,milk}$	maximum observed concentration in breast milk
$C_{max,ss}$	maximum observed concentration in plasma at steady-state
$C_{trough,milk}$	drug trough concentration immediately before the next dose in breast milk
$C_{trough,ss}$	drug trough concentration immediately before the next dose in plasma at steady-state
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
DID	daily infant dosage
EDID	estimated daily infant dosage
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
ML/PL	breast milk-plasma ratio
NCA	non-compartmental analysis
PK	pharmacokinetic
PN	preferred name
PT	preferred term
Q1	first quartile

Q3	third quartile
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RID	relative infant dose
SADR	suspected adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SM	study medication
SOC	system organ class
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
$T_{max,milk}$	time of maximum observed concentration in breast milk
$T_{max,ss}$	time of maximum observed concentration in plasma at steady-state
WHODrug	World Health Organization Drug Dictionary

1. Introduction

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 product. An extended-release 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 Food and Drug Administration-approved for the treatment of Attention-Deficit Hyperactivity Disorder in persons 6 years of age and older.

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-hydroxyviloxazine glucuronide (5-HVLX-gluc) into breast milk following repeated administration of SPN-812 600 mg, once daily (QD).

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on protocol 812P418, version 2.0, dated 02 September 2022.

2. Objectives and Endpoints

2.1 Primary Objective and Endpoints

The primary objective is to:

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

The primary endpoints of this study are as below:

- Breast milk PK parameters for viloxazine and 5-HVLX-gluc when SPN-812 reaches plasma steady-state:
    - Area under the concentration-time curve (AUC) over a 24 hour dosing interval in breast milk ($AUC_{tau,milk}$)
    - Maximum observed concentration in breast milk ($C_{max,milk}$)
    - Time of maximum observed concentration in breast milk ($T_{max,milk}$)
    - Drug trough concentration immediately before the next dose in breast milk ($C_{trough,milk}$)

- Average drug concentration in breast milk ($C_{ave,milk}$)
- Total amount of drug excreted in breast milk (Am_{milk}, mg/day) over a period of 24 hours

2.2 Secondary Objectives and Endpoints

The secondary objectives are to:

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

The secondary endpoints of this study are as below:

- Plasma PK parameters for viloxazine and 5--HVLX--gluc at plasma steady-state, if applicable:
  - AUC over a 24 hour dosing interval in plasma at steady-state ($AUC_{tau,ss}$)
  - Maximum observed concentration in plasma at steady-state ($C_{max,ss}$)
  - Time of maximum observed concentration in plasma at steady-state ($T_{max,ss}$)
  - Apparent total body clearance in plasma at steady-state (CL/F_{ss})
  - Average concentration in plasma at steady-state ($C_{ave,ss}$)
  - Drug trough concentration immediately before the next dose in plasma at steady-state ($C_{trough,ss}$)
- 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

2.3 Safety Objective and Endpoints

The safety objective is to:

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

The safety endpoints of this study are as below:

- 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

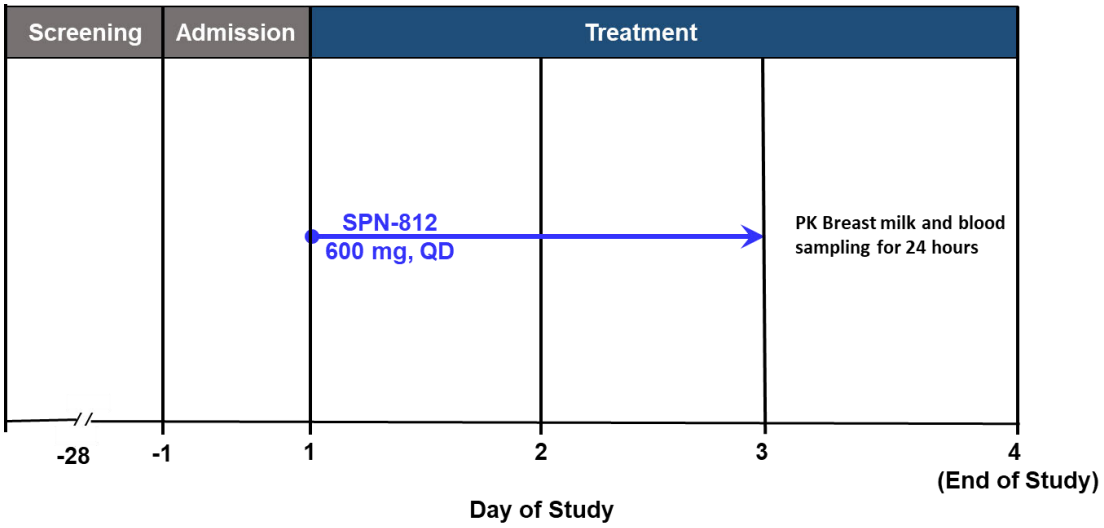
This is an open label, single treatment, lactation study of SPN-812 in healthy lactating women. The study is designed to assess the excretion of viloxazine and its major metabolite 5-HVLX-gluc into breast milk following repeated administration of SPN-812 600 mg, once daily (QD).

This study is comprised of Screening, Inpatient Admission, Treatment Period, and End of Study (EOS). The total duration of the study is up to around 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 study medication (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 13-1). Inclusion/exclusion criteria will be reviewed to determine the subjects' 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. Study medication 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 to 4 per schedule in Section 8.2 and Section 8.3, respectively. Non-PK breast milk expressed on Days -1, 1, and 2 will be collected over the time intervals in Section 8.2, 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 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 3-1 and Schedule of Events and Procedures is presented in Table 13-1.

Figure 3-1: Study Schematic



4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures will be presented with treatment. The treatment below will be used for presentations:

- SPN-812 600 mg QD

All data listings will be sorted by subject number.

No algorithm for imputation of missing data will be employed.

Study days are calculated with respect to the first dose date as below:

- If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1
- Otherwise, Study Day = Assessment/Observation Date – First Dose Date

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of SM administration, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1. Sample Size

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.

4.2. Randomization, Stratification, and Blinding

This is an open label, single treatment study, no randomization, stratification, and blinding will be used.

4.3. Analysis Population

The Enrolled Population will include all subjects who sign the informed consent form.

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).

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

5. Subject Disposition

5.1 Disposition

The following will be summarized for the Enrolled Population for all subjects:

- The number of subjects who completed screening
- The number of subjects who did not complete screening
    - Reasons for discontinuation from screening
- The number of subjects who completed study

- The number of subjects who did not complete study
    - Reasons for discontinuation from the study
- The number of subjects in each analysis population

Subject disposition data will be presented in data listings.

5.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data, and may affect the conclusion of the safety and PK analyses. Important protocol deviations will be summarized for the Safety Population. All protocol deviations will be presented in a data listing.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information collected at Screening will be presented in a data listing.

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented for the Safety Population.

6.2 Medical, Psychiatric, and Maternal History

The medical and psychiatric history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0) and presented in a data listing.

Edinburgh Postnatal Depression Scale and maternal (infant gestational age at delivery, stage of lactation, length of time postpartum, and feeding method [pumping or breastfeeding]) history will be presented in separate data listings.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications that stop prior to the first dose of SM will be classified as prior medication. Medications that start on or after the first dose of SM will be classified as concomitant. If a medication starts before the first dose of SM and stops on or after the first dose of SM, then the medication will be classified as both prior and concomitant.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 (ATC-4) and preferred name (PN) for the Safety Population. All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHODrug, version March 2023) and presented in a data listing.

7.2 Study Medication

The SM administration and drug accountability data (including treatment received, date and time of dose, and dose level administered) as collected on electronic case report form (eCRF) will be presented in a data listing.

8. Pharmacokinetics

All PK listings and individual concentration-time profiles will be presented using the Safety Population. The PK tables and mean figures will be presented using the PK Population.

8.1 Data Analyses

Data rounding specifications for PK data are documented in the PK tables, listings, and figures shells.

For presentation of the individual data and summary statistics, viloxazine and 5-HVLX-gluc breast milk and plasma concentrations below the limit of quantitation (BLQ) will be set to zero. For the PK analysis (non-compartmental analysis [NCA]), concentrations BLQ up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as “missing”.

Descriptive statistics (number of observations [n], number of BLQ values [nBLQ], mean, SD, 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. The midpoint of the breast milk collection interval will be used as the breast milk sampling time.

A listing of the actual sampling times and corresponding concentrations will be provided for all PK samples. Individual breast milk volumes collected at each time interval as indicated in section 8.2 for both PK and non-PK samples will also be presented in breast milk data listing. 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.

8.2 Breast Milk Collections

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.

Non-PK breast milk expressed on Days -1, 1, and 2 will be collected over the time intervals as below, and these samples will not be analyzed for drug concentrations:

- 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.

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.

8.3 Plasma Collections

A total of 13 blood draws 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 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. Pharmacokinetic collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings.

8.4 Pharmacokinetic Parameters

Viloxazine and 5-HVLX-gluc breast milk and plasma concentration-time data will be analyzed by NCA using Phoenix® WinNonlin® Version 8.3.4 or higher (Certara USA, Inc., Princeton, NJ). The following PK parameters will be calculated for viloxazine and 5-HVLX-gluc, where data permits:

Breast milk:

PK Parameter	Definition
$C_{max,milk}$	Maximum observed concentration in breast milk.
$C_{ave,milk}$	Average drug concentration in breast milk calculated as the ratio of $AUC_{tau,milk}/24$.
$C_{trough,milk}$	Drug trough concentration immediately before the next dose in breast milk.
$T_{max,milk}$	Time of maximum observed concentration in breast milk.
$AUC_{tau,milk}$	Area under the concentration-time curve over a 24 hour dosing interval in breast milk, calculated using the linear up/log down rule.
Am_{milk}	Total amount of drug excreted in breast milk, calculated as the sum of the product of breast milk volumes and concentrations from each time period.
ML/PL	Breast milk-plasma ratio, calculated as $AUC_{tau,milk}/AUC_{tau,ss}$.
DID	Daily infant dosage (mg/day); total drug present in breast 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 × the average maternal concentration in plasma ($C_{ave,ss}$) × 150 mL/kg/day (EDID 150) and 200 mL/kg/day (EDID 200), 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) × 100%.

Plasma:

PK Parameter	Definition
$C_{max,ss}$	Maximum observed concentration in plasma at steady-state.
$C_{ave,ss}$	Average concentration in plasma at steady-state calculated as the ratio of $AUC_{tau,ss}/24$.
$C_{trough,ss}$	Drug trough concentration immediately before the next dose in plasma at steady-state.

PK Parameter	Definition
$T_{max,ss}$	Time of maximum observed concentration in plasma at steady-state.
$AUC_{tau,ss}$	Area under the concentration-time curve over a 24 hour dosing interval in plasma at steady-state, calculated using the linear up/log down rule.
CL/F_{ss}*	Apparent total body clearance in plasma at steady-state, calculated as: $Dose/AUC_{tau,ss}$.

*not calculated for 5-HVLX-gluc

Actual sampling times and actual midpoint times will be used for the estimation of all PK parameters in breast milk and plasma, respectively.

Analysis: Viloxazine and 5-HVLX-gluc breast milk and plasma PK parameters will be presented in data listings and summarized by analyte using descriptive statistics (n, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV). T_{max} will be summarized using n, median, minimum, and maximum only.

9. Safety Analysis

All safety summaries and analyses will be based upon the Safety Population.

9.1 Adverse Events

An AE is defined as 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.

A treatment-emergent AE (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. Adverse events are recorded only after SM has been administered; therefore, all AEs are treatment-emergent.

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

A serious AE (SAE) is defined as an AE or ADR 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

The AE's relationship to SM will be evaluated by the investigator. The following relationships will be collected on eCRF: definitely related, possibly related, unlikely related, or not related.

The AEs that are evaluated as definitely related or possibly related will be considered treatment-related AEs for summary purpose.

The severity of AEs will be classified by the investigator as mild, moderate, or severe.

An overall AE summary will be generated presenting the frequency and percentage of subjects and the number of AEs for the following:

- Any TEAE
- Any treatment-related TEAE
- Any moderate TEAE
- Any treatment-related moderate TEAE
- Any severe TEAE
- Any treatment-related severe TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to study discontinuation
- Any TEAE leading to treatment discontinuation
- Any TEAE leading to treatment adjustment (including dose increased, dose reduced, or drug interrupted)
- Any death

All AEs will be coded using MedDRA version 26.0. The TEAEs will also be summarized by system organ class (SOC), PT, and by severity and relationship to SM.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more events within the same level of summarization will be counted only once in that level using

the most severe incident or most related incident. Percentages will be based on the number of subjects in the Safety Population.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, deaths, and AEs leading to treatment discontinuation.

9.2 Clinical Laboratory Evaluations

The hematology, serum chemistry, urinalysis, serology, pregnancy, and urine drug screen tests will be performed at the timepoints indicated in the schedule of assessments (Section 13).

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings and presented in a separated listing.

The actual values and change from baseline values for hematology, serum chemistry, and urinalysis at each time point will be summarized for the Safety Population. Shift from baseline in terms of low/normal/high for hematology and serum chemistry tests, and in terms of normal/abnormal for urinalysis tests will be summarized for the Safety Population.

9.3 Vital Sign Measurements

Vital signs will include orthostatic systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature, and will be measured at the timepoints indicated in the schedule of assessments (Section 13).

All vital signs will be presented in a data listing and abnormal results will be presented is a separated data listing. Weight, height, and BMI will be presented in a separate data listing.

The normal reference range for vital signs is as below:

Position	Parameter	Predose	Postdose
Sitting/Standing	Temperature	96.0-99.8 °F / 35.6-37.7 °C	95.0-100.0 °F / 35.0-37.7 °C
	Respiratory Rate	10-20 breaths/min	10-20 breaths/min
	Pulse Rate	40-100 beats/min	40-120 beats/min
	Blood Pressure	90-140 mmHg / 50-90 mmHg	90-150 mmHg / 40-100 mmHg

The actual values and change from baseline values for orthostatic systolic and diastolic blood pressure, pulse rate, respiratory rate, oral temperature, and weight at each time point will be summarized for the Safety Population. The orthostatic changes for blood pressure and pulse rate will be calculated using the measurements at standing position minus the measurements at sitting position at the same timepoint. The orthostatic changes for respiratory rate and oral temperature

will also be calculated using the measurements at standing position minus the measurements at sitting position at the same timepoint if data permit.

9.4 Physical Examinations

The physical examination will include assessments of head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen, lymph nodes, and musculoskeletal, and will be performed at the timepoints indicated in the schedule of assessments (Section 13). 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.

All physical examination results will be presented in a data listing.

9.5 Clinical Breast Examinations

The clinical breast examination is a physical examination of each breast, including visual inspection of the skin and nipples, and an assessment of the underarms and collarbone area, and will be performed at the timepoints indicated in the schedule of assessments (Section 13). 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.

All clinical breast examination results will be presented in the physical examination data listing.

9.6 Electrocardiograms

The ECG will be recorded while the subject is resting in a supine position for at least 5 minutes.

Heart rate (HR), PR interval, QRS duration, RR interval, QT interval, QT interval corrected for heart rate using Fridericia's formula (QTcF), and interpretation of ECG will be captured on the eCRF.

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of assessments (Section 13). Additional ECGs may be performed at other times if deemed necessary by the Principal/Site Investigator.

The actual values and changes from baseline values for numeric ECG data at each time point will be summarized for the Safety Population.

Shift from baseline in interpretation of ECG results will be summarized for the Safety Population using the frequency count and percentage of subjects in each category (normal, abnormal and not

clinically significant, abnormal and clinically significant, indeterminate, or not evaluable/unknown).

All ECG data will be presented in a data listing and abnormal results will be presented in a separated data listing.

The normal reference range for ECG results is as below:

Parameter	Screen/Pre-Dose	Post
HR	40-100 beats/min	40-120 beats/min
PR	120-220 ms	120-240 ms
QRS	>130 ms	80-120 ms
QTcF	<470 ms	<470 ms
QT	(already ranges for QTcF)	(already ranges for QTcF)
RR interval	(calculated off HR)	(calculated off HR)

9.7 Prospective Assessment of Suicidality

Suicidality assessment will be performed using the Columbia Suicide Severity Rating Scale Baseline/Screening and Since Last Visit. The C-SSRS will be performed at the timepoints indicated in the schedule of assessments (Section 13).

The C-SSRS findings will be presented in a data listing.

10. Interim Analysis

No interim analysis is planned.

11. Changes in the Planned Analysis

There are no changes in the planned analyses stated in the protocol.

12. References

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

13. Schedule of Assessments

Table 13-1: 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		

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)
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 8.3 for full PK blood sample collection schedule.
h. PK and Non-PK breast milk samples will be collect following the collection schedule in Section 8.2. The volume and the start and end times of each breast milk sample will be recorded.