Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

MHICC

STATISTICAL ANALYSIS PLAN

Protocol number: MSP-2017-5001

Multi-Centre, Placebo-Controlled, Phase 2 Study of Etripamil Nasal Spray (NS) for the Reduction of Ventricular Rate in Patients with Atrial Fibrillation (AF)

The ReVeRA-201 Trial

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
ASB	Annotated Study Book
AUC	Area Under the Curve
BP	Blood Pressure
BPM	Beat Per Minute
CMS	Cardiac Monitoring System
DTS	Data Transfer Specifications
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HR	Heart Rate
IA	Interim Analysis
ICF	Informed Consent Form
INR	International Normalized Ratio
ITT	Intent To Treat
IWRS	Interactive Web Randomization System
MHICC	Montreal Health Innovations Coordinating Center
NS	Nasal Spray
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medication
VKA	Vitamin K Antagonists

1 INTRODUCTION

This statistical analysis plan (SAP) presents the statistical methodology that will be used for the final analysis of Milestone Pharmaceuticals Inc. protocol MSP-2017-5001. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. It is based on the protocol Version 6.0 dated 06JUL2022 and on the Annotated Study Book (ASB) version 2.0. In case of differences in terms of descriptions or explanations between the SAP and the clinical protocol, the SAP will supersede the protocol. Any deviation from this SAP would be reported in the statistical report.

2 STUDY DESCRIPTION

2.1 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the effects of etripamil NS in patients with AF. This study includes Screening, the Treatment Period and Follow-up procedures. Each subject will receive Placebo or 70 mg etripamil NS; treatment will be randomized in a

1:1 ratio, to yield approximately 50 evaluable patients with AF (i.e. qualified for Efficacy Population, see section 3.2 for definition) in 2 groups of approximately 25. Screening and treatment procedures will be done at the same visit. Informed consent shall be obtained prior to any study procedures.

Screening Procedures
Patients with AF will be selected by the Investigator. The screening procedures will include a review of inclusion/exclusion criteria and recording of any concomitant medications.

Treatment Procedures
After screening procedures are complete, eligible patients will be randomized to receive etripamil NS or placebo. Heart rate (HR) will be measured via Holter electrocardiogram (ECG) 10 minutes prior to and immediately before drug administration; patients must exhibit a rapid ventricular rate (≥110 beat per minute (bpm) measured during 1 minute) prior to drug administration in order to be dosed.
Blinded study drug will be administered during Holter ECG monitoring, which will be conducted for at least 10 minutes prior to and for 6 hours after administration. Investigators will record adverse events and concomitant medications.
Study drug will be administered by clinical site staff. Patient must be seated for drug administration and should not perform any physical activity within 1-hour post-dose. Patient can be discharged 1 hour after drug administration.

Follow-up Procedures
Patients will undergo a safety follow-up assessment and return the Holter device approximately 24 hours post-dose. The use of telemedicine is encouraged. Patients will also be contacted by phone 7 days post-dosing for safety follow-up.

Following completion of patient participation, the Holter ECG recordings will be blindly reviewed by the Medical Monitor (or designee) to determine whether patients met the criteria for inclusion in the Efficacy Population (see section 3.2 for definition). This information will be recorded in the Interactive Web Randomization System (IWRS), which will allow to determine when enrollment can be completed (i.e. when 50 evaluable patients are confirmed by the Medical Monitor).

2.2 Study Objectives

The primary objective of this study is to demonstrate the superiority of etripamil NS over placebo in reducing ventricular rate in patients with AF.

The secondary objective is to evaluate the safety and efficacy of etripamil NS in patients with AF.

3 DATASETS ANALYZED

Subjects who were not eligible for randomization but who have been erroneously randomized into the study will be excluded from all datasets analyzed if they did not receive study product.

3.1 Modified Intent-To-Treat (mITT) Population

The mITT population will consist of all randomized subjects who receive the study drug (electronic case report form (eCRF) Form “Randomization and Drug Administration” [Date and Time of Randomization =

Not missing] and [Medication administered to the subject = Yes]) and who have a Holter recording post study drug administration (eCRF Form "Holter ECG Monitoring" [ECG data electronically transmitted = Yes]). In the mITT population, subjects allocated to a treatment group by randomization will be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

3.2 Efficacy Population

The efficacy population is all subjects included in the mITT population, excluding patients who were not in AF at time of dosing, who convert to sinus rhythm or with a significant lost ECG signal within 60 minutes post study drug administration. The efficacy population qualification status will be taken from the IWRS database. In the Efficacy population, patients will be analyzed as per treatment assigned by randomization.

3.3 Safety Population

The safety population refers to all randomized patients who receive the study drug (eCRF Form "Randomization and Drug Administration" [Date and Time of Randomization = Not missing] and [Medication administered to the subject = Yes]). Subjects in the Safety population will be analyzed as per actual treatment received.

4 EFFICACY ENDPOINTS

Efficacy variables will be obtained from the Holter recordings measured by a central core laboratory. The procedure and requirements for the delivery of CMS data (Holter ECG) from Global Instrumentation's M12A application to the Montreal Health Innovations Coordinating Center (MHICC), following review by the Milestone Pharmaceuticals Medical Reviewer, are specified in the Data Transfer Specifications (DTS) version 1.0 dated 08JUN2022. In case of conversion to sinus rhythm, only heart rate measurements prior to sinus conversion will be used to derive efficacy variables. If values of HR equal to 0 are recorded during Holter ECG monitoring, these values will be set to missing (unless the patient is dead) prior to variables derivation.

4.1 Primary Efficacy Endpoint

The primary efficacy variable will be the maximum reduction in ventricular rate, measured on Holter monitoring, within 60 minutes from drug administration.

- Baseline ventricular rate is defined as the average heart rate over five minutes immediately prior to drug administration.
- Nadir is defined as the lowest moving average heart rate over five minutes recorded in the primary evaluation period, i.e., 60 minutes post drug administration. The moving averages are 5 minutes' averages of different subsets of the full data set and are calculated by using the "shifting forward" method; that is, excluding the first number of the series and including the next value in the subset. As a general rule, HR measurements outside the primary evaluation period of 60 minutes will be used to calculate the moving averages of the last minutes of this observational period (for example, the 5-minute moving average calculated at minute 58 will

use HR measurements at minutes 58, 59, 60, 61 and 62). For patients with conversion to sinus rhythm, HR measurements starting from the time of conversion will be set to missing and moving average of the last minutes just before the conversion will be calculated on the available non missing values (for example, if sinus conversion occurs at minute 40, the 5-minute moving average at minute 36 will use HR measurements at minutes 36, 37, 38 and 39; the 5-minute moving average at minute 37 will use HR measurements at minutes 37, 38 and 39, etc.). Moving averages calculated on 2, 3 and 10 minutes will be considered for sensitivity analyses on the primary efficacy endpoint (see section 6.4.3 for details) and will be calculated using the same rule. Nadir defined as the lowest value recorded in the primary evaluation period will also be considered for sensitivity analyses on the primary efficacy endpoint.

o Maximum reduction will be calculated as the change between baseline value and nadir.

4.2 Secondary Efficacy Endpoints

The secondary efficacy variables will include:

- Elapsed time from drug administration to nadir
- Percentage of patients achieving ventricular rate of <100 bpm in the 60 minutes post drug administration.
    - Elapsed time from drug administration to ventricular rate < 100 bpm
    - Duration of ventricular rate < 100 bpm in the 60 minutes post drug administration.
      Duration will be set to zero in patients who will not achieve ventricular rate <100 bpm and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients with 10% reduction from baseline ventricular rate in the 60 minutes post drug administration.
    - Elapsed time from drug administration to 10% reduction from baseline ventricular rate
    - Duration of 10% reduction from baseline ventricular rate in the 60 minutes post drug administration.
      Duration will be set to zero in patients who will not achieve 10% reduction and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients with 20% reduction from baseline ventricular rate in the 60 minutes post drug administration.
    - Elapsed time from drug administration to 20% reduction in ventricular rate
    - Duration of 20% reduction from baseline ventricular rate in the 60 minutes post drug administration.
      Duration will be set to zero in patients who will not achieve 20% reduction and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients cardioverting into sinus rhythm (for at least 30 seconds) in the 60 minutes post drug administration
    - Elapsed time from drug administration to cardioversion into sinus rhythm

- Area under the curve (AUC) of heart rate over the 60 minutes and the 360 minutes post drug administration.
- Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9) (see the appendices for the detailed questionnaire and the calculation of the domain scores).

5 SAFETY PARAMETERS

Safety will be assessed through adverse events (AEs) and serious adverse events (SAEs) (eCRF Form "Adverse Events"), physical examination (eCRF Form "Physical Examination"), vital signs measurements (eCRF Form "Vital Signs"), concomitant medications, procedures (eCRF Form "Concomitant Medication" and "Procedures") and ECG findings (eCRF Form "Cardiac Monitoring System Data Review").

5.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically significant abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

During Screening the Investigator or designee will assess all findings from physical exams, vital signs, laboratory assessments, and diagnostic ECGs. Clinically significant findings will be recorded as medical history. Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE.

Events that occur in patients during the Treatment Period while drug is not administered are also considered AEs.

An AE is defined as treatment emergent if the first onset or worsening is within 24 hours after the administration of the study drug.

5.2 Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Result in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
- Is an important medical event

5.3 Adverse Events of Special Interest

Due to the mechanism of action of etripamil, patients could be at a higher risk of certain adverse events of special interest (AESI). Investigators should be on the alert for these events, or for symptoms which indicate an event may be present. Investigators should follow the standard protocol process for AE and SAE reporting for these AESI. Below is a list of AEs which are of particular interest if they occur within 24 hours of study drug administration.

a) Tachyarrhythmias
- i) Supraventricular: occurrence of Atrial Tachycardia or Atrial Flutter lasting longer than 30 seconds
- ii) Ventricular:
  - Non-sustained ventricular tachycardia defined as equal or greater than 3 consecutives wide beats originating in the ventricles at a rate >100 bpm and terminating spontaneously
  - Sustained ventricular tachycardia defined as wide consecutive beats originating in the ventricles at a rate >100 bpm during >30 sec or requiring termination due to hemodynamic compromise in < 30 sec

b) Bradyarrhythmia
- i) Any Sinus rate equal or less than 40 bpm lasting longer than 30 seconds
- ii) Any pause equal or greater than 3 seconds

c) Atrio-Ventricular Block
- i) New onset (not present in the ECG performed at the screening visit) of 1st° AV Block
- ii) Any occurrence of 2nd or 3rd degree AV Block (including AV dissociation or the presence of more than 2 consecutives non-conducted P waves)

d) Syncope and related events
- i) Syncope defined as a transient, self-limited loss of consciousness with an inability to maintain postural tone that is followed by spontaneous recovery.
- ii) Pre-syncope defined as a state consisting of light-headedness, muscular weakness, blurred vision, and feeling faint
- iii) Loss of consciousness defined as a partial or complete loss of consciousness with interruption of awareness of oneself and one's surroundings. When the loss of consciousness is temporary and there is spontaneous recovery, it is referred to as syncope.
- iv) Dizziness defined as a false sense of motion or spinning, light-headedness or feeling faint, unsteadiness or a loss of balance, a feeling of floating, wooziness or heavy headedness. The episode may last seconds or days and may recur.
- v) Drop attack defined as a sudden fall without loss of consciousness
- vi) Hypotension is defined as a SBP

5.4 Other Safety Parameters

Screening vital signs include blood pressure (BP), heart rate, weight, and height. Blood pressure must be monitored and recorded at 10 minutes pre-dose and immediately prior to dosing, to ensure subject eligibility prior to dosing with Systolic BP > 90 mmHg, and must be recorded at 5, 10, 15, 30, and 60 minutes post-dose.

A complete physical examination (excluding breast, genitourinary and rectal examination) will be performed at screening on the following body systems: General Appearance, Eyes, ENT/Mouth, Respiratory, Cardiovascular, Gastrointestinal, Muscular, Skin, Neurological, Endocrine (including

thyroid), Lymph Nodes, Allergy/Immunological, and Psychiatric. A symptom-directed physical examination will be performed after drug administration.

All concomitant medications and treatments used (including over-the-counter medications and herbal supplements) ongoing or started 30 days before the time of signing the ICF will be recorded in the source document and on the appropriate eCRF. Procedures (other than the study-related assessments and procedures) performed from the time of signing the ICF until 7 days post-dose, or until the patient discontinues the study, will be recorded.

Findings from electrocardiographic analysis include occurrence of tachyarrhythmias, atrioventricular blocks and bradyarrhythmias.

6 STATISTICAL METHODOLOGY

6.1 Determination of Sample Size

The primary efficacy variable for this study is the maximal reduction of ventricular rate after study drug administration. Accounting for a two-sided test with a type I error rate of α=0.05, 25 patients per group will provide 93% power to detect a 20 bpm absolute difference in ventricular rate from baseline between active drug and placebo, assuming a standard deviation of 20 bpm.

6.2 Statistical Considerations

Statistical analyses will be performed using SAS Version 9.4 or higher. Unless otherwise specified, all statistical tests will be two-sided and performed at a significance level of 0.05. No adjustment for multiple testing will be done.

Data summaries will be presented using descriptive statistics: N, mean, standard deviation, median, Q1, Q3, minimum and maximum are presented for continuous variables while count and proportion are presented for categorical variables.

Prior to all parametric analyses, basic assumptions will be checked and if they are violated, non parametric analyses will be performed or a logarithmic transformation will be applied on the variables before proceeding to the planned parametric analyses. If outliers are identified, analysis with and without the outliers may be presented.

No missing data will be imputed.

6.2.1 Interim analysis

As requested by the sponsor, two interim analyses (IAs) of the data were done while the study is ongoing (on the first 15 and 36 subjects randomized and dosed). The rationale for performing these IAs has remained, as was stated in prior study documentation, to inform the planning of next studies and the program. These interim looks included the following analyses, conducted on all the subjects included in the snapshot of database at the time of interim and fulfilling the criteria of the efficacy population (unless otherwise specified):

1) Analysis of the primary endpoint, as described in in section 6.4.1 (See shell of Table 14.2.1.1 for layout of the output)

2) Analysis of the following secondary endpoints, as described in section 6.4.2
    a. Elapsed time from drug administration to nadir (Table 14.2.2.1)
    b. Elapsed time from drug administration to ventricular rate < 100 bpm (Table 14.2.4.1)
    c. Duration of ventricular rate < 100 bpm (Table 14.2.5.1)

3) Plots of the mean change from baseline in ventricular rate vs. time (in minutes, from baseline to 60 minutes / 360 minutes) for each treatment group. Specifically, the change from baseline (baseline ventricular rate defined as the average heart rate over five minutes immediately prior to drug administration) was calculated for each minute post drug administration and the mean ± standard deviation (or ± standard error of the mean) at each minute post drug administration were plotted. A listing of these values was also provided. These plots were generated with and without some subjects with outlier values.

4) Number and proportion of subjects experiencing a treatment-emergent serious adverse events, as described in section 6.5.2.2 (Tables 14.3.1.4, 14.3.1.5 and 14.3.1.6; these tables were produced on subjects fulfilling the criteria of the safety population)

The ReVeRa-201 trial is a double-blind study but the analyses for these interim looks required that the blind be broken. At the time of the interim, the study biostatistician received the randomization list from the IWRS provider, generated the above analyses based on the true randomization list, and sent the results to the sponsor, who shared them with selected principal investigators, at its discretion. These individuals are no longer blinded. The purpose of these interim looks is not to disseminate the results at large, but rather to help plan future studies. Importantly, the study is not to be stopped or altered based on the results of these interim looks. In other words, the final and definitive analysis will remain the one that will be conducted when all 50 evaluable subjects have been randomized and followed until study completion.

6.3 Study Subjects

6.3.1 Subject Disposition

Number of subject screened, reason of screen failure, number of enrolled subjects (signing informed consent), number of subjects randomized and reasons why some enrolled subjects were not randomized will be provided. Number of subjects who receive the medication, the route of administration or the reason if not administered will also be provided. In addition, number of subjects completing the study and reasons for discontinuation will be summarized by treatment group.

Information on subject disposition will be listed.

6.3.2 Protocol Deviations

Protocol deviations collected on the eCRF Form “Protocol Deviation” will be listed.

6.3.3 Datasets Analyzed

The number of subjects in each dataset will be summarized overall and by treatment group. Reason for being excluded from a given dataset will be provided as well.

6.3.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics (including atrial fibrillation history and confirmation of AF diagnosis, medical history, vital signs, use of vitamin K antagonists (VKA) and INR result, drug administration) will be compiled for all patients of the mITT population.

Physical examination and details about Holter ECG monitoring (performed/transmitted/devices returned) will be listed.

6.4 Efficacy Analysis

Unless it is specified otherwise, all efficacy analyses will be performed using the Efficacy population.

6.4.1 Primary Analysis

The maximum reduction in ventricular rate will be compared between treatment groups using an analysis of covariance (ANCOVA) adjusting for value of ventricular rate at baseline. Specifically, the null and alternative hypotheses to be tested are:

$$H_0: \Delta_{placebo} = \Delta_{etripamil} \text{ vs.}$$
$$H_A: \Delta_{placebo} \neq \Delta_{etripamil}$$

where $\Delta_{placebo}$ is the maximum reduction in the placebo group and $\Delta_{etripamil}$ is the maximum reduction in the etripamil group. Estimates of treatment effect will be presented with 95% CI and p-values.

6.4.2 Secondary Analysis

The secondary efficacy analyses will be performed on the Efficacy Population, unless otherwise specified.

Group comparison for the following secondary endpoints will be done using the same approach as the primary analysis.

- Elapsed time from drug administration to nadir
- Duration of ventricular rate < 100 bpm in the 60 minutes post drug administration.
- Duration of 10% reduction from baseline ventricular rate in the 60 minutes post drug administration.
- Duration of 20% reduction from baseline ventricular rate in the 60 minutes post drug administration.
- Area under the curve (AUC) of heart rate over the 60 minutes. AUC will be calculated using the trapezoidal rule over the specific Holter recording period for each patient and indexed to a period of 60 minutes.

- AUC of heart rate over 360 minutes post drug administration. AUC will be calculated using the trapezoidal rule over the specific Holter recording period for each patient and indexed to a period of 360 minutes.

For the following four endpoints, group comparison will be done using a chi-square test or a Fisher exact test if more than 20% of cells have expected frequencies < 5.

- Percentage of patients achieving ventricular rate of <100 bpm in the 60 minutes post drug administration.
- Percentage of patients with 10% reduction from baseline ventricular rate in the 60 minutes post drug administration.
- Percentage of patients with 20% reduction from baseline ventricular rate in the 60 minutes post drug administration.
- Percentage of patients cardioverting into sinus rhythm (for at least 30 seconds) in the 60 minutes post drug administration (mITT population only)

Kaplan-Meier method and a Wilcoxon test for censored data will be used to compare the two groups for the following endpoints.

- Elapsed time from drug administration to ventricular rate < 100 bpm
- Elapsed time from drug administration to 10% reduction from baseline ventricular rate
- Elapsed time from drug administration to 20% reduction from baseline ventricular rate
- Elapsed time from drug administration to cardioversion into sinus rhythm (mITT population only)

Mean heart rate over time will be plotted with 95% confidence interval error bars.

Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9), domain scores (the scores of effectiveness, convenience, and global satisfaction domain, ranging from 0 to 100) and the TSQM-9 Question 2 (symptoms), will be analyzed using a t-test or a Mann-Whitney-Wilcoxon test, according to the distribution of the variable (see the appendices for the detailed questionnaire and the calculation of the domain scores).

6.4.3 Sensitivity Analysis

To support the results of the primary endpoint, the primary analysis will also be performed on the mITT population using the same ANCOVA model described in section 6.4.1. The secondary analyses described in section 6.4.2 will also be repeated on the mITT population.

As additional sensitivity analyses, the maximum reduction in ventricular rate (primary endpoint) will be calculated with a nadir based on moving averages calculated on 2, 3 and 10 minutes respectively, and also based on the lowest value of the primary evaluation period. These maximum reductions will then be analyzed on the Efficacy population using the same ANCOVA model described in section 6.4.1.

6.5 Safety Analysis

The safety analyses described in this section will be conducted on the safety population. No formal statistical testing is planned for the safety parameters.

6.5.1 Prior and Concomitant Medications

Concomitant medications will be coded with respect to therapeutic class and preferred term using the WHO drug dictionary (March 2018). Frequency of use of concomitant medications will be presented for the patients of the analysis population by both therapeutic class and preferred term.

Listing of concomitant medications will also be provided.

6.5.2 Adverse Events and Serious Adverse Events

6.5.2.1 Adverse Events

AEs will be coded by system organ class (SOC) and preferred term according to the MedDRA dictionary (version 23.1).

A treatment-emergent AE (TEAE) will be defined as an AE with onset date within 24 hours after study drug administration. In case of a missing AE onset time, the AE will be considered treatment emergent if onset date is equal to study drug administration date.

Number and proportion of subjects experiencing a TEAE will be presented by SOC and preferred term and, in addition, by severity [Mild, Moderate, Severe] and relationship to study medication [Not Related, Related]. For subjects experiencing repeated episodes, only the most severe episode and the episode with the strongest relationship will be reported.

In addition, number and proportion of patients with at least one TEAE, one TEAE related (definitely, probably or possibly) to study drug and one severe AE will be presented.

A listing of all AEs will be provided.

6.5.2.2 Serious Adverse Events

All SAEs will be listed but only treatment-emergent SAEs will be summarized as it will be done for AEs and TEAEs.

6.5.2.3 Adverse Events of Special Interest

A listing of all AESIs will be provided.

6.5.3 Procedures

Procedures will be coded by system organ class (SOC) and preferred term according to the MedDRA dictionary (version 23.1).

A listing of all procedures will be provided.

6.5.4 Other Safety Parameters

Vital signs [BP and HR] at each timepoint (10 minutes pre-dose and immediately prior to dosing for BP and HR; 5, 10, 15, 30, and 60 minutes post-dose for BP only) will be summarized by treatment arm.

As mentioned in section 6.3.4, physical examination results (at baseline and symptom directed after drug administration) will be listed.

Occurrence of tachyarrhythmias, atrioventricular blocks and bradyarrhythmias (findings from electrocardiographic analysis) will be summarized by treatment arm.

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8 APPENDIX 1 TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION (TSQM-9)

The TSQM-9 is a validated and widely-used patient reported outcome (PRO) assessment instrument designed as a general measure of treatment satisfaction with medication across medication types and patients' conditions. The TSQM-9 was chosen for use in ReVeRA-201 as it was considered to be appropriate for evaluating patient assessments associated with the acute, episodic use of a drug such as etripamil for the treatment of PSVT episodes, in contrast to other PROs such as the Short Form 36, which is used as a measure of health-related quality of life and is commonly associated with chronic use medications. Two minor modifications to the TSQM-9 (with approval by IQVIA, the owner of the questionnaire) were implemented by Milestone for use in ReVeRA-201. The term "prevent" was removed from the initial question in the questionnaire, as etripamil is not a preventative therapy, and the instructions were modified to reflect the single use of the medication.

Treatment satisfaction will be analyzed by comparing the score of TSQM for effectiveness, convenience, and global satisfaction domain in the 2 treatment groups.
TSQM scale scores range from 0 to 100 and no computed score should be lower or higher than these limits. Of note, a score can be computed for a domain only if no more than one item is missing from that domain. The calculations specific to each domain are presented in detail below:

Effectiveness:
([(Question 1 + Question 2 + Question 3) − 3] divided by 18) × 100
If one item is missing: ([(Sum(the two completed items) – 2] divided by 12) * 100

Convenience:
([(Question 4 + Question 5 + Question 6) − 3] divided by 18) × 100
If one item is missing: ([(Sum(the two completed items) – 2] divided by 12) * 100

Global satisfaction:
([(Question 7 + Question 8 + Question 9) − 3] divided by 14) × 100
If either Item 7 or 8 is missing ([(Sum(the two completed items)) – 2] divided by 10) * 100
If Item 9 is missing ([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

Treatment Satisfaction Questionnaire for Medication

1. How satisfied or dissatisfied are you with the ability of the medication to treat your condition?
   1. Extremely Dissatisfied
   2. Very Dissatisfied
   3. Dissatisfied
   4. Somewhat Satisfied
   5. Satisfied
   6. Very Satisfied
   7. Extremely Satisfied
2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
   1. Extremely Dissatisfied
   2. Very Dissatisfied
   3. Dissatisfied
   4. Somewhat Satisfied
   5. Satisfied
   6. Very Satisfied
   7. Extremely Satisfied
3. How satisfied or dissatisfied are you with the amount of time it take the medication to start working?
   1. Extremely Dissatisfied
   2. Very Dissatisfied
   3. Dissatisfied
   4. Somewhat Satisfied
   5. Satisfied
   6. Very Satisfied
   7. Extremely Satisfied
4. How easy or difficult is it to use the medication in its current form?
   1. Extremely Difficult
   2. Very Difficult
   3. Difficult
   4. Somewhat Easy
   5. Easy
   6. Very Easy
   7. Extremely Easy
5. How easy or difficult is it to plan when you will use the medication each time?
   1. Extremely Difficult
   2. Very Difficult
   3. Difficult
   4. Somewhat Easy
   5. Easy
   6. Very Easy
   7. Extremely Easy
6. How convenient or inconvenient is it to take the medication as instructed?
   1. Extremely Inconvenient
   2. Very Inconvenient

3. Inconvenient
4. Somewhat Convenient
5. Convenient
6. Very Convenient
7. Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?
   1. Not at All Confident
   2. A Little Confident
   3. Somewhat Confident
   4. Very Confident
   5. Extremely Confident
8. How certain are you that the good things about your medication outweigh the bad things?
   1. Not at All Certain
   2. A Little Certain
   3. Somewhat Certain
   4. Very Certain
   5. Extremely Certain
9. Taking all things into account, how satisfied or dissatisfied are you with this medication?
   1. Extremely Dissatisfied
   2. Very Dissatisfied
   3. Dissatisfied
   4. Somewhat Satisfied
   5. Satisfied
   6. Very Satisfied
   7. Extremely Satisfied