STATISTICAL ANALYSIS PLAN

Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia

Investigational Product:	MSP-2017 (etripamil)
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SIGNATURE PAGE

STUDY TITLE:

Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AV	Atrioventricular
AVNRT	Atrioventricular Nodal Reentry Tachycardia
AVRT	Atrioventricular Reentrant Tachycardia
CMS	Cardiac Monitoring System
DBP	Diastolic Blood Pressure
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EEAC	ECG Events Adjudication Committee
EP	Electrophysiology
HR	Heart Rate
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NS	Nasal Spray
PSVT	Paroxysmal Supraventricular Tachycardia
PT	Preferred Term
PVCs	Premature ventricular contraction
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SOC	System Organ Class
SR	Sinus Rhythm
TEAE	Treatment Emergency Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
VM	Vagal Maneuver

1. INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Milestone NODE-302 study (protocol number MSP-2017-1158). No deviations from this Statistical Analysis Plan are anticipated. However, if any deviations occur, they will be documented in the final clinical study report. No deviation from the primary analyses will be considered.

2. STUDY CHARACTERISTICS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the safety of etripamil nasal spray (NS) 70 mg when self-administered by patients with an episode of PSVT in an outpatient setting (i.e., without medical supervision).

2.1.2 Secondary Objectives

The secondary objective of this study is to evaluate the safety and efficacy of etripamil NS 70 mg for the treatment of multiple episodes of PSVT.

2.2 Study Design

The NODE-302 study is an extension of the NODE-301 Part 1 efficacy study. NODE-302 is a multi-centre, open-label study designed to evaluate the safety of etripamil NS 70 mg when self-administered by patients for spontaneous episodes of PSVT in an outpatient setting. All patients randomized in the NODE-301 Part 1 study and who meet the inclusion and exclusion criteria of the NODE-302 study are eligible for the NODE-302 study.

After each episode of PSVT, patients will have the option to continue in the NODE-302 study and manage subsequent episodes of PSVT with etripamil NS 70 mg if they do not meet any withdrawal criteria.

Each episode of PSVT will be documented by an ambulatory CMS that will be placed on the chest by the patient or caregiver when symptoms begin and will record at least 5 hours of continuous ECG.

This study will be conducted at the same sites as the NODE-301 Part 1 study.

The study will include the following:

Qualification Visit

The Qualification Visit may coincide with the NODE-301 Part 1 Final Study Visit, or it may be conducted at a future time. During the Qualification Visit, the Investigator will review the patient's recent medical status and verify the patient's eligibility for the NODE-302 study.

Treatment Period(s)

Following the Qualification Visit, eligible patients will enter the Treatment Period(s). During the Treatment Period(s), patients will perform a sequence of steps, including etripamil NS 70 mg self-administration when patients identify symptoms of an episode of PSVT. Each patient will have the option to manage up to a maximum of 11 episodes of perceived PSVT with etripamil NS 70 mg in the NODE-302 study. However, each patient will receive only 1 study kit including 1 dose of study drug at a time, and a new study kit will be dispensed at the Follow-up Visit.

Follow-up Visit(s)

Every time the patient self-administers study drug (up to a maximum of 11 doses of etripamil NS 70 mg in the NODE-302 study), the patient will be instructed to return to the site within 7 days after study drug administration for a complete assessment by the Investigator and will receive another study kit including 1 dose of study drug, if the patient does not meet any withdrawal criteria.

Final Study Visit

A complete assessment will be performed by the Investigator.

Early Termination Visit

The Early Termination Visit will occur under the following circumstances: the patient withdraws from the study after taking etripamil NS 70 mg and had a Follow-up Visit, or the patient withdraws from the study and did not take etripamil NS 70 mg. In these cases, the patient should come to the site to return the study kit and the Investigator should close the case with Interactive Response Technology.

2.2.1 Treatment Regimen and Dosage

The dose of etripamil to be evaluated in NODE-302 is 70 mg.

All patients will receive a total of 200 µL of etripamil NS 70 mg (i.e., 100 µL in each nostril via the Aptar Pharma Nasal Spray Bidose System) each time they self-administer study drug.

2.2.2 Drug Randomization

There is no statistical hypothesis in this uncontrolled open-label safety study. Based on the anticipated randomization of 500 patients in the NODE-301 Part 1 study, it is estimated that 300 to 500 patients will be eligible for the NODE-302 study.

3. EFFICACY ASSESSMENTS

Efficacy assessments will be based on the Adjudication Report provided by the ECG Event Adjudication Committee (EEAC) evaluating all ECG data recorded by patients during a symptomatic episode. If the event is related to a confirmed episode of PSVT, the primary endpoint conversion to SR after study drug administration will be adjudicated and the primary variable, the time to conversion, will be adjudicated for the primary efficacy analysis.

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as an adjudicated termination of a positively adjudicated episode of PSVT (atrioventricular nodal reentrant tachycardia [AVNRT] or atrioventricular reentrant tachycardia [AVRT] determination if possible) and conversion to Sinus Rhythm for at least 30 seconds. The primary efficacy endpoint will be evaluated using the time to conversion of an episode of PSVT to SR after study drug administration as the primary efficacy variable.

3.2 Adjudication Process

Each event from each patient who assesses symptoms as being caused by PSVT will be documented with an ambulatory CMS recording.

The cardiac monitoring core laboratory will provide the entire 5-hour ECG captured by the CMS to the Adjudication Committee.

The Adjudication Committee will comprise at least 5 members, all cardiac electrophysiologists (EPs), who are independent from the Sponsor and from Sponsor-related operational activities and the Data and Safety Monitoring Committee (DSMC). The Adjudication Committee will review all data, i.e., the entire 5-hour CMS recording, sent to them by the core laboratory for each study episode.

The EPs will adjudicate the following:

- The presence of PSVT (AVNRT or AVRT determination if possible);

  Note: Non-PSVT episodes, including, but not limited to, sinus tachycardia, atrial tachycardia, atrial fibrillation, and atrial flutter will not be included in the Efficacy analyses for PSVT episodes. Patients who do not have any PSVT episode in the study will not be included in the Efficacy Population.

- Termination of PSVT due to VM if PSVT was present; and
- Termination of PSVT to SR for at least 30 seconds after study drug administration if PSVT was present.

The Adjudication Committee will also adjudicate the time of study drug administration and PSVT termination or time to censoring if termination is not observed or is due to a medical intervention (e.g., use of IV adenosine in a medical care facility).

Further details are provided in the NODE-302 study Adjudication Committee Charter.

4. SAFETY ASSESSMENTS

Safety variables will include clinical AEs, vital signs (blood pressure and HR), laboratory testing (hematology, chemistry, and urinalysis), arrhythmias, and conduction disorders detected on surface ECG or CMS recordings.

During the Treatment Period(s), safety variables will be recorded.

The EEAC report data will include

1) The occurrence of atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds.
2) Non-sustained/unsustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats originating in the ventricles at a rate of >100bpm, terminating spontaneously.
3) Sustained Ventricular Tachycardia >30 sec or requiring termination due to hemodynamic compromise in <30 sec
4) Reoccurence of PSVT defined as a new onset of PSVT after initial conversion to sinus rhythm for at least 30 seconds
5) Any sinus rate equal or less than 40 bpm
6) Type I AV block lasting greater than 30 seconds.
7) Any occurrence of Type II or Type III AV block (including AV dissociation or the presence of more than 2 non-conducted P waves in a row).
8) Any pause equal or greater than 3 seconds.
9) The time of onset and offset of the first occurrence of safety endpoint arrhythmias will be recorded to the nearest second. Any subsequent recurrences will be noted as a comment on the case report form.

4.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

4.2 Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE,

- An event that requires hospitalization or prolongation of existing hospitalizations,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.

4.3 Pregnancy Reporting

Patients are requested to report to the Investigator any pregnancies of themselves or their partner(s) that occur within 30 days of study drug administration. The Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of notification.

4.4 Clinical Laboratory Evaluations

Standard clinical laboratory profiles for hematology, serum chemistry, and urinalysis will be evaluated at the Qualification Visit, the first Follow-up Visit for which the patient took the etripamil NS 70 mg, and at the Final Study Visit if the patient took etripamil NS 70 mg. Urine pregnancy tests will be performed on female patients of childbearing potential at the Qualification Visit and at the Follow up Visit(s). Serum pregnancy tests will be performed by the central laboratory any time blood samples are sent to the central laboratory. See Appendix B for a list of clinical laboratory analytes.

4.5 Vital Signs

Vital signs (i.e., blood pressure and HR) will be obtained at the Qualification Visit, at Follow up Visit(s), and at the Final Study Visit. Vital signs will be obtained after at least a 5-minute rest in a seated position.

4.6 Electrocardiograms

A 12-lead ECG will be performed at the Qualification Visit.

Safety variables will include clinical arrhythmias and conduction disorders detected on surface ECG or CMS recordings.

CMS recordings:

During the Treatment Period, arrhythmias, recurrence of episodes of PSVT, and conduction disorders will be reported from the CMS recording

4.7 Physical Examinations

A physical examination (including height and weight) will be performed at the Qualification Visit and the Final Study Visit.

5. STATISTICAL METHODOLOGY

5.1 Procedures for Handling Missing Data

All observed data will be used in the analyses and unless otherwise specified, missing data will not be imputed besides the partial date missing.

Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month.
- For a missing start day and month where the year is present, the start day and month will be set to January 1st.
- For a missing end day where the month and year are present, the end day will be set to the last day of the month.
- For a missing end day and month where the year is present, the end day and month will be set to December 31st.

Partial and completely missing dates will be imputed for the purposes of classifying concomitant medications as follows:

- Partial dates will be imputed following the same algorithm as above for TEAEs.
- For an entirely missing start date (i.e. day, month, and year are missing), the start date will be set to the date of informed consent signed unless the stop date is prior to the date of informed consent signed, in which case the start date will be set to the stop date.

For an entirely missing stop date (i.e. day, month, and year are missing), the medication will be treated as ongoing.

5.2 Definition of Censoring Data

The censoring rules will apply to the primary efficacy endpoint and all analyses of time to conversion.

For adjudicated episodes of PSVT, the EEAC will indicate at what time-point a patient episode should be censored. Patients who convert to another arrhythmia will be censored at the time of that conversion. Patients who receive medical intervention, or who do not convert within the 5 hour observation period will be censored at the end of the observation period.

For patients without an adjudicated episode (i.e. patients presenting another type of tachycardia or no tachycardia at all), the EEAC will determine the time to termination of this non-qualifying tachycardia and the episode will be censored at end of the observation period. If the tachycardia is not terminated at the end of the recording or if there were no tachycardia observed at all, the episode will be censored at the end of recording.

5.3 Statistical Methods

Summary tabulations will be presented that will display descriptive statistics. For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, minimum, median, and maximum values. For categorical variables, descriptive statistics will include the number and percentage of subjects in each category.

5.4 Analysis Populations

5.4.1 Efficacy Population

The Efficacy Population will include all patients who use etripamil NS 70 mg to treat a positively adjudicated episode of PSVT.

5.4.2 Safety Population

The Safety Population will include all patients who take etripamil NS 70 mg.

5.5 Subject Disposition

The numbers and percentages of subjects will be provided for subject disposition and for each study population.

For subjects who discontinue from the study, the primary reason for discontinuation will be listed and summarized.

5.6 Protocol Deviation

A listing of all protocol deviations will be provided.

5.7 Demographic and Baseline Characteristics

Summary statistics will be provided for demographic characteristics (e.g., age, gender, race, and ethnicity) and for baseline disease variables (e.g., weight, height, body mass index). A listing of all demographic data will be provided.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.0). A listing of all medical history will be provided.

5.8 Prior/Concomitant Medications

All prior and concomitant medications administered during the study will be coded using the Global March 2018 B3 version of the World Health Organization Drug Dictionary. Prior medications include medications that are started and stopped prior to the start date and time of first etripamil NS 70 mg administration. Concomitant medications include medications that start any time and are taken at any time after the start date and time of first etripamil NS 70 mg administration until the end of the follow-up period. Medications missing both start and stop

dates or having a start date prior to the start of etripamil NS 70 mg administration and missing stop date will be counted as concomitant.

The number and percentage of subjects taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred name.

A listing of all medications including the reported term, preferred term, ATC class, start and stop dates, and other relevant data will be provided.

5.9 Study Drug Exposure

Summary statistics will be provided for:

- The number of patients who experience 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 episodes;
- Number of patients who experience 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 positively adjudicated PSVT episodes;
- Number of patients who took a half dose for an episode and percent of episodes a half dose was taken for;
- Average duration on study;
- Average duration from patient enrollment until first, second, and third episode on the study; and
- The estimated number of episodes per year ((365 / Days on Study) * # Episodes)) for all enrolled patients and for patients in the Safety Population.
- The estimated number of positively adjudicated episodes per year for all enrolled patients and for patients in the Efficacy Population.

A listing of all patients taking half doses will be provided.

5.10 Analysis of Efficacy

The primary efficacy analyses will be performed on the Efficacy Population for each patient's first positively adjudicated PSVT episode treated with etripamil NS 70 mg. [For example; if a patient has two non-PSVT episodes, followed by a third episode which is PSVT, the third episode will be used for the primary efficacy analysis]

The primary efficacy variable is the time to conversion of an episode of PSVT to SR (for at least 30 seconds) after etripamil NS 70 mg administration.

5.10.1 Primary Efficacy Analysis

Patients who did not convert after 5 hours following etripamil NS 70 mg administration or who converted following medical assistance will be censored as described under section 5.2.

The Kaplan-Meier estimates of time to conversion will be calculated and reported as a Kaplan-Meier plot. The Kaplan-Meier estimate and confidence intervals of the time at which 25%, 50%, and 75% of an episode of PSVT conversions occur will be calculated.

Sample SAS code:

```
**************************************************************************
Note: STATUS = censored status (1 = censored, 0 = event occurred)
**************************************************************************;
PROC LIFETEST timelist=3 5 10 15 20 30 60 90 120 150 180 210 240 270 300;
      TIME MINUTES*STATUS (1);
      STRATA TREATMENT;
RUN;
```

5.10.2 Secondary efficacy analyses

Individual TSQM-9 questionnaire results (n, mean, median, minimum, maximum, standard deviation) will be summarized by the first treated episode.

Treatment satisfaction will be analyzed by summarized the score of TSQM-9 for effectiveness, convenience, and global satisfaction domain. Please refer to Appendix B for TSQM-9.

TSQM-9 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

Overall 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.

Descriptive statistics of the numbers of episodes of PSVT converted by performing a VM will be reported.

Descriptive statistics of the numbers of positively adjudicated episodes of PSVT converted by performing a VM will be reported.

Descriptive statistics of the number of patients that required healthcare intervention to terminate an episode of PSVT will be reported.

5.10.3 Exploratory Efficacy analyses

To further evaluate the efficacy of etripamil NS 70 mg, the following exploratory analyses will be conducted;

- The effect of first treatment episode, including whether the outcome of the first treatment episode can predict the outcome of future treatment episodes, will be explored via;
    - A logistic regression comparing response on a second episode by response observed during a patient's first episode.
    - Analysis via ANOVA mode of the proportion of episodes a patient responds to treatment compared to total episodes experienced.
    - The primary efficacy analysis will be repeated for patients second positively adjudicated PSVT episode.
    - The primary efficacy analysis will be repeated for patients third positively adjudicated PSVT episode.

- The primary efficacy will be repeated for all PSVT episodes in the study [Patients with multiple events will be counted multiple times]
- The number and percentage of patients who sought medication intervention for an episode will be presented for patients first, second, third, and fourth or more episodes. This analysis will be conducted in the Efficacy Population, and the Safety Population.
- The primary efficacy analysis will be repeated, but with patients who receive medical intervention being censored at the time of conversion to SR after medical intervention.
- The primary efficacy analysis will be repeated for patients >70 years of age, or >60 and <70 years of age on a concomitant medication of beta blocker or calcium channel blockers.

5.11 Analysis of Safety

Safety data will be summarized with descriptive statistics. Continuous safety data will be presented with n, minimum, maximum, median, mean, and standard deviation, whereas discrete safety data will be summarized with frequency counts and percentages. All safety analysis will be performed on the Safety Population.

5.11.1 Adverse Events

Adverse event verbatim text will be coded and classified by system organ class (i.e., body system) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) 21.0.

Summarization of adverse events (AEs) and treatment emergent adverse events (TEAEs) will include subject incidence of the following:

- Any AE,
- Treatment Emergent Adverse Events (TEAEs); defined as AEs with a start date occurring 0 to 24 hours after each study dose,
- TEAEs by maximum severity,

- Drug-related TEAEs,
- Drug-related TEAEs by maximum severity,
- Serious Adverse Events (SAEs),
- Drug-related Serious Adverse Events,
- AEs leading to Death,
- AEs leading to study drug discontinuation,
- Drug-related AEs leading to study drug discontinuation,
- AEs with a start date occurring 0 to 48 hours after each drug self-administration.
- AEs with a start date occurring 0 to 7 days after each drug self-administration.
- TEAEs occurring after a patient first dose
- TEAEs occurring after a patient second dose

Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of etripamil NS 70 mg based on the available date entries. Events with partial onset times which occur on the same day as drug administration day will be considered to occur after drug administration.

An overall summary table will contain the number and percentage of subjects ever having one of the above listed subsets of AEs. Detailed tables of study populations will be presented with relevant Treatment Emergent AEs. AEs will be summarized overall. AEs will be presented by MedDRA system organ class (SOC) and preferred term (PT) with the number and percentage of subjects. If a subject has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term and system organ class in the summary tables. The maximum severity occurrence of a repeat AE, as well as the most extreme relationship of the AE to etripamil NS 70 mg will be used for the analyses. AEs which are listed as possibly, probably, or definitively related will be classified as related, AEs listed as not related or unlikely related will be classified as not related.

AEs related to etripamil NS 70 mg, severe AEs, SAEs, and AEs leading to etripamil NS 70 mg discontinuation will be summarized in the same manner. That is, summaries will be provided for the numbers and percentages of subjects by SOC and PT.

All AEs will be included in by-subject listings. Specific by-subject listings of SAEs and AEs leading to etripamil NS 70 mg discontinuation will be provided. The number of days between treatment drug dose and when the AE occurred will be presented (i.e., relative study day), as will duration of the AE.

5.11.2 Clinical Laboratory Tests

Clinical laboratory results (mean, median, minimum, maximum, standard deviation) will be summarized. The change and percentage change from the qualification visit to follow-up visit and final study visit will be summarized. Incidence of laboratory (<LLN and >ULN) will be summarized. Listings of all clinical laboratory tests will be provided.

5.11.3 Vital Signs

Vital signs results (n, mean, median, minimum, maximum, standard deviation) will be summarized. The changes and percentage of change (n, mean, median, minimum, maximum, standard deviation) in HR, SBP, and DBP will be summarized.

5.11.4 Electrocardiograms and Cardiac Monitoring System recordings

Electrocardiograms results will be summarized.

Moreover, the number of subjects and percentage of subjects with conduction disorders will be reported from the CMS recordings. The number of subjects and percentage of subjects with first-degree AV block will be reported. For those patients with first-degree AV block, the PR interval measured on the CMS recordings will be reported in terms of mean, SD, min, max. These data will also be reported in the pre-identified relevant subgroups of patients (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to alter AV conduction). These data will be reported in the Safety Population.

For episodes after a patient is enrolled, the number of subjects and percentage of subjects with arrhythmias, recurrence of episodes of PSVT, and conduction disorders will be reported from the adjudication of CMS recordings. These data will be reported in the Safety Population when the CMS data is collected but etripamil NS 70 mg was not taken (successful vagal maneuver, or other reason for not taking etripamil NS 70 mg). These data will also be reported in the Safety population by treatment for CMS data which is collected after administration of etripamil NS 70 mg.

The following adjudicated data will be summarized:

1) N (%) of subjects with occurrence of atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds.

2) N (%) of subjects with non-sustained/insustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats originating in the ventricles at a rate of > 100 bpm, terminating spontaneously.

3) N (%) of subjects with Sustained Ventricular Tachycardia e> 30 sec or requirring termination due to hemodynamic compromise in < 30 sec

4) N(%) of subjects with recurrence of PSVT, defined as a new onset of PSVT after initial conversion to SR for at least 30 sec.

4) N (%) of subjects with any sinus rate equal or less than 40 bpm
5) N(%) of subjects with Type I AV block lasting > 30 seconds
6) N (%) of subjects with any occurrence of Type II or III AV block (including AV dissociation or the presence of more than 2 non-conducted P waves in a row).
7) N (%) of subjects with any pause equal or greater than 3 seconds.

5.11.5 Physical Examination

Physical examination data at each evaluation will be listed.

6. INTERIM ANALYSIS

No interim analysis has been planned.

7. SAMPLE SIZE DETERMINATION

There is no statistical hypothesis in this uncontrolled open-label safety study. Based on the anticipated randomization of 500 patients in the NODE-301 Part 1 study, it is estimated that 300 to 500 patients will be eligible for the NODE-302 study. The final number of episodes of PSVT in the NODE-302 study will depend on the frequency and timing of episodes of PSVT during the study.

8. CHANGE FROM PROTOCOL

No Change from Protocol is recorded.

9. PROGRAMMING SPECIFICATIONS

The programming specifications, including the mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents. The programming specification documents will be finalized prior to database lock. All analyses will be conducted using SAS® version 9.4 or higher.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures

Assessment	Qualification Visit[1]	Treatment Period(s)[2]	Follow-up Visit(s)[3]	Final Study Visit[4]	Early Termination Visit[5]
Informed consent	X				
Eligibility	X[6]		X		
Review post-dose AEs from NODE-301 Part 1 study	X				
Contact the Telephone Coach		X[7]			
Recent medical status	X[8]		X	X	
Concomitant medications	X		X	X	
Physical examination[9]	X			X	
Vital signs (blood pressure and heart rate)	X		X	X	
Hematology, chemistry, and urinalysis	X[10]		X[11]	X[12]	
Pregnancy test[13]	X		X	X	
12-lead ECG	X				
AEs		X	X	X	
Dispense study kit[14]	X		X[15]		
Review CMS safety report[16]	X		X	X	
Administer study drug and record time of dosing		X[17]			
Review/have patient complete patient diary entries of scoring scales		X	X	X	
Identify PSVT episode		X			
Apply and start CMS		X[18]			
Perform VM		X			
Evaluate medical intervention during the Treatment Period(s)	X[19]		X	X	
Collect study kit			X[20]	X[21]	X[21]
Identify reason(s) for study completion or withdrawal				X	X
Close case with IRT				X	X
Obtain signed withdrawal form					X

Note: Patients will be asked to sign the NODE-302 informed consent form before commencement of any study-related assessments or procedures, and the signed informed consent form will be applicable for the initial and all subsequent episodes of PSVT.

1. The Qualification Visit of this study may coincide with the NODE-301 Part 1 Final Study Visit or it may be conducted at a future time. Some procedures listed in the NODE-302 Schedule of Procedures Qualification Visit may refer to procedures conducted specifically for the NODE-301 Part 1 study. If the Qualification Visit occurs within 48 hours of the NODE-301 Part 1 Final Study Visit, the results from the NODE-301 Part 1 Final Study Visit procedures may be reviewed and used to confirm other inclusion/exclusion criteria and/or procedures in the NODE-302 Qualification Visit, as applicable. If the Qualification Visit occurs after 48 hours of the NODE-301 Part 1 Final Study Visit, the study procedures performed at the NODE-301 Part 1 Final Study Visit cannot be used and must be repeated. See the MoOP for further details.

2. The Treatment Period will begin immediately following the Qualification Visit. Eligible patients will perform a sequence of steps, including etripamil NS 70 mg self-administration when patients identify symptoms of PSVT.
3. All patients who experience an episode of PSVT and self-administer etripamil NS 70 mg will be instructed to return to the site within 7 days after each episode. Patients may continue to use etripamil NS 70 mg up to a maximum of 11 doses of etripamil NS 70 mg in the NODE-302 study. If the patient used the CMS for an episode of PSVT that subsequently was terminated by a successful VM (i.e., the patient did not use etripamil NS 70 mg), the patient will be instructed to return to the site within 7 days after the episode to ensure that all data has been downloaded from the CMS.
4. A Final Study Visit will occur under different circumstances. A complete assessment will be performed by the Investigator.
5. The Investigator should make every attempt to complete an Early Termination Visit for patients that withdraw or are discontinued from the study.
6. Confirmation of eligibility at the Qualification Visit includes confirmation of PSVT diagnosis. Acceptable source documents to confirm the PSVT diagnosis are provided in the MoOP. Results from the NODE-301 Part 1 Final Study Visit procedures may be reviewed and used to confirm other inclusion/exclusion criteria and/or procedures in the NODE-302 Qualification Visit, as applicable. See the MoOP for further details.
7. If possible, the Telephone Coach will guide the patient through the study procedures. If the patient is unable to reach the Telephone Coach, he/she may proceed with the procedures using the printed and electronic guides.
8. Since the NODE-301 Part 1 study.
9. Include height and weight.
10. Hematology, chemistry, and urine safety tests will be performed for all patients in the NODE-301 Part 1 Final Study Visit and these safety results may be used as baseline for the NODE-302 study if the NODE-302 Qualification Visit occurs within 48 hours of the NODE-301 Part 1 Final Study Visit. However, if the Qualification Visit occurs after 48 hours of the NODE-301 Part 1 Final Study Visit, the hematology, chemistry, and urine tests performed at the NODE-301 Part 1 Final Study Visit cannot be used and must be repeated. Enrollment at the Qualification Visit in the NODE-302 study may proceed without these safety results, but if there is an exclusionary safety laboratory result, upon availability of these results, the patient will be asked to return to the site and be withdrawn from the NODE-302 study.
11. Hematology, chemistry, and urine samples will be collected only at the first Follow-up Visit for which the patient took etripamil NS 70 mg.
12. Hematology, chemistry, and urine safety tests will be performed only if the patient took the etripamil NS 70 mg.
13. For females of childbearing potential only. Urine pregnancy test required at the Qualification Visit and at the Follow-up Visit(s). Serum pregnancy tests will be performed by the central laboratory any time blood samples are sent to the central laboratory.
14. The study kit will include the study drug (etripamil NS 70 mg), a CMS, a study identification card, patient's study instructions, and other study-related material.
15. After the initial study kit is dispensed, patients that decide to continue in the study will receive a new study kit including new study drug (up to a maximum of 11 doses of etripamil NS 70 mg in the NODE-302 study) after each episode of PSVT. Patients may retain the study identification card (if unused, otherwise it will be replaced). The patient will be provided with a new diary (TSQM and relief of symptoms numeric scoring scales). The CMS safety report for the treated episode of PSVT must be reviewed before an additional drug kit is dispensed.
16. The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site. The operational aspects are described in the MoOP. These reports will be sent to the site and the Medical Monitor. The presence of an episode of PSVT and termination will be evaluated by an independent Adjudication Committee. The Adjudication Committee's evaluations will be done using the complete CMS ECG recorded during the patient's PSVT episode.
17. During the Treatment Period(s), etripamil NS 70 mg should only be administered if the VM does not resolve the patient's symptoms. The patient will push the CMS event marker button to record the time of dosing immediately prior to self--administering etripamil NS 70 mg intranasally as instructed. If symptoms of an episode of PSVT have not resolved within 20 minutes after study drug administration, patients should seek appropriate medical care. In all cases, the presence of an episode of PSVT and termination will be reported to the Investigator by the cardiac monitoring core laboratory as well as potential arrhythmia or conduction issues identified on the 5-hour recording.
18. The CMS recording during an episode of PSVT should continue for at least 5 hours regardless of treatment outcome.
19. For the Treatment Period in the NODE-301 Part 1 study.
20. Including used study drug and CMS. The CMS will be checked to ensure that all data was downloaded and transmitted to the core laboratory prior to being given back to the patient.
21. Including used or unused study drug and CMS and study identification card.

AE = adverse event; CMS = Cardiac Monitoring System; CMS safety report = analysis of the ECG tracing by a core laboratory for cardiac safety; ECG = electrocardiogram; IRT = Interactive Response Technology; MoOP = Manual of Operations and Procedures; NS = nasal spray; PSVT = paroxysmal supraventricular tachycardia; TSQM = Treatment Satisfaction Questionnaire for Medication; VM = Vagal Maneuver.

APPENDIX B: TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION

It is essential that the TSQM is administered in the native language of the respondents. Additionally, adequate time must be provided for completion of the TSQM (5-15 minutes). The text of the TSQM should be of sufficient size to allow for easy readability. Please note that any large type version of the TSQM must maintain the standardized content and format of the original instrument, and must be submitted via email to tsqm@Quintiles.com for review and approval. If a respondent cannot read but can respond to the TSQM questions independently, then staff may provide verbatim oral instructions.

The TSQM was developed to be administered in paper format 2-3 weeks after the medication is used. For each item, the respondent is asked to indicate his/her level of satisfaction or dissatisfaction with the medication over the last two to three weeks or since the most recent use by placing a single check mark next to the response that most closely corresponds to his or her own experiences.

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

APPENDIX C: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

- Alanine aminotransferase
- Albumin
- Gamma-glutamyl transferase
- Bicarbonate
- Aspartate aminotransferase
- Calcium
- Urea nitrogen
- Glucose
- Chloride
- Potassium
- Creatinine
- Total bilirubin
- Magnesium
- Direct bilirubin
- Inorganic phosphorus
- Estimated glomerular filtration rate
- Sodium
- Total protein

Hematology

- Hematocrit
- Hemoglobin
- Platelets
- Erythrocyte count
- Leukocyte cell count and differential
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Additional Hematology

- Mean cell volume
- Mean cell hemoglobin concentration
- Mean cell hemoglobin

Urinalysis

- Bilirubin
- Blood
- Glucose
- Ketones
- Leukocyte esterase
- pH
- Nitrite
- Specific gravity
- Protein
- Urobilinogen

Urine and Serum Pregnancy Test (for females of childbearing potential only)

An on-site urine pregnancy test will be performed at the Qualification Visit and at the Follow-up Visit(s). A serum pregnancy test will be performed by the central laboratory any time blood samples are sent to the central laboratory.