STATISTICAL ANALYSIS PLAN

Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia

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SIGNATURE PAGE

STUDY TITLE:

Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of 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
CI	Confidence Interval
CMS	Cardiac Monitoring System
DBP	Diastolic Blood Pressure
DSMC	Data Safety Monitoring Committee
EEAC	ECG Events Adjudication Committee
ECG	Electrocardiogram
eCRF	Electric Case Report Form
EDC	Electronic Data Capture
EP	Electrophysiology
HR	Heart Rate
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MoOP	Manual of Operations and Procedures
NS	Nasal Spray
OR	Odds Ratio
PAC	Premature atrial contraction
PSVT	Paroxysmal Supraventricular Tachycardia
PT	Preferred Term
PVC	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-301 study (protocol number MSP-2017-1138). 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 determine whether etripamil nasal spray (NS) 70 mg self-administered by patients is superior to placebo at terminating episodes of Paroxysmal supraventricular tachycardia (PSVT) in an outpatient setting.

2.1.2 Secondary Objectives

The secondary objective of this study is to evaluate the safety of etripamil NS 70 mg when self-administered by patients without medical supervision.

2.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the safety, hemodynamic, and cardiac conduction effects of a test dose of etripamil NS 70 mg
- To evaluate the safety and efficacy of etripamil NS 70 mg in various subgroups of interest (e.g., concomitant medications).

2.2 Study Design

NODE-301 is a multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etripamil NS 70 mg self-administered by patients who experience an episode of PSVT in an outpatient setting. Each episode will be documented by an ambulatory Cardiac Monitoring System (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 electrocardiogram (ECG).

The study will comprise of 2 parts, Part 1 and Part 2.

Part 1 will consist of patients dosed with the double-blind study drug or discontinued from the study on or before the date of the adjudication of the 150th positively adjudicated PSVT episode. The data from patients in Part 1 will be cleaned and locked, on a per-patient basis, and will be included in pivotal analyses. Pivotal analyses will include primary, secondary, and exploratory efficacy analyses for patients in Part 1 only and safety analyses on all enrolled patients. Data from patients in Part 1 only will be unblinded after data is locked for the pivotal analysis.

Part 2 will consist of patients not included in Part 1, i.e., Part 2 will consist of patients who were not dosed with double-blind study drug or had not discontinued the study before the date of the adjudication of the 150th positively adjudicated PSVT episode or were randomized after this date. The data from patients in Part 2 will be combined with that from Part 1 and will be included in exploratory analyses. Analyses after Part 2 will include safety; and primary, secondary, and exploratory efficacy analyses for Parts 1 and 2 combined. Data from patients in Part 2 will be unblinded only at the end of the study. Part 2 will end when one of the following criteria is met:

- 75% of patients in Part 2 have completed the study (Final Study Visit), or
- Approximately 9 months after the date of the adjudication of the 150th positively adjudicated PSVT episode.

Based on the results of the pivotal analyses from Part 1, the planned statistical analyses and conduct of Part 2 may be amended. However, in no case will the Part 2 dataset be integrated with the Part 1 pivotal dataset for primary efficacy analyses.

See SAP Annex 1 for more details on analyses conducted on the Part 2 dataset.

This study will be conducted at approximately 75 sites.

This is an event-driven study; 46 adjudicated terminations occurring within 5 hours after study drug administration without external interventions are required, approximately 100 randomized patients presenting with a positively adjudicated episode of PSVT and treated with the study drug are required to control the type I error rate at the desired alpha = 0.01. Since the time from enrollment to when patients experience their first positively adjudicated episode of PSVT treated with study drug cannot be predicted, the study is projected to randomize up to 500 patients. The final number of randomized patients and adjudicated episodes of PSVT will depend on the frequency and timing of episodes of PSVT during the study.

The study will include a Screening Visit, a Test Dose Randomization Visit, Follow-up Visits, a Treatment Period, and a Final Study Visit. Please refer to Appendix A for the schedule of procedures.

Screening Visit

Prospective study patients will be asked to sign the informed consent form before the commencement of any study-related assessments or procedures. Once the informed consent is signed, patients will be considered enrolled in the study.

Test Dose Randomization Visit

The initial Test Dose Randomization Visit must occur within 28 days after the Screening Visit. Prior to randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients on the study procedures.

Follow-up Visits

Follow-up Visits will occur approximately monthly from the time of randomization and can be conducted by patients returning to the investigative site (preferred) or by the site personnel contacting patients by telephone.

Treatment Period

All randomized patients will perform a sequence of steps, including study drug self-administration when patients identify symptoms of an episode of PSVT. A caregiver may help the patient with these procedures, and this should be annotated in the electronic case report form.

Final Study Visit

A Final Study Visit will occur at the study site within 7 days after the final Treatment Period day with usage of the study drug, or if for any other reason the patient has completed participation in the study.

2.2.1 Treatment Regimen and Dosage

The dose of etripamil to be evaluated in NODE-301 is 70 mg. The same formulation will be used for the Test Dose Randomization Visit and for the Treatment Period.

The formulation of placebo reproduces the same pH as the etripamil formulation. All patients will receive a total of 200 microL of etripamil NS 70 mg or placebo (i.e., 100 microL in each nostril via the Aptar Pharma Nasal Spray Bidose System).

2.2.2 Drug Randomization

At the Screening Visit, a unique patient identification number will be established for each patient at the investigational site. This patient identification number will be used for patient identification throughout the study and in all study-related documentation.

Prior to randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients for the procedures. The test dose administration will take place at the study site under medical supervision while the patient is in sinus rhythm (SR). Patients who pass the test dose will be randomized in a 2:1 ratio to etripamil NS 70 mg or placebo using IRT. The Investigator or designee must electronically contact the IRT to acquire a treatment assignment for each patient.

This study will be conducted in a double-blind manner and all Sponsor, investigative site, ECG Events Adjudication Committee (EEAC), and Clinical Research Organization (CRO) personnel involved in the study will be blinded to the treatment assignment with the following exceptions:

- Sponsor Clinical Study Supplies Coordinator and personnel directly involved in manufacturing/packaging of the study drug;
- The Data and Safety Monitoring Committee (DSMC) (if unblinded safety data is requested); and
- IRT services personnel.

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.

The patient will report symptoms of the episode of PSVT and treatment satisfaction in the Treatment Satisfaction Questionnaire for Medication (TSQM).

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 Secondary Efficacy Endpoints

The secondary efficacy endpoints will include:

- Relief of specific symptoms (i.e., heart palpitations, rapid pulse feeling, chest pain, anxiety, shortness of breath, dizziness, and fainting) potentially associated with the current episode of PSVT and Rating of TSQM.

3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will include:

- The number of positively adjudicated episodes of PSVT terminated by a VM,
- The percentage of patients requiring additional medical intervention to terminate an episode of PSVT, and
- To repeat of key efficacy endpoints in various subgroup of interest (e.g., concomitant medications).

3.4 Adjudication Process

Each episode 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 ECG captured by the CMS to the EEAC.

The EEAC will comprise at least 5 members, all cardiac electrophysiologists (EPs), who are independent from the Sponsor and from Sponsor-related operational activities and the DSMC. The

EEAC will review all data for each study episode, i.e., the entire CMS recording and the clinically relevant data sent by the medical monitor.

Primary Endpoint

1) Supraventricular tachycardia (SVT) with a narrow QRS rate greater than 100 bpm that excludes sinus tachycardia, atrial fibrillation, atrial flutter, or a lack of a 1:1 AV relationship that may suggest atrial tachycardia.
2) Time of "Drug Taken"- the time to the nearest second that the patient event marker occurs and labeled as "Drug Taken" by the patient as demonstrated on an ECG strip supplied by Preventice (cardiac monitoring core laboratory). If no patient event marker is present, the time of onset of the recording will be used as the time of ''Drug Taken". If multiple event markers are present, the earliest event marker labeled as "Drug Taken" by the patient will be used as the time of "Drug Taken".
3) SVT analysis- AVNRT shall be considered present if no P wave is visible or there is a clear P wave at the terminal portion of the QRS complex. If a P wave occurs later in the ST segment, AVNRT or AVRT can be present at the discretion of the reader, however the reader may choose the option of indeterminate if either AVNRT or AVRT are possible.
4) Time of termination- the time to the nearest second that the arrhythmia terminates, defined as the time of the 1st conducted sinus P wave after termination, but only if sinus rhythm remains the main atrial mechanism for at least 30 seconds beyond this point. If SVT resumes or an alternate atrial mechanism ensues within 30 seconds of the initial sinus P wave, termination is not present, and analysis for termination as defined above occurring later in the recording is required. However, Premature atrial contraction (PAC) or Premature ventricular contraction (PVC) within a primary sinus mechanism do not nullify termination.
5) Vagal maneuver outcome- if PSVT is converted to SR before any patient event marker occurs and Medical Monitor (MM) confirms that no study drug was taken, the VM will be considered successful and the event will be counted in the exploratory endpoint i.e., the number of positively adjudicated episodes of PSVT terminated by a VM.
6) If the patient takes the drug during a period of SR, the episode will not be part of the efficacy dataset (Efficacy Population), if one or several episodes of PSVT are present after drug administration these PSVT will be counted as recurrences.
7) If PSVT is converted to SR before any patient marker occurs, and Medical Monitor (MM) confirms that study drug was taken, the patient will have been considered to have taken study drug while in SR, and the PSVT will not be included in the efficacy population, which is the population used for the primary analysis.

Any subsequent recurrences will be noted as a comment on the adjudication case report form.

The EPs will adjudicate the following:

The presence of:

1) PSVT (AVNRT or AVRT determination if possible)

    Note: Sinus tachycardia, sinus rhythm, atrial tachycardia, atrial fibrillation, and atrial flutter will not be included in the Efficacy Population

2) termination of PSVT to SR for at least 30 seconds after study drug administration if PSVT was present

3) elapsed time between study drug administration and PSVT termination. If termination follows a medical intervention (e.g., use of IV adenosine in a medical care facility) the patient will be censored at the time of conversion. If PSVT is still present 5 hours after study drug administration the patient will be censored at 5 hours.

4) termination of PSVT due to VM without drug administration or before drug administration

Any bias will be limited by the adjudicators being fully blinded to the patient identifiers and study treatment.

Further details are provided in the NODE-301 study ECG Events 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 etripamil test dose period, vital signs (SBP, DBP, HR measurements), arrhythmia, conduction disorders on the ECGs, and clinical AEs will be recorded. These data will be reported in the Overall Safety Population. These safety assessments will be summarized in some or all of the pre-identified relevant subgroups of patients (see Appendix E .e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction) for pre-defined subgroup analyses.

During the Treatment Period, safety variables will be recorded.

The EEAC report data will include

1) The occurrence of sinus tachycardia, atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds.
2) The occurrence of PVCs greater than 6 PVCs/45 seconds.
3) Non-sustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats.
4) Any significant bradycardia, i.e., sinus rate equal or less than 40 bpm
5) Type I AV block lasting greater than 30 sec
6) 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) Any pause equal or greater than 3 seconds.
8) 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 Screening Visit and at the Final Study Visit. Serum pregnancy tests will be performed on female patients of childbearing potential at the Screening Visit and at the Final Study Visit, and a urine pregnancy test will be performed at the Test Dose Randomization Visit. See Appendix C for a list of clinical laboratory analytes.

4.5 Vital Signs

Vital signs (i.e., SBP, DBP, and HR) will be obtained at the Screening Visit, at the Test Dose Randomization Visit, and at the Final Study Visit. At the Test Dose Randomization Visit, vital signs will be obtained after at least a 5-minute rest in a seated position and immediately before test dose administration. Following etripamil administration, vital signs will be obtained every 5 minutes for 30 minutes. Vital signs will also be obtained if the patient reports any symptom potentially related to drop in blood pressure.

4.6 Electrocardiograms

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

Electrocardiograms
A 12-lead ECG will be performed at the Test Dose Randomization Visit within 10 minutes pre-test dose and 30 minutes post-test dose. PR interval and abnormal results will be reported by the PI in the CRF.

At the Final Study Visit a 12-lead ECG will be performed and any new anomaly will be reported by the PI.

CMS recordings:
During the etripamil test dose, conduction disorders will be reported from the CMS recording. In case of first-degree AV block, the PR interval measured on the CMS recordings, will be reported.

During the Treatment Period, arrhythmias, recurrence of episodes of PSVT, and conduction disorders will be reported from the CMS recording. The adjudication committee will report the following safety endpoints;

1) The occurrence of atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds.
2) The occurrence of PVCs greater than 6 PVCs/45 seconds.
3) Non-sustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats.
4) Any significant bradycardia, i.e., sinus rate equal or less than 40 bpm
5) Type I AV block lasting greater than 30 sec
6) 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) Any pause equal or greater than 3 seconds.
The time of onset and offset of the first occurrence of safety endpoint arrhythmias will be recorded to the nearest second.

4.7 Physical Examinations

A physical examination will be performed at the Screening Visit and at the Final Study Visit. Body height and weight will be measured at the Screening Visit.

5. STATISTICAL METHODOLOGY

The statistical analysis will comprise of 2 round of analysis, pivotal analysis and exploratory analysis.

Pivotal analysis will be conducted when the 150th positively adjudicated PSVT episode take place. Only patients with the double-blind study drug or have discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode will be included in the primary, secondary and exploratory efficacy analysis. Safety, disposition, and demographic data will be presented for all enrolled patients.

Exploratory analysis will be conducted when the study is finished. Data from all enrolled patients will be included in this round of analysis.

Based on the results of the pivotal analysis from Part 1, the exploratory analysis may be amended. However, in no case will the Part 2 dataset be integrated with the Part 1 pivotal dataset for primary efficacy or primary safety analysis.

5.1 Procedures for Handling Missing Data

All observed data will be used in the analyses and missing data will not be imputed.

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.

For adjudicated episodes of PSVT, the EEAC will indicate at what time-point a patient episode should be censored. This should correspond to the time of first conducted p wave starting a 30-second of SR after any medical intervention (e.g., use of IV adenosine in a medical care facility) or to the last available recorded time, at 5 hours if the PSVT is not terminated at 5 hours

For patients without an adjudicated episode (i.e., patients presenting another type of tachycardia or no arrhythmia), the EEAC will determine the time to termination of this non-qualifying tachycardia and the episode will be censored at this time. 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 Control of type 1 error

All statistical analyses will be tested at nominal alpha of 0.01, unless specified otherwise.

For label claim, in order to control the overall type 1 error to no more than 0.01, a gatekeeper strategy will be used as proposed below:

1. Test the primary efficacy endpoint of time to conversion in the Efficacy Population at alpha of 0.01.

   If statistically significant:

2. Test the secondary efficacy endpoints TSQM Overall Satisfaction, Effectiveness and Convenience Scores in the Efficacy population at alpha of 0.01 using Holm's approach.

   For Holm's adjustment, the p-values are first ordered from the smallest to the largest. Suppose that p(1) represents the smallest p-value, p(2) the next-smallest p-value, p(3) the third-smallest p-value. The test begins by comparing the smallest p-value, p(1) to 0.01/3. If this p(1) is less than 0.0033, the treatment effect for the endpoint associated with this p-value is considered significant. The test then compares the next-smallest p-value, p(2) to an endpoint-specific alpha of 0.01/2 for the second smallest p-value. If $p(2) < 0.01$, then the treatment effect for the endpoint associated with this p(2) is also considered significant. The test then compares the next ordered p-value, p(3) to 0.01.

   The procedure stops, whenever a step yields a non-significant result. Once an ordered p-value is not significant, the remaining larger p-values are not evaluated, and it cannot be concluded that a treatment effect is shown for those remaining comparisons.

5.4 Statistical Methods

Summary tabulations will be presented that will display descriptive statistics for each treatment group. 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.

5.5 Analysis Populations

5.5.1 Efficacy Population

The Efficacy Population includes all randomized patients who use the study drug to treat a positively adjudicated episode of PSVT. This population does not include patients who take the study drug for a negatively adjudicated episode of PSVT (i.e., symptoms not associated with an episode of PSVT, or PSVT episodes that resolve prior to taking study drug). The subjects will be included in the treatment arm in which they were randomized.

5.5.2 Modified intent-to-treat (mITT) Population

The mITT Population includes all randomized patients who take the randomized study drug,. The subjects will be included in the treatment arm in which they were randomized.

5.5.3 Test Dose Only Population

The Test Dose Only (TD) Population includes all patients who receive a Test Dose but do not self-administer double blind randomized drug (Overall safety population, minus the safety population).

5.5.4 Safety Population

The Safety Population includes all randomized patients who take the randomized study drug. The subjects will be included in the treatment arm according to actual received treatment.

5.5.5 Overall Safety Population

The Overall Safety Population includes all patients who take any study drug i.e., the Safety Population and the Test Dose Only Population combined.

5.6 Subject Disposition

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

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

For TD patients who do not proceed to randomization, the primary reason for discontinuation will be listed.

5.7 Protocol Deviation

Protocol deviations are specified in the protocol deviation plan. A listing of all protocol deviations will be provided.

5.8 Demographic and Baseline Characteristics

Summary statistics will be provided by treatment group for demographic characteristics (e.g., age, gender, race, and ethnicity) and for baseline disease variables (e.g., age at confirmation of PSVT, demonstrated history of sustained PSVT, number of PSVT in the past year, number of visits to emergency department in life time, and past disease or surgery). A listing of all demographic data will be provided. Summary statistics for demographic of special interest will be provided. Please refer to Appendix E for special interest subgroup.

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

5.9 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 the test dose. Concomitant medications include medications that start any time and are taken at any time after the start date and time of the test dose 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 test study drug 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 by treatment group.

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

5.10 Study Drug Administration

eCRF data detailing the administration of the test dose and the administration of the study drug (etripamil or placebo) to randomized patients will be listed. If the study drug device is not fully deployed, half dose will be reported.

5.11 Analysis of Efficacy

The primary and secondary efficacy analyses will be performed on the Efficacy Population. Additional sensitivity efficacy analyses and exploratory efficacy analyses will be performed on the mITT Population .

The primary efficacy variable is the time to conversion of an episode of PSVT to SR after study drug administration.

5.11.1 Primary Efficacy Analysis

For the primary efficacy endpoint analyses, the proportional hazards assumption will be tested. first by examining plots of complementary log-log (event times) versus log (time). If the proportional hazard assumption remains valid the statistical analysis for the time to conversion will be performed using the log-rank test. If the proportional hazard assumption raises concerns, the statistical analysis for time to conversion will be performed using the Peto-Peto test. Patients who did not convert after 5 hours following study drug administration or who converted following medical intervention will be censored as described under section 5.2. The hazard ratio and 95% confidence interval (CI) will be calculated using the Cox proportional hazards model. If non-proportional hazards are observed, a stratified Cox regression model or an extended Cox regression model will be used, as appropriate.

In addition to the primary analysis of the primary endpoint, Kaplan Meier estimates of time to conversion will be calculated and reported as a Kaplan Meier plot. Conversion rates at 3, 5, 10, 15, 20, 30, 60, and every 30 minutes thereafter through 300 minutes after study drug administration will be reported for the etripamil group and the placebo group. The odds ratio (OR), and the CI for the OR, will be calculated, and descriptive statistics presented. The Kaplan-Meier estimate of the time at which 25%, 50%, and 75% of adjudicated episodes of PSVT conversions occur will be calculated.

Sample SAS code:

```
**************************************************************************
Note: STATUS = censored status (1 = censored, 0 = event occurred)
TREATMENT = treatment group (0 = Placebo, 1=MSP-2017 70 mg)
**************************************************************************;
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;
PROC PHREG;
      CLASS TREATMENT;
      MODEL TIME*STATUS (1) = TREATMENT;
RUN;
PROC FREQ;
      TABLES TIME * TREATMENT;
      EXACT OR;
RUN;
```

5.11.1.1. Sensitivity analysis

A sensitivity analysis for the primary efficacy endpoint of time to conversion will be performed including all patients in the mITT Population, i.e., all patients with ‘misidentification of PSVT by the patient” as well as the patients who had an adjudicated PSVT who took the study drug.

An additional sensitivity analysis for the primary efficacy endpoint of time to conversion will be performed on patient subgroups identified in Appendix E. For each one of the variable identifying the subgroups (for example, Country, Sex, Age groups, etc.), a Cox model with each subgroup variable as factor, treatment and the interaction subgroup-by-treatment will be performed to evaluate the impact of each subgroup on efficacy. Hazard ratio and 95% CI will be presented within each subgroup in summary tables as well as in Forest plots.

Censoring rules as described in section 5.2 will be followed.

5.11.2 Secondary Efficacy Analysis

For the secondary efficacy endpoint analysis, collection of specific symptoms (i.e., heart palpitations, rapid pulse feeling, chest pain, anxiety, shortness of breath, dizziness, and fainting) associated with the termination of an episode of PSVT by the study drug will be summarized by treatment group.

The second question from TSQM will be used for the analysis of relief of specific symptoms which are collected for an episode. Specific symptoms are collected as a Yes/No answer for a patient episode in the eCRF, these symptoms include Rapid Pulse, Palpitations, Shortness of Breath, Chest Tightness, Feeling Dizzy or Lightheaded, Fainting or Passing Out, and Anxiety. The effect of etripamil on each symptom will be analyzed by taking the score on TSQM question 2 "How Satisfied are you with the way the medication relieves your symptoms", and comparing the average score between treatment groups ONLY for patients who checked "Yes" for whether the symptom was present.

Treatment satisfaction will be analyzed by comparing the score of TSQM for effectiveness, convenience, and global satisfaction domain in the 2 treatment groups. Please refer to Appendix B for TSQM.

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

The Effectiveness, Convenience and Global satisfaction scores, and the TSQM question 2 for patients with specific symptoms will be analyzed using an ANOVA model. In the ANOVA model, the scores will be the dependent variable and treatment will be factor. The least square means, 95% confidence intervals and p-value will be presented.

Sample SAS code:

```
PROC MIXED;
      CLASS TREATMENT;
      MODEL SCORE = TREATMENT;
      LSMEANS TREATMENT;
RUN;
```

5.11.3 Exploratory Efficacy Analysis

Exploratory efficacy endpoint analysis includes descriptive statistics of the number of patients who received any concomitant procedures, and the number of patients with PSVT terminated by additional medical intervention. These descriptive statistics will be presented by treatment group. Descriptive statistics of the number of positively adjudicated episodes of PSVT converted by performing a VM will be provided. Specifically, the number of patients and episodes with VM performed, and the number of patients and episodes with a successful VM.

5.12 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, the TD Population or the Overall Safety Population, as appropriate (i.e. specified in the specifications programming document).

5.12.1 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 test dose and prior to randomized study drug dose or with a start date occurring 0 to 24 hours after randomized study drug dose,
- AEs by maximum severity,
- Drug-related AEs,
- Drug-related AEs 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,
- Test-Dose Emergent AEs (TDEAE); defined as AEs with a start date occurring 0 to 24 hours after test dose, and prior to randomized study drug dose,
- Randomized-Treatment Emergent AEs (RTEAE): defined as AEs with a start date occurring 0 to 24 hours after randomized out patient drug administration.

- AEs with a start date occurring 0 to 48 hours after randomized out patient drug administration.
- AEs with a start date occurring 0 to 7 days after randomized out patient drug administration.

Adverse events (AEs) are defined as those AEs with onset after the first dose of test study drug or existing events that worsened after the first test study drug dose during the study. 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 study drug based on the available date entries. Events with partial onset times which occur on the same day as a test dose or 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 Test-Dose Emergent or Randomized-Treatment Emergent AEs. AEs will be summarized overall (both treatment groups combined) and where relevant for each treatment group. 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 AEas well as the relationship of the AE to the study drug 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 study drug, severe AEs, SAEs, and AEs leading to study drug 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 study drug discontinuation will be provided. The number of days between test dose or randomized-treatment drug dose and when the AE occurred will be presented (i.e., relative study day), as will duration of the AE.

5.12.2 Clinical Laboratory Tests

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

5.12.3 Vital Signs

Vital signs results (n, mean, median, minimum, maximum, standard deviation, median,) will be summarized by visit and treatment. and visit. The changes and percentage of change (n, mean, median, minimum, maximum, standard deviation) in HR, SBP, and DBP from pre-test dose to 5, 10, 15, 20, 25, and 30 minutes post-test dose will be summarized.

5.12.4 Electrocardiograms and Cardiac Monitoring System recordings

Electrocardiograms results will be summarized by visit and treatment. The change in PR interval (mean, median, min, max, SD) from 10 minutes pre-test dose to 30 minutes post-test dose will be summarized. A listing of all ECG results will be provided.

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 Overall Safety Population.

For episodes after a patient is randomized, 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 Overall Safety Population when the CMS data is collected but study drug was not taken (successful vagal maneuver, or other reason for not taking study drug). These data will also be reported in the Safety population by treatment for CMS data which is collected after administration of study drug.

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 occurrence of PVCs greater than 6 PVCs/45 seconds.
3) N (%) of subjects with non-sustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats.
4) N (%) of subjects with any sinus rate equal or less than 40 bpm and Type I AV block greater than 30 seconds.
5) 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).
6) N (%) of subjects with any pause equal or greater than 3 seconds.

5.12.5 Physical Examination

Physical examination data at each evaluation will be listed.

6. INTERIM ANALYSIS

No interim analysis has been planned.

7. SAMPLE SIZE DETERMINATION

It is assumed that 30% of the episodes of PSVT will be converted to SR in the placebo group and 70% in the etripamil group at 10 minutes. Based on these numbers and assuming exponential survival curves, a hazard ratio of 3.38 is estimated. This represents a difference in median times to conversion of 13.6 minutes (median time to conversion of 5.8 minutes and 19.4 minutes in the etripamil and placebo group, respectively). These assumptions are based on results obtained in the NODE-1 study (MSP-2017-1109).

Assuming a type I error rate of alpha = 0.01 and a 2:1 ratio in the number of positively adjudicated episodes of PSVT etripamil:placebo, a minimum of 46 positive conversion events would be required in order to attain 90% power on the primary variable of time to conversion (using a 2-sided log-rank test).

However, since patients will be randomized before they have a qualifying episode of PSVT, it is

unlikely that the 2:1 etripamil:placebo PSVT episodes ratio will match the 2:1 randomization ratio. In such a case, it is preferable to target a higher sample size to cover for the worst-case scenarios in terms of unbalance.

A total of 150 positively adjudicated PSVT episodes will ensure at least 90% power for extreme cases of unbalance in the etripamil:placebo PSVT episodes ratio.

Only episodes of positively adjudicated PSVT that occur by the date of the adjudication of the 150th episode of true PSVT will be included in the primary efficacy analysis.

It is anticipated that as many as 500 patients may need to be randomized in order to accrue a sufficient number of patients in the Efficacy Population within 18 months.

8. CHANGE FROM PROTOCOL

The definition of Test Dose Only Population has been further specified in the SAP. Also in the SAP and tables, the Test Dose Population will be referred to as the 'Test Dose Only Population'.

In the protocol it states 'The Test Dose Population includes all patients who receive the test dose of etripamil NS 70 mg. The Test Dose Population will also include pre-identified relevant subgroups of patients (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction) for pre-defined subgroup analyses.'

The intention was for this to be the population of patients who receive the Test Dose Only (no randomized drug). As written, the protocol could be interpreted as the TD population being the same as the Overall Safety Population. For further specificity, the SAP defines the TD population as 'The Test Dose Only (TD) Population includes all patients who receive a Test Dose but do not receive randomized drug (Overall safety population, minus the safety population).' Furthermore, subgroup analyses are being conducted on selected safety and efficacy endpoints in multiple populations, as most appropriate to the tested endpoint, not in the Test Dose Only population.

The protocol states that for secondary efficacy analyses, relief of specific symptoms associated with the termination of an episode of PSVT by the study drug will be analyzed by comparing the numeric scoring scale scores in the 2 treatment groups, and treatment satisfaction will be analyzed by comparing the rating of the TSQM in the 2 treatment groups. Additional clarification on this analysis was added to the SAP in Section 5.11.2.

In this protocol the timing of an AE is important to clinical relevance, due to the acute nature of the indication and the study treatment. In order to make safety tables more informative, and to avoid comparing data from fundamentally different patient populations (those in sinus rhythm during a test dose, and those in PSVT or possible PSVT during an episode) tables will often present Test-Dose Emergent AEs (those occurring within 0 to 24 hours post Test Dose, and before a randomized study drug administration), and Randomized-Treatment Emergent AEs (those occurring within 0 to 24 hours post randomized study drug treatment) rather than all AEs. Summaries of all AEs regardless of timing will be included in the tables for reference.

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	Screening Visit	Test Dose Randomization Visit[1]	Follow-up Visit[2]	Treatment Period[3]	Final Study Visit[4]
Informed consent	X				
Eligibility	X[5]	X[6]	X[7]		
Contact the Telephone Coach				X[8]	
Demographics/medical history	X				
Concomitant medications	X	X	X		X
Physical examination	X[9]				X
Vital signs (blood pressure and heart rate)	X	X[10]			X
Hematology, chemistry, and urinalysis	X				X[11]
Pregnancy test[12]	X	X			X
12-lead ECG[13]	X	X			X[14]
Test dose administration[15]		X			
Patient training on PSVT episode assessments[16]		X	X		
Randomization (via IRT)		X			
AEs		X	X	X	X
Dispense study kit[17]		X			
Ensure all CMS data was downloaded and send to cardiac monitoring core laboratory		X	X		X[18]
Review the CMS report[19]		X			X
Identify PSVT episode				X	
Apply and start CMS		X		X[20]	
Perform VM		X		X	
Administer study drug and record time of dosing				X[21]	
Complete patient paper diary and numeric scoring scale				X	
Evaluate medical intervention during the Treatment Period					X
Collect study kit (used and unused)					X
Identify reason(s) for study completion or withdrawal					X
Close case with IRT					X
Assess eligibility for open-label extension study					X

1. The Test Dose Randomization Visit must occur within 28 days after the Screening Visit. The CMS identifier number will be recorded in the EDC system for the test dose. A re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period).
2. Follow-up Visits to occur approximately monthly via site visit (preferred) or telephone (site visit required for patients who have an episode of PSVT terminated by VM).
3. Treatment Period occurs from randomization until patient has an episode of PSVT treated with study drug.
4. Final Study Visit to occur within 7 days after the final Treatment Period day for patients who fail the test dose or have an episode of PSVT treated with study drug. For patients who failed the test dose, the reason for failure will be identified

(predefined list is in the MoOP), the patient's medical status will be evaluated before discharge, the CMS ECG summary report will be reviewed, and the case will be closed with IRT. For all other patients, the reason for study completion will be identified, the patient's medical status will be evaluated, the patient paper diary entries of scoring scales will be reviewed, and the case will be closed with IRT.

5. Confirmation of eligibility at Screening includes confirmation of PSVT diagnosis. Acceptable source documents to confirm the PSVT diagnosis are provided in the MoOP.
6. Additional eligibility criteria apply to pass the test dose at the Test Dose Randomization Visit only.
7. Eligibility assessments at Follow-up Visits based on review of patient's concomitant medications or changes in health status.
8. 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.
9. Including height and weight.
10. Vital signs will be obtained pre-test dose and every 5 minutes for 30 minutes post-test dose.
11. Blood and urine tests will be performed on all patients who pass the test dose and are randomized.
12. For females of childbearing potential. Serum pregnancy test required at the Screening Visit and at the Final Study Visit, and a urine test required at the Test Dose Randomization Visit.
13. The paper speed for these recordings should be 25 mm/sec. A continuous on-screen monitoring ECG will remain until the end of the test for the Test Dose Randomization Visit.
14. A 12-lead ECG will be performed on all patients who pass the test dose and are randomized.
15. Before randomization, all patients will be trained on VMs and will receive a test dose of etripamil NS 70 mg to evaluate tolerability. The test dose procedures are described in the MoOP. Patients who pass the test dose will be randomized. If the patient fails the first test dose and the Investigator can identify a potential reversible cause for the failure, a second test dose may be administered within a 14-day window from the initial test dose. If the Investigator cannot identify a reversible cause, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Population. During each patient's Test Dose Randomization Visit, the test dose CMS ECG data will be reviewed by the cardiac monitoring core laboratory and a report will be sent to the site. The operational aspects of the use of the CMS during the test dose are described in the MoOP.
16. Randomized patients will be trained on how to identify and report symptoms, use of the Telephone Coach, set up and use of the CMS, performance of VMs, self-administration of study drug (as described in the MoOP), recording time of study drug administration, use of paper diary, and reporting AEs to the sites during the study for evaluation. A caregiver may assist in these procedures.
17. The study kit will include the blinded study drug (placebo or etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material.
18. Only if patients took the study drug in the NODE-301 study.
19. The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site in a report based on the mobile system's proprietary arrhythmia detection algorithms and automatic ECG collection. During each patient's Test Dose Randomization Visit, the cardiac monitoring core laboratory will generate a summary report of the patient's ECG data that will state whether or not any protocol-defined ECG test failure criteria were met. This report is expected to be made available within 1 to 2 hours of the receipt of ECG data and will be used by the site to determine if patients pass or fail the test dose and eligibility for randomization. During the Treatment Period, the cardiac monitoring core laboratory will generate a summary report within 48 hours of the receipt of ECG data. The operational aspects are described in the MoOP. These reports will be sent to the site, the Medical Monitor, and the Sponsor.
20. The CMS recording during an episode of PSVT should continue for at least 5 hours, regardless of treatment outcome.
21. During the Treatment Period, study drug should only be administered if the VM does not resolve the patient's symptoms. If symptoms of the PSVT episode have not resolved within 20 minutes after study drug administration, patients may seek appropriate medical care.

AE = adverse event; CMS = Cardiac Monitoring System; ECG = electrocardiogram; EDC = electronic data capture; IRT = Interactive Response Technology; MoOP = manual of operations and procedures; NS = nasal spray; PSVT = paroxysmal supraventricular tachycardia; VM = vagal maneuver.

APPENDIX B: 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

APPENDIX C: PSVT SYMPTOMS RECORDS IN ECRF

List of available PSVT symptoms:

- Repaid pulse
- Palpitations
- Shortness of breath
- Chest tightness, pain or pressure
- Feeling dizzy or lightheaded
- Fainting or passing out
- Anxiety

APPENDIX D: 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)

APPENDIX E: SUBGROUPS OF INTEREST

1. US, Canada, Other.
2. Male, female
3. Patients ≥70 years old, Patients ≥70 years old with concomitant cardiovascular treatment (agent or treatment identified as for a cardiovascular indication; i.e. PSVT prophylaxis, anti-hypertensive, or other cardiovascular treatments), Patients ≥60 and < 70 years old receiving concomitant cardiovascular treatment.
4. Patients currently receiving any of the following classes of concomitant medication regardless of indication: Beta-blockers, Calcium channel blockers.
5. Patient receiving any concomitant medication indicated for antihypertensive treatment: Monotherapy, Bi-therapy, Triple therapy or more, Dihydropyridine calcium channel blocker (e.g., amlodipine), Beta-blocker.
6. Type of PSVT: AVNRT, AVRT, Unknown.