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

Investigational Product:	MSP-2017 (etripamil)
Protocol Number:	MSP-2017-1138 (NODE-301)
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Confidentiality Statement

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. The RAPID Study (NODE-301 Part 2)

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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
BDS	Aptar Pharma Nasal Spray Bidose System
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
mITT	Modified Intent To Treat
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 complex
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
SR	Sinus Rhythm
TEAE	Treatment Emergency Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	An abbreviated TSQM based on 9 items
TTC	Time to Conversion
ULN	Upper Limit of Normal
VM	Vagal Maneuver

1. INTRODUCTION

This statistical analysis plan (SAP) is based on Milestone Pharmaceutical's "RAPID Study" that is Part 2 of NODE-301, Protocol Number MSP-2017-1138, Version 8, dated 14 January 2022.

This document provides details on statistical analysis methodologies to be used to analyze the efficacy and safety data from Part 2 of the NODE-301 study, including definitions for study populations, the rules to derive variables such as censoring variables and rules to handle missing data, as well as details on analysis models and methods to be used. It should be noted that this SAP is prepared specifically for Part 2 of the NODE-301 study (referred to as the RAPID study). A separate SAP for Part 1 of NODE-301 was developed and executed prior to the unblinding of that dataset.

This document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be completed, approved by the Sponsor, submitted to regulatory agencies as applicable, and placed on file before the database is locked and treatment codes are unblinded. The approved plan will be used to carry out all analyses for the clinical study report. Deviations, if any, from the approved plan will be noted in the clinical study report.

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) self-administered by patients is superior to placebo at terminating episodes of paroxysmal supraventricular tachycardia (PSVT) in a at-home setting.

2.1.2 Secondary Objectives

The secondary objective of this study is to evaluate the safety of etripamil NS 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,
- To evaluate the safety and efficacy of etripamil NS in various subgroups of interest (e.g., concomitant medications), and
- To evaluate the safety and efficacy of a treatment regimen of etripamil NS which allows a repeat dose of etripamil NS to terminate episodes of PSVT in an at-home setting.

2.2 Study Design

NODE-301 is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etripamil NS self-administered by patients who experience an episode of PSVT in an at-home setting. Each episode 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. Each CMS will be identified by a unique number.

The NODE-301 study will comprise of 2 parts, Part 1 and Part 2. This SAP will pertain to Part 2 of the NODE-301 study (the RAPID study).

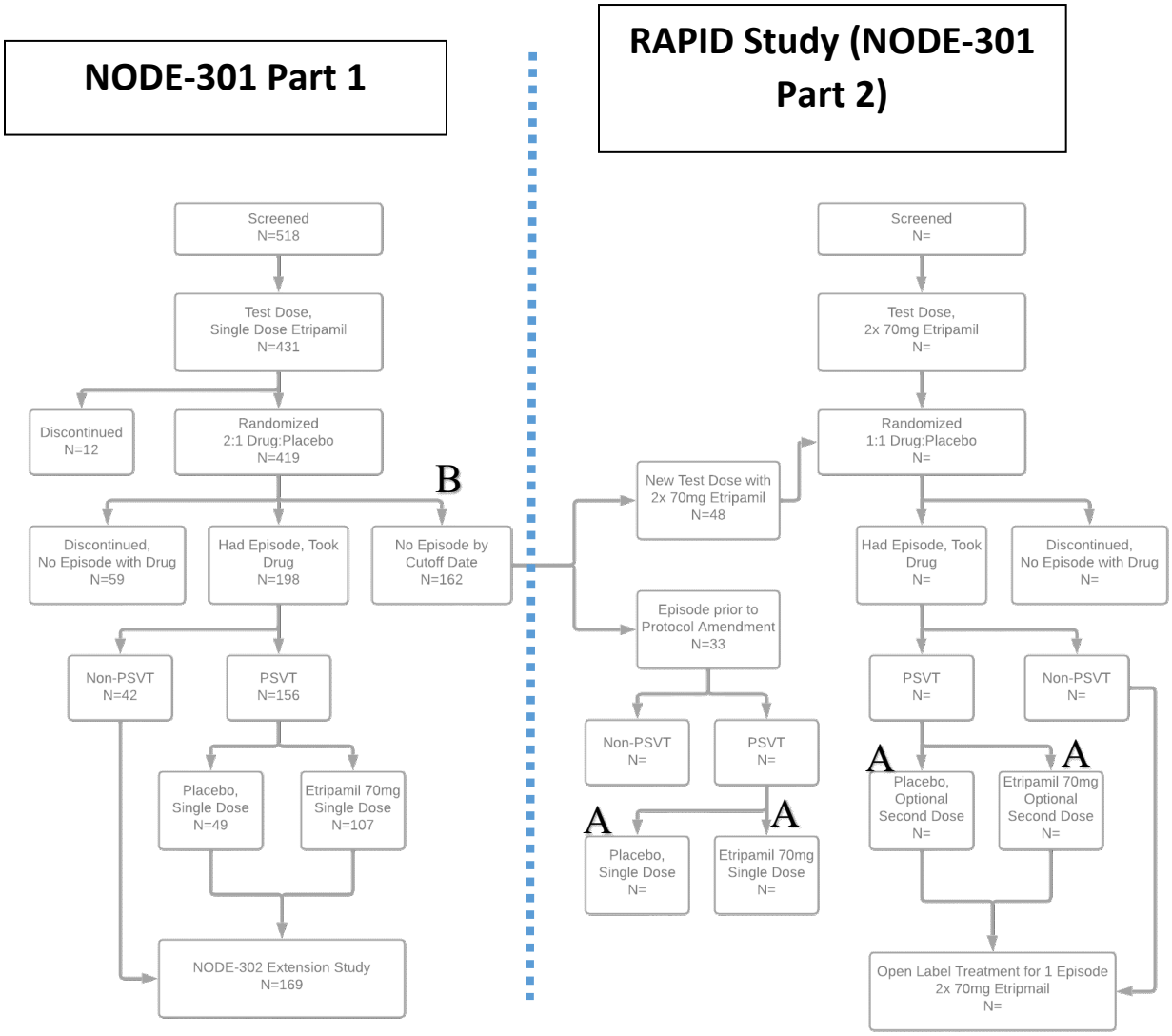
RAPID (NODE-301 Part 2) will consist of:

- New patients enrolled following protocol version 6.0 (and subsequent versions) implementation
- Patients enrolled prior to protocol version 6.0 implementation and who were not dosed with the double-blind study drug, or had not discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode in Part 1.

The RAPID study will test the treatment effect of etripamil (a dosing regimen of either single dose or second dose, if symptoms persist after 10 minutes), in a population of patients having a perceived episode of PSVT in an at-home setting, as measured by time to conversion.

Enrollment into RAPID will continue until the 180th positively adjudicated PSVT episode in Part 2 patients. See the sample size determination section (Section 9.2.6 of the protocol) for additional details. RAPID will continue for approximately 6 months after the date of the adjudication of the 180th positively adjudicated PSVT episode. All patients not unblinded as part of the RAPID pivotal analysis will be unblinded at the end of the study.

Figure 1. NODE-301 Patient Flow, Part 1 and Part 2



A. Primary Analysis for RAPID study will pool the Etripamil single dose and optional second dose arms from Part 2 only, and compare to the pooled Placebo single dose and optional second dose arms from Part 2 only
B. All patients who did not have an episode by cutoff date in Part 1 remain fully blinded
Note: PSVT and non-PSVT determined by independent adjudication committee

The study will include a Screening Visit, a Test Dose Randomization Visit, Monthly Follow-up Visits, a Randomized Treatment Period, a Randomized Treatment Period Follow-Up Visit, an Open-Label Treatment Period, and a Final Study Visit.

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

See Section 6.2 for a full list of Test Dose Randomization Visit procedures. As detailed in that section, it is permitted to conduct the Screening and Test Dose Randomization Visit procedures on the same day, using a local laboratory to conduct preliminary clinical safety evaluations.

Newly Enrolled Patients: The initial Test Dose Randomization Visit for newly enrolled patients must occur within 28 days after the Screening Visit.

Patients previously enrolled under NODE-301 Part 1: A Test Dose Randomization Visit to assess the safety of a second dose of etripamil NS 70 mg was required for patients previously enrolled under NODE-301 Part 1. This visit should occur at the time of reconsent of patients for Version 6 and subsequent versions of the protocol.

Before randomization, all patients will receive a test dose of the etripamil NS dosing regimen (an initial dose of etripamil NS 70 mg followed by a second dose of etripamil NS 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose) to evaluate tolerability and to train patients on the study procedures. All patients who pass the test dose of the etripamil NS dosing new regimen will be given a study kit, which includes the blinded study drug (2 devices pre-filled with placebo or etripamil NS 70 mg), a CMS, a study identification card, patient's study instructions, and other study-related material.

Both doses of the etripamil dosing regimen must be administered for the test dose to be considered evaluable. 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 of the etripamil NS dosing regimenwill be randomized to in a 1:1 ratio to etripamil or placebo using an Interactive Response Technology (IRT) system, and will be given a study kit, including double-blind study medication to treat a PSVT episode in an at-home setting.

Monthly Follow-up Visits

Follow-up Visits will occur approximately monthly from the time of randomization until the patient has completed the study (i.e., during the Randomized and Open-Label Treatment Periods).

These visits can be conducted by patients returning to the investigative site or by the site personnel contacting patients by telephone.

Randomized Treatment Period

When randomized patients identify symptoms of an episode of PSVT, they will perform a sequence of steps, including placement of CMS device on his/her chest and study drug self-administration. A caregiver may help the patient with these procedures, and this should be annotated in the electronic case report form. Self-administration of the study drug regimen

during a PSVT episode is as follows: an initial dose of etripamil NS 70 mg (or placebo) followed by a second dose 10 minutes later if the patient continues to experience PSVT symptoms (patients who are symptom-free before 10 minutes do not repeat dosing).

Randomized Treatment Period Follow-Up Visit

A Randomized Treatment Period Follow-Up Visit will occur at the study site within 7 days after a patient self-administers study drug during the Randomized Treatment Period. Patients without tolerability issues will be entered into the Open-Label Treatment Period.

Open-Label Treatment Period

All patients will perform a sequence of steps, including etripamil 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. Self-administration of the study drug regimen during a PSVT episode is as follows: an initial dose of etripamil NS 70 mg followed by a second dose 10 minutes later if the patient continues to experience PSVT symptoms (patients who are symptom-free before 10 minutes do not repeat dosing).

Final Study Visit

A Final Study Visit will occur at the study site within 7 days after a patient self-administers study drug during the Open-Label Treatment Period, or if for any other reason the patient has completed participation in the study.

End of Study Telephone Follow-Up

An End of Study Telephone Follow-Up Visit will be completed approximately 30 days after the Final Study Visit to assess adverse events (AEs). This visit is not required for patients who did not use study drug within 14 days prior to their Final Study Visit.

2.2.1 Treatment Regimen and Dosage

Investigational Product and Dosage: The formulation of etripamil will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid (EDTA), and sulfuric acid. The dose of etripamil to be evaluated in the RAPID study is 70 mg per nasal spray device, using the dosing regimens described previously. The same formulation will be used for the Test Dose Randomization Visit and for the Treatment Periods.

Reference Product: The formulation of placebo will consist of water, sodium acetate, disodium EDTA, and sulfuric acid to reproduce the same pH as the etripamil formulation.

Mode of Administration: Each nasal spray device delivers a total of 200 µL of etripamil NS 70 mg or placebo (i.e., 100 µL in each nostril via the Aptar Pharma Nasal Spray Bidose System [BDS]). The devices will be prefilled and packaged into child-resistant boxes. Instructions for its use are provided in the MoOP and will be provided in the study drug kit.

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. This will be a 6-digit hyphenated number of the following format: XXX-YYY, where XXX is the unique site identification number and YYY is a sequential unique number assigned to the patient at that site. Each patient number will be assigned only once and will not be reassigned to another patient if a patient fails during the Screening Visit. The IRT will not allow repeat of numbers. This unique identifier is used in all study documentation for that patient from first to last contact.

Patients previously enrolled in Part 1 who subsequently pass a test dose of the etripamil dosing regimen will be re-randomized in RAPID (1:1 etripamil to placebo), however they will keep the same patient identification number.

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, Adjudication Committee, and Clinical Research Organization 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.

2.2.3 Study Drug Administration

Each nasal spray device delivers a total of 200 µL of etripamil NS 70 mg or placebo (i.e., 100 µL in each nostril via the Aptar Pharma Nasal Spray Bidose System [BDS]). The devices will be prefilled and packaged into child-resistant boxes. Instructions for its use are included in each study drug kit and are provided in the MoOP.

Prior to administration, patients should be seated with their head in an upright position. Patients will be instructed to hold their breath and avoid inhaling during study drug administration (a caregiver may help the patient with this procedure). For 10 minutes after each drug administration, patients are to remain in a seated position with their head upright, breathe normally, and refrain from blowing their nose. Patients may gently blow their nose to remove any excess fluid build-up prior to administration of a second dose. A second dose of study drug should be taken not earlier than 10 minutes, and not later than 15 minutes after the first dose. This applies to test dose procedures, as well as during Randomized and Open-Label Treatment

Periods to treat perceived PSVT episodes (if symptoms of PSVT persist 10 minutes after the first dose of study drug).

In the event that a full dose of etripamil NS 70 mg is not administered during the initial dose (e.g., due to misuse of device or device malfunction), the patient should wait at least 10 minutes before self-administering a second dose, if needed.

Patients should not take a second dose of study drug if they are experiencing tolerability issues believed related to the first dose (e.g., symptoms of lightheadedness/dizziness). If patients report feeling lightheaded/presyncope, they should be instructed to lie down and put their feet up until the symptoms resolve.

Patients will receive study drug as determined by their treatment group assignment. If the BDS does not deploy, it will be considered a missed or partial dose, as applicable.

3. EFFICACY ASSESSMENTS

Efficacy assessments will be based on the data derived from CMS recordings. The Adjudication Committee will evaluate the ECG data recorded from patients to determine if a true PSVT episode occurred. To avoid potential bias, the determination of true PSVT should be made based on the portion of the ECG recordings excluding any ECG after study drug is administered. 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 and rate symptoms of the episode of PSVT and its evolution as well as overall treatment satisfaction in the patient PSVT Symptom Questionnaire and TSQM.

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as time to an adjudicated termination of a positively adjudicated episode of PSVT and conversion to SR for at least 30 seconds within 30 minutes of start of study drug dosing. This is calculated as the time in seconds from study drug initiation to termination of the PSVT episode as determined by the independent Adjudication Committee.

3.2 Additional Efficacy Endpoints

The additional efficacy endpoints will include:

- Time to conversion at time points prior to, and later than, 30 minutes;
- Time to conversion in patients with the option of repeat administration;
- The percentage of patients requiring additional medical intervention in emergency department to terminate an episode of PSVT
- 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

- Rating of TSQM-9 and symptoms.
- The repeat of key efficacy endpoints in various subgroups of interest (e.g., concomitant medications) See Appendix E for listing.

3.3 Adjudication Process for Randomized Treatment Period

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 4 and up to 6 members, all cardiac electrophysiologists (EPs), who are independent from the Sponsor and from Sponsor-related operational activities and the 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:

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

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

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

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

The Adjudication Committee will also adjudicate the time between start of study drug administration and PSVT termination, time to loss of recording signal (if applicable), time of a successful medical intervention (e.g., use of IV adenosine in a medical care facility), or if termination is not observed within 5 hours. The Adjudication Committee will review the full disclosure of the 5-hour CMS recording and will report arrhythmias and conduction disturbances in the eCRF.

Further details are provided in the RAPID (NODE-301 Part 2) study Adjudication Committee Charter.

3.4 Adjudication Process for Open-Label Treatment Period

A similar process to the one used for double blind treatment will be followed to adjudicate PSVT events treated with etripamil during the Open-Label Treatment Period.

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 NS 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 (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction; see Appendix E) for pre-defined subgroup analyses.

Detailed AE assessments can be found in Section 8 of the protocol.

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, at the Randomized Treatment Follow-Up 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 within 10 minutes before test dose administration. Following etripamil administration, vital signs will be obtained every 5 minutes (±1 minute) for 45 minutes after the first dose of etripamil NS 70 mg. Vital signs will also be obtained if the patient reports any symptom potentially related to drop in blood pressure.

4.6 Electrocardiograms

A 12-lead ECG will be performed at the Screening Visit, at the Test Dose Randomization Visit, and at the Final Study Visit.

During the Test Dose Randomization Visit, patients should be sitting comfortably for a minimum of 5 minutes before starting the procedure. The test dose procedure must not be carried out in the standing or fully supine position. The MoOP will provide the details for interpreting ECGs and on-screen continuous monitoring.

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 pivotal analyses will be conducted after the 180th positively adjudicated PSVT episode is documented. Only patients who have dosed with double-blind study drug or have discontinued the study before the adjudication of the 180th positively adjudicated PSVT episode will be included in the primary, secondary and exploratory efficacy analyses of the pivotal analysis.

5.1 Analysis Populations

5.1.1 Overall Safety Population

The Overall Safety Population includes all patients who take any study drug (test dose or randomized study drug, or both).

5.1.2 Safety Population

The Safety Population includes all randomized patients who take the randomized study drug for a perceived episode of PSVT. The patients will be included in the treatment arm according to actual received treatment. The safety population also includes all patients who take the Open-Label study medication for a perceived episode of PSVT.

The primary safety analyses will be based on this Safety Population.

5.1.3 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).

Safety data for the TD Population will also be presented.

5.1.4 Modified intent-to-treat (mITT) Population

The mITT Population includes all randomized patients who take the randomized study drug for a perceived episode of PSVT. The patients will be included in the treatment arm in which they are randomized to.

The mITT population is expected to be the same as the Safety Population unless patients take the drug that is different from what they are randomized to receive. Data for mITT may not be presented separately unless the two populations are differed by more than 10 patients.

5.1.5 Efficacy Population

The Efficacy Population includes all mITT patients who take the study drug to treat a positively adjudicated episode of PSVT. This population will exclude 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 first administration of study drug. These excluded patients will be included in mITT population.

The primary efficacy analyses will be based on this Efficacy Population.

5.2 General Convention

5.2.1 Treatment Group

Patients enrolled or re-enrolled after NODE-301 protocol amendment 6 (starting of the RAPID Study and addition of optional second dose) are randomized to one of the two treatment groups: Etripamil Group (Active Group) or Placebo Group (Control Group). Most patients within each group will have the opportunity to take an optional second dose of study drug, self-administered only if PSVT episode symptoms do not resolve within 10 minutes after first dose. A small set of patients (n=33) who took study drug for an episode after the Part 1 cutoff date, but prior to amendment 6 are in the single dose arms, reflecting their absence of an option of a repeat dose.

Unless otherwise stated, Active Group will refer to the pooled etripamil arms in Part 2 (single dose arm, and optional second dose arm) and Placebo Group will refer to the pooled placebo arms in Part 2 (single dose arm, and optional second dose arm). The primary comparisons will be between Active Group and the Placebo Group.

5.2.2 Data Presentation Convention

Unless otherwise stated, all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p values that are less than 0.001 will be presented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on case report forms (CRFs) by study drug, center, and patient number.

5.2.3 Baseline Convention

Unless otherwise stated, the baseline is the last observed measurement prior to or on the date of randomization.

5.2.4 Software Convention

Unless otherwise stated the following software will be used:

- Analyses will be performed using SAS Version 9.4;
- All medical history and AEs will be coded using MedDRA v 21.0;
- All prior medication and concomitant medication will be coded using WHODrug Global March 2018 B3.

5.2.5 Missing Value Imputation Convention

Unless otherwise stated missing values will not be imputed. Missing AE and concomitant medication dates will be imputed based on the methods outlined in Appendix F.

5.2.6 SAP Version Control Convention

The first approved versions of the SAP will be numbered sequentially as Version 1.00. As mentioned in the introduction, the SAP may evolve over time due to reasons such as protocol amendment or regulatory feedback, the subsequent approved version will be numbered as sequentially as Version 1.0i. The reason for the changes must be documented in the SAP history log. The final version to be used for the analysis must be filed before the data base lock and

labelled as Final Version 1.xy. The Clinical Study Report will document any changes made after the Final Version.

5.3 Description of Study Population

5.3.1 Disposition

Patient disposition summaries will be presented by treatment arm and will include the number of patients randomized, the number and percentage of randomized patients in each of the pre-defined study populations, the number and percentage of patients who received drug during the open-label follow-up period, as well as the number and percentage of patients who complete the study. The summaries will also include the reasons for early discontinuation from the study, and the alternative diagnoses for patients who were not in PSVT as the time they took study drug for a perceived episode.

For TD patients who do not proceed to randomization, or randomized patients who do not proceed to the open-label follow-up period, the primary reason for discontinuation will be listed.

5.3.2 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.

5.3.3 Medical History

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.

5.3.4 Prior and Concomitant Medication

All prior and concomitant medications administered during the study will be coded using ATC Level 4 of the WHO Drug Dictionary March 2018 B3 version. 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 patients 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.

5.3.5 Study Drug Administration

The 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. Whether a patient took one or two doses of study drug, and the time of second dose administration, and whether the patient was in PSVT when taking a second dose for a perceived episode will also be listed. If the study drug device is not fully deployed for a device, half dose will be reported.

5.4 Efficacy Analyses

The estimand of the study is to test the rapid treatment effect of Etripamil (a dosing regimen of either single or optional second dose) in a population of patients having an episode of PSVT in an at-home setting, as measured by time to conversion. The main estimator is the Kaplan Meier analysis of time from study drug initiation to conversion from PSVT into normal sinus rhythm. The main estimate is the relative hazard ratio between Etripamil and Placebo treatment. A key intercurrent event is patients who seek rescue medical intervention prior to conversion to normal sinus rhythm.

Patients enrolled or re-enrolled after NODE-301 protocol amendment 6 (starting of the RAPID Study and addition of optional second dose) are randomized to one of the two treatment groups: Etripamil Group (Active Group) or Placebo Group (Control Group). Most patients within each group will have had the opportunity to self-administer an optional second dose of study drug, only if the PSVT episode does not resolve within 10 minutes after first dose. A small set of patients who took study drug for an episode after the Part 1 cutoff date, but prior to amendment 6 are in the single dose arms.

Unless otherwise stated Active Group will refer to the pooled etripamil arms in Part 2 (single dose arm, and optional second dose arm) and Placebo Group will refer to the pooled placebo arms in Part 2 (single dose arm, and optional second dose arm). The primary comparisons will be between the Active Group and the Placebo Group.

In addition, analyses based on the single dose arms and the optional second dose arms will also be provided. The purpose of these analyses is not to detect a significant difference, due to the small sample size in single dose arms;rather, these analyses are performed to evaluate any trend.

5.4.1 Primary Efficacy Endpoint Analyses

The primary endpoint is Time to Confirmed Conversion by Minute 30 (TTC30) defined as time to adjudicated termination of a positively adjudicated episode of PSVT and conversion to sinus rhythm (SR) for at least 30 seconds within 30 minutes of study drug dosing.

5.4.1.1 Derivation of Primary Endpoint

The following rules will be used to derive the conversion time and censoring rules for adjudicated episodes of PSVT:

1. For patients who achieved a confirmed conversion by Minute 30, TTC30 will be set to the conversion time with the censoring indicator equal to 0 (No).
2. For patients who fail to achieve the confirmed conversion and who have achieved the confirmed conversion after Minute 30, TTC30 will be set to 31 with the censoring indicator equal to 1 (Yes).
3. For patients who receive medical intervention (e.g., taking or being administered a rescue medication or physician assisted VM) to treat their current episode before Minute 30, TTC30 will be set to Minute 31 with the censoring indicator equal to 1 (Yes).
4. For patients whose recordings are interrupted (e.g., mechanical failures) before Minute 30, TTC30 will be set to the time when the interruptions occur with the censoring indicator equal to 1 (Yes).
5. Minute 0 will be set as the time of administration of the first dose of study drug.

5.4.1.2 Primary Analysis of Primary Endpoint

Analysis of Primary Endpoint TTC30 will be analyzed via SAS Lifetest procedure using Wilcoxon test.

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. The Kaplan-Meier estimate of the time at which 25%, 50%, and 75% of adjudicated episodes of PSVT conversions occur will be calculated, if estimable.

Conversion rates at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 300 minutes will be summarized descriptively. The percentages, the differences between the percentages, odds ratio, relative risk ratio, and the 2-sided 95% confidence intervals of the difference will be presented.

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= 5 10 15 20 25 30;
      TIME TTC30*STATUS (1)/ test=WILCOXON;
      STRATA TREATMENT;
RUN;
PROC PHREG;
      CLASS TREATMENT;
      MODEL TIME*STATUS (1) = TREATMENT;
```

```
RUN;
```

5.4.2 Secondary Endpoint Analyses - Patient Reported 9-Item Treatment Satisfaction Questionnaire for Medication and Symptom Outcomes

5.4.2.1 Treatment Satisfaction Questionnaire for Medication 9-Item (TSQM-9)

TSQM-9 is an abbreviated 9-item TSQM. Ratings on TSQM-9 (please refer to Appendix B for TSQM) are captured in the eCRF.

The second question from TSQM-9 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.

Treatment satisfaction will be analyzed by comparing the score of TSQM-9 for effectiveness, convenience, and global satisfaction domain in the 2 treatment groups. 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

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

5.4.2.2 Analyses of TSQM-9

The Effectiveness, Convenience and Global satisfaction scores, and the TSQM-9 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;
```

5.4.2.3 Individual Patient Symptoms

Patients will be asked "How long was it from the start of your SVT episode, until you took study drug?" The answers will be summarized by treatment group. Furthermore, as soon as possible after the SVT episode is over, patients will rate their symptom severity (1=Mild and 5=Severe) and symptom outcome (Very much worse, Much worse, Minimally worse, No change, Minimally improved, Much improved, Very much improved) for the following 7 symptoms:

- Rapid Pulse (my heart rate is very fast)
- Palpitations (I can feel my heart pounding in my chest)
- Feeling Dizzy or Lightheaded
- Shortness of Breath (it is hard for me to catch my breath)
- Anxiety
- Chest Tightness, Pain, or Pressure
- Passing Out or Fainting

5.4.2.4 Analyses of Individual Patient Symptoms

The severity score for each symptom will be analyzed via a ANOVA model with treatment effects. In the analysis, the severity score will be imputed as 0 for patients who answer "No" to "Did you have this symptom." The treatment effects, the differences in treatment effects, and the two-sided 95% confidence intervals of the differences will be presented.

Symptom outcome for each symptom will be analyze as percentage of responder where a responder is defined as outcome="Much improved" or "Very much improved." In these analyses, patients who have not provide answers will be treated as non-responders. The percentages of the responders, the differences in the percentages of the responders, and the two-sided 95% confidence intervals of the differences will be presented.

5.4.3 Other Secondary Efficacy and Robustness/Sensitivity Analyses.

To evaluate internal consistency and robustness/sensitivity of the efficacy assessment, the following sensitivity analyses will be performed:

1. TTC30 will be analyzed via LIFETEST based 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.
2. TTC30 will be analyzed via Wei Lin Weissfeld method, on a composite endpoint where conversions to sinus rhythm due to additional medical intervention are considered a negative recurrent event, and conversions to sinus rhythm without additional medical intervention a positive terminating event.
3. TTC30 will be analyzed via LIFETEST using Log-Rrank test
4. TTC30, and TTC300 will be analyzed via LIFETEST using Wilcoxon method, with with patients censored at time of conversion due to medical intervention.
5. TTC10, TTC15, TTC45, TTC60, TTC90, TTC120, TTC180, and TTC300 will be analyze via LIFETEST using Wilcoxon method.
6. Analysis of the 2x70 dose reimen; Percent of patients randomized to the optional second dose arms who take the optional second dose within etripamil and placebo arms will be analyzed via PROC FREQ based on CMH (Cochran-Mantel-Haenszel) method.
7. Analysis of the 2x70 dose reimen; TTC30 for patients who take the optional second dose will be analyzed via LIFETEST using Wilcoxon method.
8. Analysis of the 2x70 dose reimen; TTC30 for patients in the Efficacy population who have not taken the optional second dose will be analyzed via LIFETEST using Wilcoxon method.
9. TTC30 for patients randomized into the single-dose arms (ie, not given the option of a repeat dose) will be analyzed via LIFETEST using Wilcoxon method.
10. TTC30 for patients randomized into the optional second-dose arms (ie, given the option of a repeat dose) will be analyzed via LIFETEST using Wilcoxon method.
11. Percent of patients who seek additional medical intervention will be analyzed via PROC FREQ based on CMH method together and if appropriately, by individual types of intervention (went to ED regardless of conversion; oral pill-in-pocket; IV medication; and physician administered VM).
    a. Analyzed for medical intervention after randomized treatment only
    b. Any treatment for any subject perceived episode of PSVT (includes OL treatment).
    c. Analyzed for medical intervention after randomized treatment only pooling Part 1 and Part 2 data.
12. TTC30 will be analyzed via LIFETEST for 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.
13. TTC30 will be analyzed via LIFETEST for patients who took placebo as their double-blind treatment and then etripamil for the open-label treatment visit. This cross-over analysis will utilize the placebo adminsitration as control, and open-label administration as the active arm.
14. TTC30 will be reported for the open label treatment visit in patients with positively adjudicated PSVT, who take etripamil during PSVT during that open label drug administration.

15. The durability of conversion will be analyzed via PROC FREQ for placebo versus etripamil of the percent of patients who, after converting to sinus rhythm, experience a recurrence of PSVT during the 5 hour observation window.
16. If more than 10 patients in the total efficacy population have a recurrence of PSVT within 5 hours, the impact of the definition of conversion for the primary endpoint will be tested by analyzing TTC30 via LIFETEST, where conversion is defined as being in sinus rhythm for ≥1 minute, ≥2 minutes, and ≥5 minutes.
17. A number needed to treat analysis will be conducted on the Efficacy population and Safety Population, based on conversion to SR at 5, 10, 15, 30, 45, or 60 minutes.

5.4.4 Controlling Type I Error for Multiple Comparisons

TTC30 is the only primary endpoint. The null hypothesis (no treatment difference) with respect to TTC30 will be tested at a two-sided 0.05 significant level for superiority claim. Once the superiority claim is made, the superiority claims for the following efficacy endpoints will also be tested at two-sided significance level of 0.05 in the order specified below:

1. Kaplan Meier estimates of time to conversion over 10 minutes
2. Kaplan Meier estimates of time to conversion over 45 minutes
3. Percent of patients who seek additional medical intervention within 5 hour observation window. This analysis will be conducted using pooled double-blind data from Part 1 and Part 2 of the 301 study.
4. TSQM-9 Effectiveness
5. TSQM-9 Global Satisfaction
6. Kaplan Meier estimates of time to conversion over 60 minutes
7. Improvement of symptoms of rapid pulse feeling
8. Improvement of symptoms of heart palpitations
9. Improvement of symptoms of anxiety
10. Improvement of symptoms of chest pain
11. Improvement of symptoms of shortness of breath
12. Improvement of symptoms of dizziness and/or fainting

To control for family-wise Type I error rate at 0,05, a null hypothesis for a efficacy variable can be rejected only if all null hypotheses before it are also rejected.

5.5 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).

5.5.1 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 patient 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, or with a start date occurring 0 to 24 hours after open-label Follow-up period 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 outpatient drug administration;
- Open-Label Follow-up AEs (OLFAE); defined as AEs with a start date occurring 0 to 24 hours after Open label outpatient drug administration.
- AEs with a start date occurring 0 to 48 hours after randomized drug administration or open-label outpatient drug administration;
- AEs with a start date occurring 0 to 7 days after randomized drug administration or open-label outpatient 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, see Appendix F.

An overall summary table will contain the number and percentage of patients ever having one of the above listed subsets of AEs. Detailed tables of study populations will be presented with relevant

- Test-Dose Emergent TDEAE,
- Randomized-Treatment Emergent RTEAEs
- Open-Label Follow-up Emergent OLFAEs.
- AEs will be summarized overall (both treatment groups, Etripamil and Placebo combined) for periods when both groups receive study drug (Test-dose and Open-label treatment emergent AEs)
- For each treatment group separately for Randomized-Treatment Emergent AEs.
- AEs for patients who took a single dose of study drug compared to patients who took the optional second dose of study drug will be presented.

AEs will be presented by MedDRA system organ class (SOC) and preferred term (PT) with the number and percentage of patients. If a patient 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 highest grade 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 patients by SOC and PT.

All AEs will be included in by-patient listings. Specific by-patient listings of SAEs and AEs leading to study drug discontinuation will be provided. The number of days between test dose, or randomized-treatment or open-label treatment drug dose and when the AE occurred will be presented (i.e., relative study day), as will duration of the AE.

5.5.2 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 abnormalities (<LLN and >ULN) will be summarized. Listings of all clinical laboratory tests will be provided.

5.5.3 Vital Signs

Vital signs results (n, mean, median, minimum, maximum, standard deviation, median,) will be summarized by visit and treatment.. 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, 30, 35, 40 and 45 minutes post-test dose will be summarized.

5.5.4 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 45 minutes post-test dose will be summarized. A listing of all ECG results will be provided.

The change in heart rate (as measured by the CMS) from prior to drug administration to 5, 10, 15, 20, 25, and 30 minutes after administration of double blind study drug will be summarized by treatment group.

The number of patients and percentage of patients with conduction disorders will be reported from the CMS recordings. The number of patients and percentage of patients with first-degree AV block will be reported. For 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, see Appendix E). These data will be reported in the Overall Safety Population.

For episodes after a patient is randomized, the number of patients and percentage of patients 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), and when data is collected after taking Open-label Follow-up period study drug. These data will also be reported in the Safety population by treatment for CMS data which is collected after administration of randomized double-blind study drug but prior to Open-label Follow-up period study drug administration.

The following adjudicated data will be summarized:

1) N (%) of patients with occurrence of atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds.
2) N (%) of patients with non-sustained ventricular tachycardia defined as equal or greater than 3 wide consecutive beats.
3) N (%) of patients with sustained ventricular tachycardia defined as equal or greater than 10 wide consecutive beats
4) N (%) of patients with any sinus rate equal or less than 40 bpm and Type I AV block greater than 30 seconds.
5) N (%) of patients 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 patients with any pause equal or greater than 3 seconds.
7) N (%) patients bradycardia less than 40 bpm

5.5.5 Physical Examination

Physical examination data at each evaluation will be listed.

6. INTERIM ANALYSIS

No interim analysis has been planned.

7. SAMPLE SIZE DETERMINATION

A total sample size of 180 patients in Part 2 with a positively adjudicated PSVT episode, randomized at a range of 1:1 to 2:1 ratio (active : control) provides at least 90% power to detect a significant treatment difference for the primary endpoint at a two-sided significance level of 0.05. This sample size was calculated based on internal modeling of the Part 1 data where etripamil had a higher conversion rate (54% versus 35% at 30 minutes), and also a more rapid conversion rate (32% versus 14% at 10 minutes).

Assuming a type I error rate of alpha = 0.05 and a ratio in the number of positively adjudicated episodes of PSVT etripamil:placebo between 1:1 and 2:1, a minimum of 80 positive conversion events will be required. Based on internal modeling, 180 patients with a positively adjudicated PSVT episode and 80 positive conversion events will attain greater than 90% power on the primary variable of time to conversion (using a 2-sided Wilcoxon test).

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

8. 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.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures

Assessment	Screening Visit[1]	Test Dose Randomization Visit[2]	Monthly Follow-up Visit[3]	Randomized Treatment Period[4]	Randomized Treatment Follow-Up Visit	Open-Label Treatment Period[4]	Final Study Visit[5]	End of Study Telephone Follow-Up Visit
Informed consent	X							
Eligibility	X[6]	X[7]	X[8]					
Contact the Telephone Coach[9]		X		X		X		
Demographics/medical history	X							
Concomitant medications	X	X	X		X		X	
Physical examination	X[10]						X	
Vital signs (blood pressure and heart rate)	X	X[11]			X		X	
Hematology, chemistry, and urinalysis[12]	X						X[13]	
Pregnancy test[14]	X	X			X		X	
12-lead ECG[15]	X	X					X[16]	
Test dose administration[17]		X						
Patient training on PSVT episode assessments[18]		X	X		X			
Randomization (via IRT)		X						
AEs		X	X	X	X	X	X	X
Dispense study kit[19]		X			X			
Ensure CMS data downloaded and sent to cardiac monitoring core lab		X	X[20]		X		X	
Review the CMS report[21]		X			X		X	
Identify PSVT episode				X		X		
Apply and start CMS		X		X[22]		X[22]		
Perform VM		X		X		X		
Administer study drug and record time of dosing				X[23]		X[23]		
Complete patient questionnaires				X		X		
Evaluate medical intervention during the Treatment Period					X		X	
Collect study kit (used and unused)					X		X	
Identify reason(s) for study completion or withdrawal							X	
Close case with IRT							X	

Note: 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.

1. Screening Visit can be conducted with Test Dose Randomization Visit for purposes of avoiding an extra on site visit in extenuating circumstances

2. The Test Dose Randomization Visit should occur within 28 days after the Screening Visit for newly enrolled patients and should occur at the time of reconsent for patients previously randomized in NODE-301 Part 1. If the Test Dose Randomization visit cannot be conducted within 35 days after the Screening Visit, new blood and urine samples must be collected and sent for central laboratory evaluations at the Test Dose Randomization Visit prior to Test Dose procedures. Patients who pass the Test Dose criteria and are randomized will be instructed to not use double-blind study medication until it is confirmed that no exclusionary criteria were met following the analysis of the newly collected samples. 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 dosing regimen 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). Screening and Test Dose Randomization Visits can be incorporated into one visit for purposes of avoiding an extra on site visit in extenuating circumstances
3. Monthly Follow-up Visits to occur approximately monthly via site visit or telephone (site visit preferred for patients who have an episode of PSVT terminated by VM).
4. Randomized Treatment Period occurs from randomization until patient has an episode of PSVT treated with study drug. Open-Label Treatment Period occurs from after Randomized Treatment Follow-up Visit until the patient has an at-home episode treated with Open-Label drug.
5. Randomized Treatment Follow-up Visit to occur within 14 days after a patient self-administers study drug during the Randomized Treatment Period. Final Study Visit to occur within 14 days after the Open-label Treatment Period, or within 14 days of the test dose administration for patients who fail the test dose.
6. Confirmation of eligibility at Screening includes confirmation of PSVT diagnosis. Acceptable source documents to confirm the PSVT diagnosis are provided in the MoOP.
7. Additional eligibility criteria apply to pass the test dose at the Test Dose Randomization Visit only.
8. Eligibility assessments at the Monthly Follow-up Visits based on review of patient's concomitant medications or changes in health status.
9. If possible. The Telephone Coach will guide the patient through the study procedures. For the Test Dose Randomization Visit only, the Telephone Coach should be contacted once the 10 minutes of baseline recording with the CMS is complete. If the patient is unable to reach the Telephone Coach, he/she may proceed with the procedures using the printed and electronic guides.
10. Including height and weight.
11. Vital signs will be obtained within 10 minutes pre-test dose and every 5 minutes (±1 minute) for 45 minutes post first test dose.
12. Blood / urine samples can be analysed locally for purposes of preliminary enrolment if Screening/Test Dose Randomization Visits are combined; samples **also** to be sent to Central lab. Central lab results will **allow** enrollment in study
13. Blood and urine tests will be performed on all patients who pass the test dose and are randomized.
14. 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 and the Randomized Treatment Follow-Up Visit.
15. The paper speed for these recordings should be 25 mm/sec. A continuous on-screen ECG monitoring (at least 2-leads) is required from the beginning until the end of the test dose for the Test Dose Randomization Visit.
16. A 12-lead ECG will be performed on all patients who pass the test dose and are randomized.
17. Before randomization, all patients will be trained on VMs and will receive a test dose of etripamil regimen (an initial dose of etripamil NS 70 mg followed by a second dose of etripamil NS 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose) 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 Only 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.
18. 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 patient diary, and reporting AEs to the sites during the study for evaluation. A caregiver may assist in these procedures.
19. The study kit will include the study drug (2 devices of placebo or etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material. Patients will also be provided with patient questionnaires to be completed after experiencing a PSVT episode. At the Randomized Treatment Follow-up Visit, Open-Label etripamil will be provided with the CMS device (sites to ensure device has been reset) and new patient questionnaires.
20. Download of CMS data during Follow-Up Visit if patient applied device without dosing study drug (e.g., VM-terminated PSVT).
21. 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 test dose report within approximately 1 to 2 hours of the receipt of the ECG data. This report will be used by the site to determine if the patient passes or fails the test dose and if the eligibility criteria to be randomized in the study have been met. During the Randomized Treatment Period and the Open-Label 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 and the Medical Monitor.

22. The CMS recording during an episode of PSVT should continue for at least 5 hours, regardless of treatment outcome.
23. During the Randomized Treatment Period and the Open-Label Treatment Period, study drug 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 the study drug intranasally as instructed. If symptoms of the PSVT episode have not resolved within 30 minutes after start of 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 BASED ON AN ABBREVIATED 9 ITEMS (TSQM-9)

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

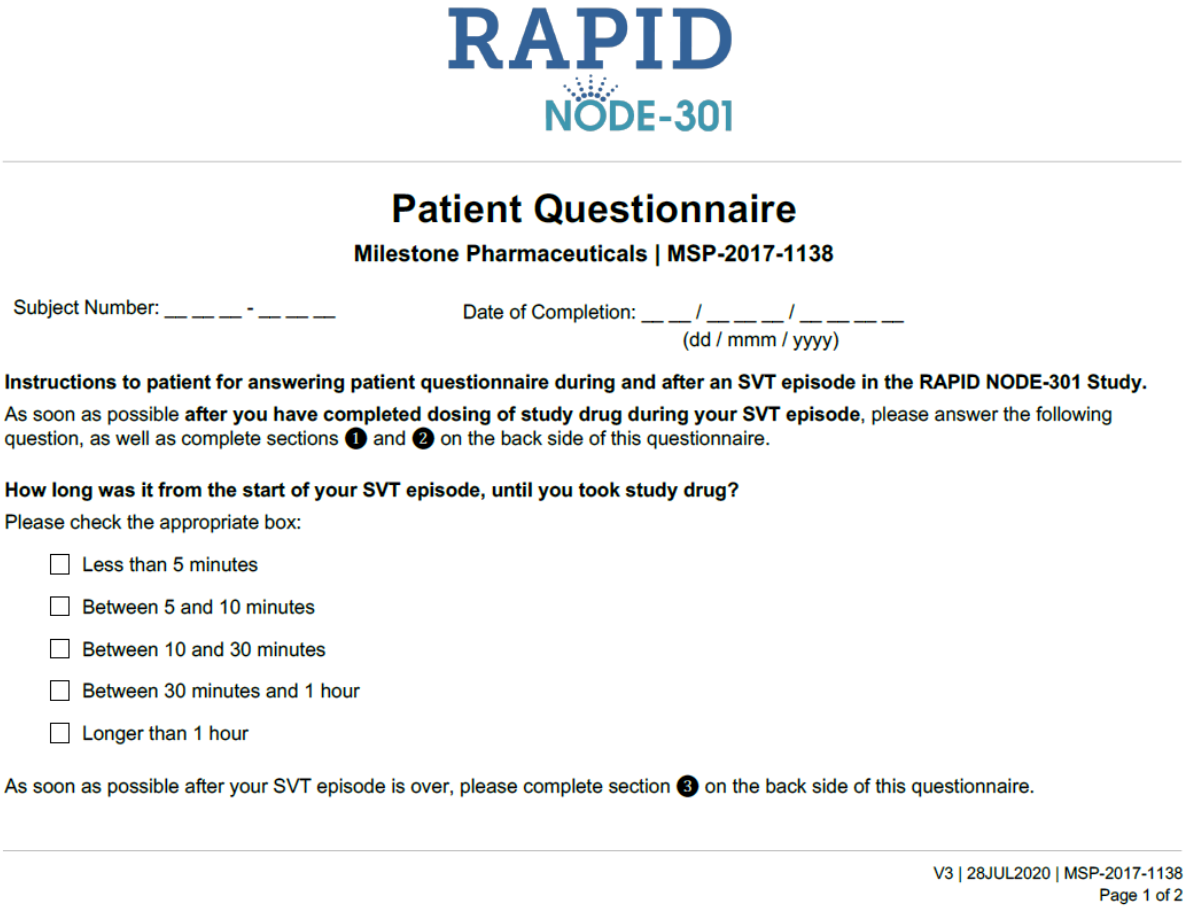
6. How convenient or inconvenient is it to take the medication as instructed?
   1. Extremely Inconvenient
   2. Very Inconvenient
   3. Inconvenient
   4. Somewhat Convenient
   5. Convenient
   6. Very Convenient
   7. Extremely Convenient
7. Overall, how confident are you that taking this medication 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:

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

Screenshots of the PRO tool are provided below



RAPID
NODE-301

Patient Questionnaire

Milestone Pharmaceuticals | MSP-2017-1138

Subject Number: __ __ __ - __ __ __ Date of Completion: __ __ / __ __ __ / __ __ __ __
(dd / mmm / yyyy)

Instructions to patient for answering patient questionnaire during and after an SVT episode in the RAPID NODE-301 Study.

As soon as possible **after you have completed dosing of study drug during your SVT episode**, please answer the following question, as well as complete sections ❶ and ❷ on the back side of this questionnaire.

How long was it from the start of your SVT episode, until you took study drug?

Please check the appropriate box:

- ☐ Less than 5 minutes
- ☐ Between 5 and 10 minutes
- ☐ Between 10 and 30 minutes
- ☐ Between 30 minutes and 1 hour
- ☐ Longer than 1 hour

As soon as possible after your SVT episode is over, please complete section ❸ on the back side of this questionnaire.

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	❶ Did you have this symptom?		❷ How severe was this symptom? *If you marked "No" that you did not have the symptom, leave this question blank.* *Please complete as soon as possible* ***after you have completed dosing of study drug during your SVT episode.***					❸ How much did <u>the nasal spray</u> worsen or improve this symptom? *If you marked "No" that you did not have the symptom, leave this question blank.* *Please complete as soon as possible* ***after your Episode is over.***						
	Yes	**No**	**Mild 1**	**2**	**3**	**4**	**Severe 5**	**Very much worse**	**Much worse**	**Minimally worse**	**No Change**	**Minimally Improved**	**Much Improved**	**Very much Improved**
Rapid Pulse (my heart rate is very fast)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Palpitations (I can feel my heart pounding in my chest)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Feeling Dizzy or Lightheaded	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shortness of Breath (it is hard for me to catch my breath)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Anxiety	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chest Tightness, Pain, or Pressure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Passing Out or Fainting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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. Region (North America and Europe, and by individual country where N > 10)
2. Male, female
3. Patient age by quartile
4. Patients ≥70 years old,
5. 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),
6. Patients ≥60 and < 70 years old receiving concomitant cardiovascular treatment (Beta blockers, calcium channel blockers, ARBs or ACEs).
7. Patients currently receiving any of the following classes of concomitant medication regardless of indication: Beta-blockers, Calcium channel blockers, ARBs or ACEs.
8. 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.
9. Type of PSVT: AVNRT, AVRT, Indeterminate.
10. Duration from onset of symptoms to taking of study drug (<=Median duration and > median duration)

APPENDIX F: IMPUTATION OF MISSING DATES

This section describes missing date imputation methods.

For Adverse Events
If onset date is completely missing, onset date is set to date of randomization.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of randomization, then set month and day to month and day of randomization
- If year < year of randomization, then set month and day to December 31.
- If year > year of randomization, then set month and day to January 1.

If month and year are present and day is missing:

- If year = year of randomization and
    - If month = month of randomization then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month
- If year < year of randomization then set day to last day of month
- If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

For determination of TEAE, time of dosing will be truncated to minutes (exclude the seconds) to match what is recorded for AEs. For example an AE with onset of 13:55 and study drug dosing time of 13:55:35 will be considered to be post drug administration and a TEAE.

For Concomitant Medications
Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant. If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.