The NODE-303 Trial

Multi-Centre, Multi-National, Open Label, Safety Study of Etripamil Nasal Spray for Patients with Paroxysmal Supraventricular Tachycardia

NODE-303
Etripamil Clinical Research in PSVT

Investigational Product: Etripamil (MSP-2017)
Protocol Number: NODE-303
Version #2.1, Revision to Amendment No. 1, 16MAR2021
Version #2.0, Amendment No. 1, 15FEB2021
Version #1.0, 21JUN2019

Milestone PHARMACEUTICALS
Sponsor: Milestone Pharmaceuticals Inc.

STUDY PROTOCOL

COMPOUND NAME/NUMBER:	Etripamil (MSP-2017)
PROTOCOL NUMBER:	NODE-303
US IND NUMBER:	IND #114386
EUDRACT NUMBER:	2019-001857-13
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	Multi-Centre, Multi-National, Open Label, Safety Study of Etripamil Nasal Spray for Patients with Paroxysmal Supraventricular Tachycardia
PROTOCOL VERSION:	Version 2.1
PROTOCOL DATE:	16 March 2021
CONTRACT RESEARCH ORGANIZATION:	IQVIA Biotech 1700 Perimeter Park Drive Morrisville, NC 27560, United States

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law.

APPROVAL SIGNATURES

PROTOCOL NUMBER:	NODE-303
PROTOCOL VERSION:	2.1, 16MAR2021
PROTOCOL TITLE:	Multi-Centre, Multi-National, Open Label, Safety Study of Etripamil Nasal Spray for Patients with Paroxysmal Supraventricular Tachycardia

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Francis Plat

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INVESTIGATORS:	A current list of clinical investigators will be maintained in the Trial Master File (TMF)

Investigator Agreement

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Milestone Pharmaceuticals Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Milestone Pharmaceuticals Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Milestone Pharmaceuticals Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with my governing Regulatory Authority (FDA, EMA, Regional/Country Authority) Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonization Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

_____

Site Name/City/Country

1. SYNOPSIS

PRODUCT NAME/NUMBER	Etripamil (MSP-2017)
PROTOCOL NUMBER	NODE-303
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	Multi-Centre, Multi-National, Open Label, Safety Study of Etripamil Nasal Spray for Patients with Paroxysmal Supraventricular Tachycardia
INDICATION	Paroxysmal Supraventricular Tachycardia (PSVT)
OBJECTIVES	Primary: 1. The primary objective is to evaluate the safety of self-administered etripamil nasal spray (NS) outside of the clinical setting Secondary Objectives: 1. To evaluate the efficacy of self-administered etripamil NS outside of the clinical setting, and 2. To evaluate the impact of etripamil NS on PSVT disease burden, and 3. To evaluate the safety and efficacy of etripamil NS when used for multiple PSVT episodes
STUDY POPULATION	The study will enroll up to 3000 patients with a documented history of PSVT.
STUDY ENTRY CRITERIA	**Inclusion Criteria:** A patient will be eligible for study participation if they meet all of the following criteria: 1) Has been diagnosed with PSVT by a medical professional, and reports having at least one previous episode of PSVT. For clarity, PSVT refers to episodic SVT that includes the AV node as a critical part of reentrant circuit. See Section 6.4 for details on diagnostic criteria. 2) Is at least 18 years of age. 3) Signed NODE-303 written informed consent. 4) Women of child-bearing potential must be willing to use at least 1 form of contraception during the trial and must be willing to discontinue from the study should they become or plan to become pregnant. Postmenopausal females are defined as having amenorrhea for at least 12 months prior to Screening without an alternative medical cause.

	5) Willing and able to comply with study procedures. **Exclusion criteria:** A patient will be excluded from the study if they meet any of the following criteria: 1) Patients with only a history of atrial arrhythmia that does not involve the atrioventricular (AV) node as part of the tachycardia circuit (*e.g.* atrial fibrillation, atrial flutter, intra-atrial tachycardia) are not eligible. Patients with a history of these tachycardias who are also diagnosed with PSVT are eligible. 2) History of allergic reaction to verapamil. 3) Current therapy with digoxin, or any Class I or III antiarrhythmic drug. Patients may be eligible if these drugs are stopped at least five half-lives before the administration of etripamil NS. The only exception is oral amiodarone which must be stopped 30 days before enrollment. 4) History or evidence of ventricular pre-excitation, *e.g.,* delta waves, Wolff-Parkinson-White syndrome. 5) History or evidence of a second- or third-degree AV block. 6) History or evidence of severe ventricular arrhythmia (*e.g.*, torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia). 7) Symptoms of congestive heart failure New York Heart Association Class II to IV. 8) SBP < 90 mmHg at Screening, Baseline or any Follow-up Visit. 9) Severe symptoms of hypotension experienced during PSVT episodes. 10) Significant physical or psychiatric condition including alcoholism or drug abuse, which, in the opinion of the Investigator, could jeopardize the safety of the patient, or impede the patient's capacity to follow the study procedures. 11) History of syncope due to an arrhythmic etiology at any time, or history in last 5 years of unexplained syncope. 12) Is pregnant or breastfeeding. 13) Previously enrolled in a clinical trial for etripamil and received study drug or participation in any clinical trial for other investigational products or medical devices within 30 days of Screening. 14) History of ACS or stroke within 6 months of Screening. 15) Evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the Screening Visit as follows: a) <60mL/min/1.73m^2 for patients <60 years of age;

	b) <40mL/min/1.73m^2 for patients ≥60 and <70 years of age c) <35mL/min/1.73m^2 for patients ≥70 years of age
STUDY DESIGN	NODE-303 is a multi-center, open label (OL) study to evaluate the safety of etripamil NS in patients with PSVT. Patients will be provided with an ambulatory Cardiac Monitoring System (CMS) to help document PSVT episodes. The CMS will be self-applied by the patient when they feel the onset of PSVT symptoms. Patients will self-administer etripamil NS if the vagal maneuver (VM) is ineffective. After an episode of perceived PSVT for which etripamil NS is administered, the patient will return to the investigative site and have the option to continue in NODE-303 and manage subsequent episodes of PSVT with etripamil NS. The study will include: A Screening Visit during which the Investigator will verify that the patient meets the eligibility criteria of the NODE-303 study, will obtain the signed informed consent, take blood and urine for laboratory evaluations, and conduct other screening procedures. The informed consent for NODE-303 will be applicable for the total duration of participation in the study, to include the treatment of up to 4 perceived PSVT episodes. A Baseline Visit during which the site will confirm eligibility, concomitant medications, train the patient on study procedures, and give the patient study drug, patient reported outcome (PRO) materials, and the CMS materials. A Treatment Period during which the patient will complete the monthly PRO survey, self-identify symptoms of PSVT, use the CMS, perform a VM, and self-administer etripamil NS if the symptoms do not resolve during or after the VM. Patients may be contacted during this period for reminders and training on what to do during a PSVT episode. Patients will also complete a per episode survey after any PSVT episode they experience. During the Treatment Period, Follow-up Visits will occur at the study site up to 14 days after a perceived episode of PSVT which is treated with etripamil NS, and during which the Investigator will evaluate the results of the last usage of etripamil NS and reassess patient's eligibility to continue in the study based on study inclusion and exclusion criteria. Patients who are eligible to continue in the study will receive two additional kits containing study medication. A Final Study Visit that will occur when a patient discontinues or withdraws from the study, or when the overall study is completed, or the patient has completed the maximum number of 4 treated perceived PSVT episodes. NODE-303 will continue until enough documented self-administrations of etripamil NS are included in the safety database to meet regulatory requirements for the etripamil NS development program. The common study end date (CSED) for the entire study will depend on the rate of accrual of the primary endpoint, unique patients with an episode.

	When the criteria for concluding the study have been met, the Sponsor will announce the common study end date (CSED) for the entire study and sites will be informed in advance to schedule all final patient visits prior to the CSED. Safety Monitoring will be conducted from the time of consent throughout study participation. New Adverse Events (AEs) will be collected at every study visit. At the time of the final study visit, any AEs which are ongoing will be followed for up to 30 days. Serious Adverse Events (SAEs) will be captured and reported regardless of when they occur. All SAEs should be followed until satisfactory resolution, even after database lock. **Screening Visit:** See Section 9.1.1 for a full list of Screening Visit procedures. Clinical sites will: • Obtain Informed Consent. • Evaluate the patient's medical status and concomitant medications. • Confirm the diagnosis of PSVT based on a clinician's diagnosis and a patient report of at least one episode of PSVT. See Section 6.4 for details on diagnostic criteria. • Perform a 12-lead safety ECG and upload it. Site personnel will review ECG for safety concerns and eligibility. • Take blood and urine for clinical laboratory evaluations. • Assessment of patient's eligibility for NODE-303 according to the inclusion/exclusion criteria; patients who have signed the ICF and are deemed non-eligible for the study will be considered screen failures. **Baseline Visit:** See Section 9.1.2 for a full list of Baseline Visit procedures. As detailed in that section, it is permitted to conduct the Screening and Baseline Visit procedures on the same day, using a local laboratory to conduct preliminary clinical safety evaluations. Clinical sites will: • Review concomitant medication information. • Confirm patient eligibility. • Train the patient on study procedures and give them study materials. • Have the patient execute their first patient reported outcome measurements.

	Each qualified patient will be given a study kit which will include two kits of etripamil NS, a CMS kit, a study identification card, and study training and informational material. **Treatment Period:** See Section 9.1.3 for a full list of Treatment Period procedures. The patients will be instructed to perform the following steps after they have identified symptoms they consider to be consistent with PSVT: • Apply and activate the CMS to record cardiac activity. • Perform a VM. If the VM is successful in relieving symptoms, the patient will not self-administer study drug and will remove the CMS and the patient will remain in the study for a subsequent episode. • If symptoms do not resolve after completion of the VM, self-administer etripamil NS as instructed, and wear the CMS for at least 1 hour after administration. • After the episode has resolved, patients will complete the relevant per episode survey. If the patient took etripamil NS for the episode, they will contact the site for a Follow-up Visit. If the symptoms of PSVT have not resolved within 30 minutes after the initial study drug administration, the patient should seek appropriate medical care as needed. If the patient goes to a medical facility for PSVT treatment, they must give the study identification card included in the study kit to the on-site medical personnel. This study identification card will contain a brief description of the study, a description of study drug, and the Investigator (study physician) contact information. Patients will also complete the monthly PRO measures during the Treatment Period. Sites should follow up with patients failing to complete the PRO. **Follow-up Visits:** See Section 9.1.4 for a full list of Follow-up Visit procedures. During the Treatment Period, patients who take study drug for an episode will be instructed to return to the site within 14 days after the episode for the following assessments by the Investigator or designee: • Obtain Patient Informed Consent again in the event its contents were modified since initial consent was obtained. • Evaluation of the patient's medical status. • Collect used and unused study drug. • Recording of any adverse events (AEs). • Review of available CMS data (See Section 9.3.2.4 for more details on the CMS).

	• Evaluate any additional medical intervention the patient received for PSVT episodes during the Treatment Period including any concomitant medications. • Assess patient's eligibility to continue in study NODE-303 for treatment of subsequent episodes of PSVT with etripamil NS, and provide two new study drug kits. • Provide any additional CMS materials and patient training or retraining required. • Follow-up Visit assessments should be completed for the first three treated perceived PSVT episodes. Once the patient has had the fourth treated perceived PSVT episode, complete a Final Study Visit, not a fourth Follow-up Visit. **Final Study Visit:** See Section 9.1.5 for a full list of Final Study Visit Procedures. Upon completion of the overall study (Common Study End Date), discontinuation or withdrawal of a patient, or after receiving study treatment for the fourth perceived PSVT episode the site should have the patient return for the Final Study Visit procedures below. • Evaluation of the patient's medical status. • Recording of any adverse events (AEs). • Review of available CMS data (See Section 9.3.2.4 for more details on the CMS). • Evaluate any additional medical intervention the patient received for PSVT episodes during the Treatment Period including any concomitant medications. • Collect CMS. • Collect used and unused study drug. • Complete patient's End of Study form in the eCRF.
INVESTIGATIONAL PRODUCT	The formulation of etripamil will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid (EDTA), and sulfuric acid. The investigational product for self-administration will be in prefilled and packaged Aptar Pharma Nasal Spray Bidose System devices, each containing etripamil NS 70 mg (*i.e.*, 200 µL).
REFERENCE PRODUCT	There is no reference product in this study.

TREATMENT REGIMEN	The treatment regimen of etripamil to be evaluated is an initial dose of etripamil NS 70 mg (one spray of 100 µL in each nostril), to be followed by a second dose (one spray of 100 µL in each nostril) 10 minutes later (not to exceed 15 minutes) if the patient continues to experience PSVT symptoms. Patients who are symptom-free within 10 minutes after the first dose do not repeat the dose.
PRINCIPAL INVESTIGATOR	Francis Plat, MD
PLANNED STUDY SITES	This study will be conducted at up to 400 sites globally.
CRITERIA FOR EVALUATION	**Efficacy Variables:** The primary objective of this study is to evaluate the safety of self-administered etripamil NS. Efficacy variables will be collected as secondary or exploratory analyses. The secondary efficacy endpoints will include: • Frequency of additional medical intervention to treat PSVT, as measured by emergency department (ED) visits, hospital admissions, and concomitant medication use. • Improvement in patient quality of life, as measured by the BIPQ, CAQ, SF-36 questionnaire and other surveys. • Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and other questions. • Termination of PSVT episodes within 1 hour of the start of study drug administration or initiation of CMS recording. The exploratory endpoints will include: • Frequency of PSVT episodes, and use of etripamil NS for those episodes, as captured by the PRO. • Characteristics of patient PSVT episodes, as measured by the data collected by the CMS. **Safety Variables:** Safety variables will include clinical adverse events (AEs), vital signs, and arrhythmias and conduction disorders detected on surface ECG or CMS recordings.

STATISTICAL METHODS	**Analysis populations:** All patients who are enrolled will be included in the Overall Population. Patients who receive any amount of study drug will be included in the Safety Population. Patients who receive at least two sprays of study drug for an episode determined to be PSVT will be included in the Efficacy Population. **Efficacy analyses:** The efficacy analyses will be performed on the Efficacy Population. Comparative analyses may be conducted on data available from patients in Safety Population. Efficacy endpoint analyses will include summaries, both over time and as comparisons between the Efficacy Population and the Safety Populations for the endpoints of; medical interventions, patient quality of life, treatment satisfaction, and PSVT episode characteristics. Continuous efficacy data will be presented with n, minimum, maximum, median, mean, and standard deviation, whereas discrete efficacy data will be summarized with frequency counts and percentages. **Safety analyses:** Safety analyses will be performed on the Safety Population. 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. Additional analyses will be described in detail in the Statistical Analysis Plan (SAP).
SAMPLE SIZE DETERMINATION	There is no statistical hypothesis in this uncontrolled OL safety study. NODE-303 will continue until the end of the development program, *i.e.,* when enough patients with documented self-administrations (1000 to 1500 across all studies) of etripamil NS are included in the safety database. It is anticipated that as many as 3000 patients may need to be enrolled in NODE 303 in order to accrue a sufficient number of patients with perceived PSVT episodes in the Safety Population within 24 months.

STUDY AND TREATMENT DURATION	Patients may continue in the study until they receive treatment for a maximum of 4 perceived PSVT episodes at which time they will complete the study and be eligible for participation in an early access program in line with local country regulations. The duration of treatment will depend on the frequency of a patient's PSVT episodes. After each episode of perceived PSVT is treated with the study drug, eligible consenting patients will have the opportunity to continue in NODE-303 and self-manage up to a maximum of four perceived episodes of PSVT with etripamil NS. The patient may receive two new treatment kits after every episode treated with etripamil NS provided that no adverse effect nor any eligibility criteria would preclude another administration of etripamil NS. NODE-303 will continue until the end of the development program, *i.e.,* when enough documented self-administrations of etripamil NS are included in the safety database.

2. TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

2.1 List of Tables

2.2 List of Figures

3. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular reentrant tachycardia
BDS	Aptar Pharma Nasal Spray Bidose System
BIPQ	Brief Illness Perception Questionnaire
CAQ	Cardiac Anxiety Questionnaire
CFR	Code of Federal Regulations
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CMS	Cardiac monitoring system
CRA	Clinical research associate
CRO	Clinical research organization
CSED	Common study end date
CSR	Clinical study report
ECG	Electrocardiogram
ED	Emergency department
EDTA	Disodium ethylene-diamine-tetra-acetic acid
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ENT	Ears nose throat
EP / EPL	Electrophysiology / Lab
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HR	Heart rate
IB	Investigator's brochure

ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Intranasal
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
MFD	Maximum feasible dose
NA	Not available / Not applicable
NS	Nasal spray
OL	Open label
PK	Pharmacokinetic
PRO	Patient reported outcome
PSVT	Paroxysmal supraventricular tachycardia
SAE	Serious adverse event
SBP	Systolic blood pressure
SAP	Statistical analysis plan
SC	Steering committee
SD	Standard deviation
SF-36	Short form (36) health survey
SOC	System organ class
SR	Sinus rhythm (normal)
TSQM-9	Treatment satisfaction questionnaire for medication
USB	Universal serial bus
VM	Vagal maneuver

4. INTRODUCTION

4.1 Background

Etripamil (also referred to as MSP-2017 in study documents), an L-type calcium channel antagonist and short-acting verapamil analog, is being developed by Milestone Pharmaceuticals Inc. (hereinafter Milestone) for the treatment of paroxysmal supraventricular tachycardia (PSVT), hereinafter used in reference to both the disorder and its associated tachyarrhythmia. A relatively common disorder, PSVT is characterized by episodes of tachyarrhythmia typically with a heart rate (HR) over 100 bpm and a QRS duration of <120 msec.[1] Etripamil is directed towards the 2 most common subtypes of PSVT, atrioventricular (AV) nodal reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT), together accounting for approximately 90% of PSVT cases.[1] In both conditions, a pharmaceutical agent capable of transiently prolonging AV conduction time can result in arrhythmia termination and restoration of normal sinus rhythm (SR).

Historically, intravenous (IV) verapamil has been used as an effective agent for treatment of acute episodes of PSVT.[2] However, it has been replaced in recent years by IV adenosine, which is equally effective in terminating acute episodes of PSVT.[3] Adenosine has the advantage of having a very short half-life, as it is rapidly metabolized during the time required to terminate an episode of PSVT.[4] However, the short half-life of adenosine renders it ineffective when given via routes of administration other than IV. As both of these medications require the establishment of IV access, they are not appropriate for a patient self-administration paradigm in an outpatient setting.

4.2 Clinical Experience

4.2.1 Phase 1 PK Study

A Phase 1 study (MSP-2017-1096) evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etripamil, with the aim of determining the maximum tolerated dose or maximum feasible dose (MFD) of 2 different formulations administered via the intranasal (IN) route in 30 healthy, adult male subjects. All etripamil doses were generally well tolerated, and there was no difference in the safety profile and PK between the 2 etripamil formulations (MSP-2017A and MSP-2017B). The study of formulation A was stopped at 60 mg, and formulation B was studied at 105 mg and 140 mg. Pharmacokinetic analyses demonstrated rapid absorption and elimination following IN administration of etripamil (across the dose range tested), and a dose proportional systemic exposure (area under the curve and maximum plasma concentration for MSP-2017 and its inactive metabolite [MSP-2030]) following administration of up to 140 mg of MSP-2017. The 140 mg dose was the MFD because neither the concentration (350 mg/mL) nor the volume (200 µL) of solution administered in each nostril could be increased.

MSP-2017-1205 (NODE-102) study was a randomized, double-blind, placebo-controlled, single dose, 4-way crossover, single dose Phase I study to assess the PK, PD, and safety and tolerability of etripamil NS at three dose levels and placebo in healthy Japanese and non-Japanese adults. The primary objective was to assess the safety and tolerability of etripamil in healthy Japanese and non-Japanese volunteers. The secondary objectives were to assess the PK and PD of etripamil in healthy Japanese and non-Japanese volunteers and the exploratory objectives were to assess the PK and PD of etripamil in healthy male and female volunteers.

A maximum of 24 participants, 12 Japanese and 12 non-Japanese, were planned and enrolled in the study and 23 completed the study (1 Japanese subject discontinued prematurely due to the

development of an adverse event). After signing the ICF, potential participants underwent screening procedures within 28 days of Day 1. Participants were admitted to the clinical unit on Day -1 and screening procedures were repeated to confirm their eligibility. Participants fasted overnight for at least 10 hours. On Day 1, participants were randomized to 1 of 3 treatment sequences (Placebo-70 mg-35 mg, 35 mg-Placebo-70 mg, or 70 mg-35 mg-Placebo) and received either a single intranasal dose of etripamil or placebo followed by a 2-week washout period between doses. Etripamil NS up to 105 mg was administered using the Phase 3 formulation Aptar Bi-dose nasal spray device (i.e., up to 3 sprays of 100 µL of 350 mg/mL etripamil formulation in each nostril). After the third period, all participants received a dose of 105 mg etripamil. The total study duration was approximately 3 months, including the screening and follow-up. Blood for PK assessments was collected before each dose and at 0.5, 1.5, 3, 5, 7, 10, 15, 25, 50, 90, 360, 720, and 1440 minutes after dosing. Urine for PK analysis was collected before dosing and over the intervals of 0-2 hours, 2-4 hours, 4-6 hours, 6-12 hours, and 12-24 hours after dosing. Vital signs and ECGs were measured at the corresponding PK time points.

Slightly more Japanese participants experienced a TEAE compared with non-Japanese participants and there were more TEAEs at the 105 mg dose compared with the 35 mg and 70 mg doses. However, at the 35 mg and 70 mg doses, the percentage of participants with TEAEs was within the range of values associated with placebo treatment. The most frequent TEAEs (>10%) were increased lacrimation, burning nose sensation, and rhinorrhea, occurring at all doses (including placebo). Each of these was considered by the investigator as related to treatment. Most TEAEs were mild or moderate in intensity, except 1 instance of burning nose sensation (non-Japanese participant at 105 mg etripamil dose) which was severe. There were no serious adverse events. One Japanese participant discontinued due to TEAEs (tearing, facial burning sensation, rhinorrhea). There were no trends in clinical laboratory changes and there were no TEAEs due to changes in clinical laboratory values. There were no meaningful changes in vital signs. Changes in ECGs were generally transient and judged to be not clinically significant by the Investigator.

In both Japanese and non-Japanese participants, etripamil exposure increased in a dose-proportional manner between 35 mg and 70 mg, while exposure at the highest dose of 105 mg was similar to what was seen at 70 mg.

4.2.2 Phase 2 Study

NODE-1 (MSP-2017-1109), a Phase 2 study, was conducted in the electrophysiology laboratory (EPL) as a proof-of-concept and dose response study in patients with documented history of PSVT. This Phase 2 study assessed the ability of etripamil to terminate an episode of PSVT induced in the EPL and was also designed to identify the dose(s) that will be taken in subsequent studies. The primary objective was to demonstrate the superiority of at least 1 dose of IN etripamil over placebo in terminating an episode of PSVT induced in the EPL. The secondary objectives were to establish a dose-related trend for etripamil, to determine the minimal effective dose of etripamil, and to evaluate the safety of etripamil in a clinical setting.

During a pre-study visit, patients were randomly assigned to 1 of the 5 following study groups in a 1:1:1:1:1 ratio: placebo, or etripamil nasal spray (NS) at 35, 70, 105, or 140 mg. Induction of PSVT was attempted using standard pacing and programmed stimulation methods. If PSVT could not be induced after a reasonable number of attempts, or could be induced but did not sustain for 5 minutes, IV isoproterenol was infused. After a minimum of 5 minutes in induced, sustained PSVT, patients were administered double-blind study drug NS via 4 pre-filled Aptar Pharma Unit

dose spray devices by EPL personnel using a double-dummy, multiple-dose design. Each device delivered 100 µL of either placebo or 35 mg of etripamil. The appropriate combination of active and placebo devices was used to deliver etripamil according to the dose (0, 35, 70, 105, or 140 mg) assigned at randomization and arranged so that all the active medication was administered prior to any placebo.

In total, 199 patients were randomized into the double-blind study; 95 withdrew prior to dosing: 70 due to inability to induce (n = 42) or sustain (n = 28) PSVT, 5 based on physician discretion, 1 lost to follow-up, 1 due to withdrawal of consent, and 18 for other reasons. In total, 104 patients had PSVT induced and sustained for ≥5 minutes and were dosed with study drug. In the population of the 104 patients who received the study drug, 56.7% were females and the mean age was 52.2 years. Isoproterenol was given to 46.2% of patients. The mean HR in PSVT at time 0 was 177 bpm in the placebo group and 168, 173, 180, and 155 bpm in the etripamil NS 35, 70, 105, and 140 mg groups, respectively. Overall, 87% of patients who were induced into PSVT had AVNRT.

Of the 104 patients in the Evaluable Population, 20 received etripamil NS 35 mg, 23 received etripamil NS 70 mg, 20 received etripamil NS 105 mg, 21 received etripamil NS 140 mg, and 20 received placebo. The percentage of patients in whom PSVT converted to SR within 15 minutes after study drug administration and in whom SR was maintained for at least 30 seconds (primary efficacy endpoint) was 35%, 65%, 87%, 75%, and 95% in the placebo and etripamil NS 35, 70, 105, and 140 mg groups, respectively. Applying the pre-specified hierarchy for determining significance, the 3 highest etripamil doses of 140, 105, and 70 mg showed statistically significantly greater conversion rates compared with placebo (see Table 1).

Table 1. Summary of Induced, Sustained Paroxysmal Supraventricular Tachycardia to Sinus Rhythm Conversion Within 15 Minutes After Study Drug Administration

	Placebo (N = 20)	**MSP-2017 35 mg (N = 20)**	**MSP-2017 70 mg (N = 23)**	**MSP-2017 105 mg (N = 20)**	**MSP-2017 140 mg (N = 21)**
Number (%) of patients converted to sinus rhythm within 15 minutes after study drug	7 (35.0)	13 (65.0)	20 (87.0)	15 (75.0)	20 (95.2)
Treatment comparisons					
Odds ratio (vs. placebo)	NA	3.45	12.38	5.57	37.14
95% CI of odds ratio (vs. placebo)	NA	(0.79, 15.46)	(2.28, 82.26)	(1.19, 27.63)	(3.84, 1654.17)
Fisher's exact test p-value (vs. placebo)	NA	0.1128	0.0006	0.0248	<0.0001
CMH p-value (vs. placebo)	NA	0.0802	0.0006	0.0125	<0.0001
Cochran-Armitage test p-value (trend test)	<0.0001				

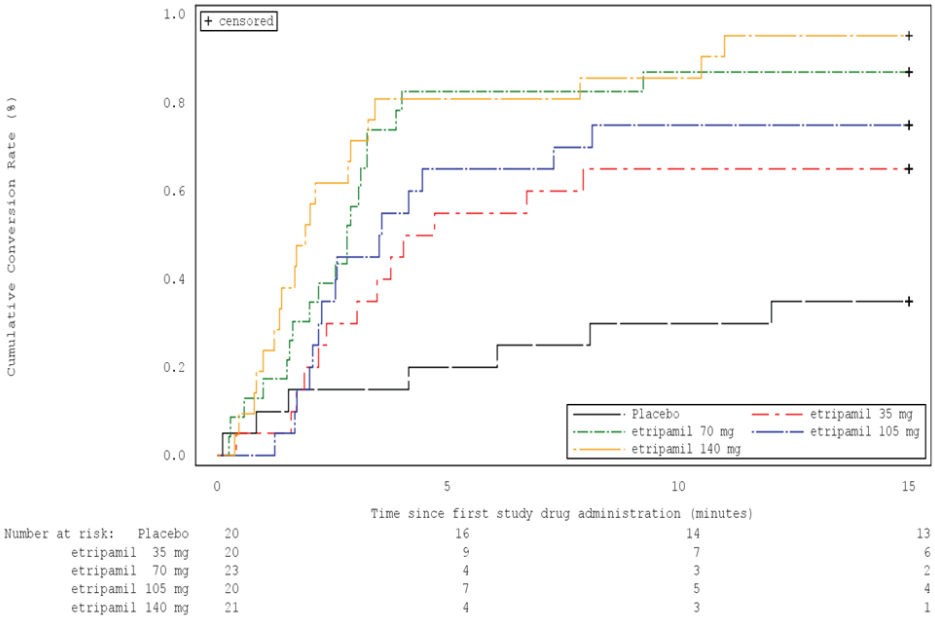
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = the number of patients in the Evaluable Population in the given group; NA = not available; vs. = versus.
Source: Clinical Study Report MSP-2017-1109

For the 3 etripamil doses with statistically significant conversion rates compared with placebo (70, 105, and 140 mg), mean times to conversion were all <3 minutes, with a shortest median time to conversion of 1.8 minutes in the etripamil NS 140 mg group. Only 7 (35%) patients had a successful conversion of PSVT within 15 minutes in the placebo group; therefore, 13 patients were censored at 15 minutes, and the median time to conversion is not available. The time to conversion

for the 7 patients who converted within 15 minutes was more widely dispersed in the placebo group compared with the etripamil groups.

Figure 1 shows the distribution of time to conversion for each patient reported as a Kaplan-Meier plot. Patients who did not convert within 15 minutes after study drug administration were censored at 15 minutes.

Figure 1. Kaplan-Meier Plot of Conversion 15 Minutes After Study Drug Administration



Note: Patients who did not convert within 15 minutes after study drug administration were censored at time 15.
Source: Clinical Study Report MSP-2017-1109

At least 1 adverse event (AE) considered related to the study drug, according to the Investigator assessment, was reported in 17 (85.0%) patients in the etripamil NS 35 mg group, 18 (78.3%) patients in the 70 mg group, 15 (75.0%) patients in the 105 mg group, 20 (95.2%) patients in the 140 mg group, and 4 (20.0%) patients in the placebo group. The incidence of AEs was not dose dependent.

Most AEs were mild (44.2%) or moderate (24.0%) across all treatment groups. A total of 3 severe AEs were considered possibly related to etripamil; 1 patient who received etripamil NS 35 mg experienced facial flushing, shortness of breath, and chest discomfort; and 2 patients who received etripamil NS 105 mg had nausea and vomiting (1 patient) and a serious AE (SAE) of cough (1 patient). There were no AEs that led to study discontinuation or death.

Adverse events that occurred with an incidence of >10% in any etripamil group and ≤10% in the placebo group were nasal discomfort, nasal congestion, oropharyngeal pain, rhinorrhea, cough, dysgeusia, increased lacrimation, vomiting, and nausea.

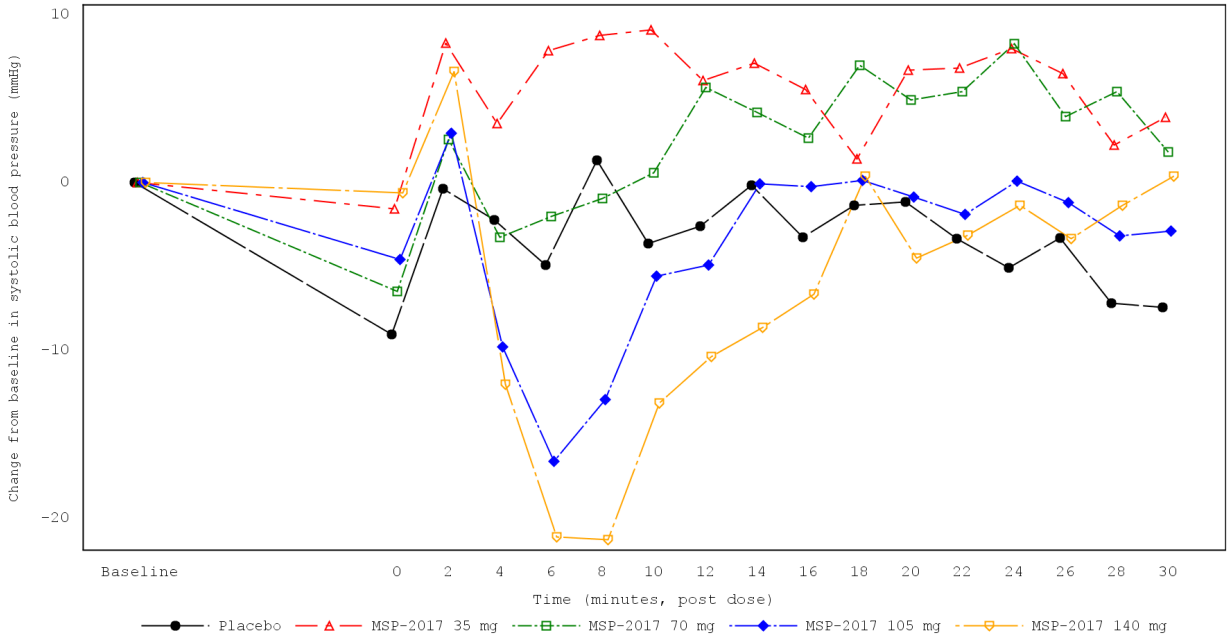
Of note, 1 patient had an episode of second-degree AV block with hypotension beginning 5 minutes after conversion to SR immediately following administration of etripamil NS 140 mg. Atrioventricular block resolved after 43 minutes, and ablation was subsequently performed.

The mean systolic blood pressure (SBP) was decreased from the baseline measurements (before PSVT induction) to measurements done in PSVT before study drug administration (time 0). A decrease of 7 mmHg was statistically significant in the placebo group only (Figure 2).

Compared with baseline, SBP measurements taken from 2 minutes to 16 minutes post-study drug administration demonstrated no decrease in mean SBP in the placebo and the etripamil NS 35 mg group, a minor change of 2 mmHg at 4 minutes post-dose in the etripamil NS 70 mg group, and decreases of 17 mmHg ($p<0.05$ versus baseline) 6 minutes post-dose in the etripamil NS 105 mg group, and 20 mmHg at 6 minutes and 8 minutes post-dose ($p<0.05$ versus baseline) in the etripamil NS 140 mg group.

There was no decrease in mean SBP compared to baseline from 16 to 30 minutes post-study drug administration when all patients were back in normal SR.

Figure 2. Mean Change in Systolic Blood Pressure (mmHg) Over Time



Note: Baseline is defined as the average of the 20 and 10 minutes pre-dose measurements. Time 0 is defined as the average of the measurement during PSVT between 0 and 5 minutes before study drug administration.
Source: Clinical Study Report MSP-2017-1109

4.2.3 NODE-301 Phase 3 Efficacy and Safety Study

NODE-301 (MSP-2017-1138), was a Randomized, Double-Blind, Placebo-Controlled Phase 3 safety and efficacy study of etripamil NS in patients with PSVT receiving the drug in an at-home setting. The study was conducted in the United States and Canada. Patients first received etripamil NS at the clinical site while in normal sinus rhythm during a Test Dose Visit. Patients who showed an acceptable safety and tolerability profile in the Test Dose Visit were randomized in a 2:1 ratio to receive either etripamil NS or matching placebo. They returned home and waited for a PSVT episode to occur, at which time they may have taken etripamil NS or placebo. Each episode was documented by an ambulatory Cardiac Monitoring System (CMS) that was placed on the chest by the patient or caregiver when symptoms began and recorded at least 5 hours of continuous electrocardiogram (ECG). After taking etripamil NS or placebo for the treatment of one PSVT

episode, a patient completed the NODE-301 study and was eligible for the open label extension study NODE-302.

In NODE-301 Part 1, 419 out of 431 subjects (97%) who received the test dose were randomized into the study. 198 subjects self-administered the study drug for a perceived episode of PSVT of which 156 subjects (79%) had positively adjudicated PSVT episodes; 107 (68.6%) subjects received etripamil and 49 (31.4%) subjects received placebo. Etripamil (70 mg) did not achieve its primary endpoint of time to conversion of PSVT to sinus rhythm compared to placebo over the 5-hour period following study drug administration. The hazard ratio (95% CI) at 5 hours was 1.086 (0.726, 1.623); P value 0.12 in favor of etripamil. The median time to conversion was 25 minutes [95% CI: 16, 43] for etripamil *vs.* 50 minutes [95% CI: 31,101] for placebo. A post hoc efficacy analysis of the NODE-301 Part 1 study demonstrated that within 30 minutes after drug administration, etripamil was highly effective, with a sinus rhythm conversion rate of 54% of etripamil subjects *vs.* 35% of placebo subjects, *i.e.*, approximately a 19% absolute difference. These results are consistent with the rapid onset of action of etripamil and the PK/PD profile of the drug and are similar to those observed in Phase 2 (NODE-1). Overall, the prolonged 5-hour efficacy observation period likely confounded the results of the primary analysis of the Phase 3 clinical trial.

A total of 431 subjects have received a test dose of etripamil 70 mg NS while in sinus rhythm and 198 subjects received study drug (138 etripamil 70 mg; 60 placebo) during a perceived episode of PSVT. There were no new or clinically relevant safety findings seen in NODE-301 Part 1 study. A total of 308 subjects have had at least one adverse event (AE). The maximum severity was mild (49.8%) or moderate (17.6%). The most commonly reported TEAEs occurring after study drug administration were nasal discomfort, nasal congestion, rhinorrhea, throat irritation and lacrimation. Severe TEAEs included throat irritation, drug hypersensitivity, rhinorrhea, epistaxis and hypotension, each reported in one subject. Fourteen serious adverse events were reported and were assessed by the Investigator as not related to the study treatment.

Of note, two subjects experienced syncope 168 and 68 days after the test dose of etripamil. One subject reported “near-syncope” prior to etripamil administration. Therefore, none of these events was related to the drug administration.

4.2.4 NODE-302 Phase 3 Open Label Extension Study

NODE-302 (MSP-2017-1158) was an open label extension study for NODE-301. This study is now closed and enrolled PSVT patients who had previously completed NODE-301, and followed them for multiple at-home administrations of 70 mg etripamil NS. Each episode was documented by an ambulatory CMS. As of the cut-off date (10 December 2020), 105 subjects have received at least one dose of etripamil 70 mg NS. This study is currently in the reporting phase.

There have been no new or clinically relevant safety findings seen in the MSP-2017-1158 study. A total of 57 (54.3%) subjects have had at least one AE. The maximum severity of treatment emergent adverse events (TEAEs) for most subjects was mild (44.8%) or moderate (7.6%). Severe AEs were reported in 2 (1.9%) subjects (rhinorrhea in 1 subject, and two episodes of epistaxis in 1 subject). These severe AEs were assessed as definitely related to the study treatment by the Investigator.

Eleven SAEs were reported in 9 (8.6%) subjects including 5 episodes of supraventricular tachycardia (3 moderate episodes in 1 subject), a mild and a moderate episode in 1 each subject,

bradycardia in 1 subject, syncope in 1 subject, ataxia in 1 subject, troponin increased in 1 subject, diverticular perforation in 1 subject and pancreatitis in 1 subject. All these SAEs were assessed by the Investigator as not related to the study treatment. The most commonly reported TEAEs to date (regardless of relationship to study drug) were nasal discomfort, nasal congestion, and rhinorrhea.

Of note, two subjects reported an episode of syncope 49 and 126 days from the last etripamil administration. None of them were considered related to etripamil by the Investigator.

4.2.5 NODE-301 Part 2, the RAPID study

NODE-301 is a multicenter, randomized, double-blind, placebo-controlled, efficacy, and safety study of etripamil NS 70 mg for the termination of spontaneous episodes of PSVT. This study consists of 2 parts:

- NODE-301 Part 1 consisted of subjects that were dosed with the double-blind study drug or had discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode.
- NODE-301 Part 2 (the RAPID Study, ongoing) consists of subjects randomized into Part 1 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, and new subjects enrolled into the study following the completion of Part 1.

Based on the results of Part 1, subjects in Part 2 of NODE-301 (RAPID) will be randomized to a dosing regimen that will permit a second 70 mg dose if symptoms still persist at 10 minutes after the first dose. The primary efficacy endpoint is defined as time to an adjudicated termination of a positively adjudicated episode of PSVT and conversion to sinus rhythm for at least 30 seconds within 30 minutes of start of study drug dosing.

4.3 Rationale for the Study

The primary objective of this study is to characterize the safety of etripamil NS for the patient-administered treatment of acute episodes of PSVT outside of the clinical setting. The secondary objectives of the study are to further evaluate the efficacy of etripamil NS for the patient-administered treatment of acute episodes of PSVT outside of the clinical setting, to evaluate the impact of etripamil NS on PSVT disease burden (as measured by CMS, PROs, and healthcare utilization data) and to evaluate the safety and efficacy of etripamil NS when used for multiple PSVT episodes. The study is designed to capture safety data when using etripamil NS in a real-world setting.

Etripamil NS addresses an unmet medical need since there are currently no short-acting products available for patient self-administered treatment of episodes of PSVT. The only currently available acute pharmacological therapy is IV treatment with adenosine or verapamil in a hospital environment, which is expensive and greatly inconveniences the patient. A self-administered product for PSVT would give patients the option to safely terminate acute episodes of PSVT without the need for a hospital visit. An episodic treatment option may also allow selected patients to discontinue chronic prophylactic therapy with Class I, II (*e.g.*, beta-blockers), III, and/or IV (*e.g.*, calcium channel blockers) antiarrhythmic agents, thus avoiding the side effects and quality of life implications associated with these medications. Furthermore, patients weighing the risks of bridging therapy and an invasive catheter ablation procedure to address their PSVT would have

the opportunity to consider episodic management with etripamil NS as a viable alternative treatment option. This large study will further characterize the benefit to risk assessment.

4.4 Summary of Potential Risks and Benefits

The potential risks of study participation include those associated with exposure to etripamil NS.

The assessment includes the risks of medical evaluation, including venipuncture. Adverse events (AEs) associated with etripamil NS include nasal irritation, nasal discomfort, and throat irritation. Potential adverse events which have been rare or not observed in studies to date include other cardiac arrhythmias, or AEs associated with drops in blood pressure (dizziness, headache).

The primary benefit of this study is that patients may be able to safely and rapidly terminate acute episodes of PSVT without the need for a hospital visit to receive IV medication. Patients may also be able to discontinue chronic prophylactic therapies they are taking for PSVT. Patients who are waiting for, ineligible, or unwilling to undergo ablation procedures may have an option for at-home treatment of their PSVT episodes.

A summary of the pharmaceutical properties and known potential risks of etripamil NS is provided in the current version of the Investigator's Brochure (IB).

5. OBJECTIVES

5.1 Primary Objective

The primary objective is to evaluate the safety of self-administered etripamil NS outside of the clinical setting.

5.2 Secondary Objectives

The secondary objectives are;

1. To evaluate the efficacy of self-administered etripamil NS outside of the clinical setting, and
2. To evaluate the impact of etripamil NS on PVST disease burden, and
3. To evaluate the safety and efficacy of etripamil NS when used for multiple PSVT episodes.

6. STUDY DESIGN

6.1 Overall Study Design and Plan

NODE-303 is a multi-center, open label (OL) study to evaluate the safety of etripamil NS in patients with PSVT. Patients will be provided with an ambulatory Cardiac Monitoring System (CMS) to help document PSVT episodes. The CMS will be self-applied by the patient, when they feel the onset of PSVT symptoms. Patients will then self-administer the dose regimen of etripamil NS if vagal maneuver (VM) is ineffective. After each episode of perceived PSVT for which etripamil NS was administered, the patient will return to the investigative site, and have the option to continue in NODE-303 and manage subsequent episodes of PSVT with etripamil NS.

The Study is divided into four parts: A Screening Visit, a Baseline Visit, a Treatment Period (with up to 3 Follow-up Visits), and a Final Study Visit.

6.1.1 Screening Visit (Within 30 days of Baseline)

See Section 9.1.1 for a full description of study procedures during the Screening Visit.

Prospective study patients will be required to sign an informed consent form before the commencement of any study-related assessments or procedures.

If a screened patient meets at least 1 exclusion criterion, the patient will be considered a screening failure. Re-screening may be allowed after consultation between the Investigator and Medical Monitor, or should the inclusion/exclusion change.

During the Screening Visit the Investigator or designee will obtain the signed informed consent, will verify that the patient meets the eligibility criteria of the NODE-303 study, take blood and urine for laboratory evaluations, and conduct other screening procedures. The informed consent for NODE-303 will be applicable for the total duration of participation in the study including up to 4 treated perceived PSVT episodes.

The Screening Visit may occur up to 30 days prior to the Baseline Visit to allow time for safety laboratory parameters, review of the safety ECG, and any washout of background medications. Screening ends when the patient completes a Baseline Visit and is dispensed study drug or is determined to be a Screen failure.

6.1.2 Baseline Visit

See Section 9.1.2 for a full description of procedures to conduct during the Baseline Visit.

The Baseline Visit will occur after screening procedures are completed, and clinical laboratory evaluations are available. As detailed in Section 9.1.2, it is permitted to conduct the Screening and Baseline Visits on the same day, using a local laboratory to conduct preliminary clinical laboratory evaluations. The site will confirm patient eligibility, record any changes to concomitant medications, train the patient on study procedures (drug administration, PRO, CMS), and give the patient study drug, PRO materials, and the CMS materials. Patients will complete their first PRO measure on-site at the Baseline Visit. The site will provide the patient with training and any other study materials.

6.1.3 Treatment Period

Full details on the procedures a patient and site perform can be found in Section 9.1.3.

The Treatment Period refers to the duration of the study after a patient has completed their Baseline Visit and been given study drug and sent home until they discontinue from the study, complete the study, or the overall study is completed. During the Treatment Period, when a patient has a perceived episode AND takes study drug, they will return to the clinic for a Follow-up Visit and return their used and unused nasal spray devices. If the patient does not take study drug for a perceived PSVT episode, they may continue in the Treatment Period if they have sufficient CMS materials to record another episode (See Section 9.3.2.4 for CMS details). Patients may continue in the study until they have treated a total of 4 perceived PSVT episodes. After the fourth treated episode patients will complete a Final Study Visit and may be eligible for participation in an early drug access program in line with local regulations.

Patients

During the Treatment Period, patients will complete a monthly survey regarding their quality of life and PSVT. Patients will receive reminders via the PRO platform regarding study participation and how to use etripamil NS and the CMS. Site phone contacts for patients not completing the PRO questionnaires regularly will also be made. During the Treatment Period, the patient should self-identify symptoms of PSVT. When an episode occurs, they will apply the CMS, then perform a VM, and self-administer etripamil NS if the symptoms do not resolve during or after the VM. Patients will complete the TSMQ-9 questionnaire (if they administer etripamil NS) and other specified questions related to an episode within 24 hours after each episode resolves.

If the symptoms of PSVT have not resolved within 30 minutes after initial study drug administration, the patient may seek appropriate medical care as needed. If the patient goes to a medical facility for PSVT treatment, they must give the study identification card included in the study kit to the on-site medical personnel. This study identification card will contain a brief description of the study, a description of study drug, and the Investigator (study physician) contact information.

Sites

During the Treatment Period sites will follow up via phone with patients who have failed to complete two consecutive monthly electronic surveys. During this follow-up phone call, sites should remind patients to complete their monthly PRO, and to schedule a Follow-up Visit if they have a perceived episode and take study drug. Sites will be notified of patients who fail to complete their electronic PRO as required. They should also contact patients who have had a perceived episode as identified by the PRO system to schedule any required Follow-up Visits or provision of new CMS materials.

Details on the use of CMS can be found in Section 9.3.2.4. Details on the patient reported outcome can be found in Section 9.3.1.1.

6.1.4 Follow-Up Visits (up to 14 days after an episode)

A full description of the procedures to be conducted during a Follow-up Visit is provided in Section 9.1.4.

After a patient experiences a perceived PSVT episode AND takes study drug, they should return to the clinic for a Follow-up Visit. During this visit, the Investigator will evaluate the results of the last usage of etripamil NS and will decide whether the patient can continue in the study and receive two additional study drug kits.

To continue in the study patients will:

1. Continue to meet the inclusion/exclusion criteria of the most current protocol version
2. Have completed the latest version of the Informed consent form (ICF)
3. Express a willingness and desire to continue in the study
4. Have treated less than 4 perceived PSVT episodes with etripamil NS in this study

If the patient continues in the Treatment Period, the site will provide any required retraining and dispense two additional study drug kits, and any CMS materials required. Patients who have

treated 4 perceived PSVT episodes with etripamil NS in this study may be eligible for the early drug access program as per local regulations.

6.1.5 Final Study Visits

See Section 9.1.5 for a full description of procedures during a Final Study Visit.

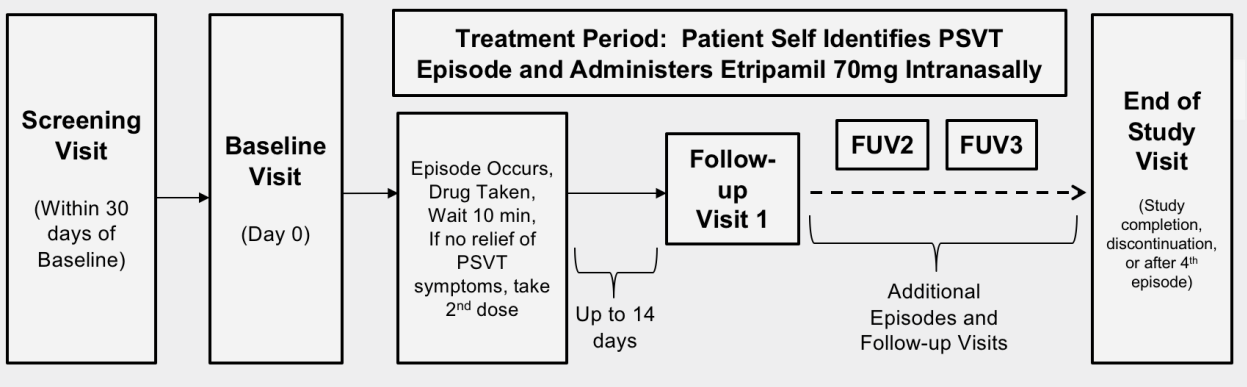
Final Study Visits will occur when a patient discontinues or withdraws from the study, completes the study (reaches the maximum number of treated perceived PSVT episodes in the study), or when the overall study is completed. These visits have similar procedures to a Follow-up Visit, except no new study drug is dispensed.

6.2 Discussion of Study Design

Comparative double-blind efficacy and safety data on self-administered etripamil NS in patients with PSVT is being collected in the ongoing Phase 3 study NODE-301 and uncontrolled safety and efficacy is being collected in the open-label extension study NODE-302. To further characterize the safety of etripamil NS, a larger number of patients need to be studied outside the clinical setting. The NODE-303 design is appropriate to provide a measurement of etripamil NS safety in a use setting which closely mimics a real-world setting.

The study design is depicted in Figure 3.

Figure 3. NODE-303 Study Design



6.3 Rationale for Dosing

The choice of the dose level of etripamil NS (70 mg) was made according to the data obtained in Phase 1 and Phase 2 studies. The selected dose is also being studied in the ongoing Phase 3 program, Studies NODE-301 and NODE-302.

In the Phase 1 study, etripamil 140 mg was determined to be the MFD with the current formulation based on the maximal concentration of etripamil and the required volume of administration (up to 220 µL of the solution) in each nostril. The 4 highest doses tested in Phase 1 (30, 60, 105, and 140 mg) produced an increase in the PR interval of the ECG that was consistent with the necessary PD effect required to convert reentry tachycardia involving the AV node to SR (see Section 4.2).

Four doses (35, 70, 105, and 140 mg) were tested in the NODE-1 Phase 2 study. The 3 highest doses (70, 105, and 140 mg) were statistically significantly superior compared with placebo for terminating induced PSVT in the EPL within 15 minutes of dosing; in addition, the time to

conversion of PSVT to SR was shorter with these doses compared with placebo. The E_{max} model of dose response indicates that these 3 doses are at the plateau of the dose response, whereas the 35 mg dose is in the ascending portion of the curve (see Section 4.2.2).

A drop in SBP versus baseline was observed with the 105 and 140 mg doses between 4 and 10 minutes after etripamil administration, with mean reductions of 11.4% (105 mg), and 15.6% (140 mg) mmHg. These decreases were generally asymptomatic and quickly resolved. Mean SBP did not drop following administration of etripamil 35 and 70 mg.

Etripamil NS 70 mg satisfies the need to balance benefit and risk. The required delivery dose (70 mg) is well tolerated; efficacy (measured in PSVT termination rate) is at the plateau of the dose response curve; and the AE profile is acceptable, with no post-dose reductions observed in SBP.

The protocol Version 2.0, Amendment No. 1 introduces a new etripamil NS dose regimen to the study protocol. The treatment regimen of etripamil to be evaluated is an initial dose of etripamil NS 70 mg (one spray of 100 µL in each nostril), to be followed by a second dose (one spray of 100 µL in each nostril) 10 minutes later (not to exceed 15 minutes) if the patient continues to experience PSVT symptoms. Patients who are symptom-free within 10 minutes after the first dose do not repeat the dose.

In study MSP-2017-1096, two 30 mg doses given 10 minutes apart demonstrated that drug exposure and PR interval increased and remained elevated for a longer period as compared to the single 30 mg dose. Based on these clinical data, combined with the post hoc analysis of the NODE-301 Part 1, a new dosing regimen was adopted for the RAPID study (NODE-301 Part 2) that allows subjects to receive a second dose of etripamil NS 70 mg 10 minutes after the first dose if the symptoms of PSVT persist (*i.e.*, a total of 140 mg etripamil NS only to subjects who do not respond to etripamil NS 70 mg at 10 minutes post dose). This new dosing regimen aims to increase etripamil exposure and its overall PD effect. In addition, the split-dose regimen reduces the volume of spray administered at one time in the nostrils, compared to what would be required to administer a higher dose of drug in a single administration (a lower spray volume is associated with greater bioavailability). Therefore, it is legitimate to study the same dose regimen in this large open label study.

6.4 Inclusion/Exclusion

To enroll in the study a patient should be diagnosed with PSVT by a medical professional, and report having had at least one previous episode of PSVT. For clarity, PSVT refers to episodic SVT that includes the AV node as a critical part of the reentrant circuit.

Documentation of patient's PSVT should be similar to what would be generated in a real-world setting. The study does not require that AV nodal involvement be confirmed by electrocardiographic study, and suspected AV nodal dependent SVT is sufficient for inclusion. Suspected AV nodal dependency on an electrocardiographic recording is based on the following criteria: regular rhythm, heart rate above 100 bpm, narrow QRS complex, and possibly retrograde P waves. Appropriate documentation to support enrollment of a patient in NODE-303 would include;

- Electrocardiographic documentation such as:
    - 12-lead ECG

  - Holter study
  - Ambulatory monitor, including mobile or wearable devices
  - Electrophysiology study
- Confirmation of arrhythmia conversion after adenosine or CCB administration
- Documentation (report, hospital or ED discharge summary, or physicians' notes) confirming a history of PSVT from an electrophysiologist, cardiologist, or emergency physician who had obtained electrocardiographic evidence of PSVT in the past
- Documentation from other medical personnel should be discussed with the medical monitor

Patients who have had an ablation should have evidence (electrocardiographic and repeated clear symptoms) of PSVT occurring after the ablation in order to be enrolled in NODE-303.

Patients who plan to have an ablation may be enrolled in the study if they are expected to have at least one PSVT episode prior to the planned ablation. It is not required that patients agree to participate in the study for the maximum 4 episodes in order to be enrolled, only 1 episode is required.

Patients to be enrolled in the study should generally experience symptomatic PSVT episodes which last more than 5 minutes. Patients with asymptomatic PSVT, or with short duration of episodes are unlikely to benefit from etripamil and should not be enrolled in the study. *Note that an actual tracing showing PSVT for longer than 5 minutes is not required for inclusion in the study.*

7. STUDY POPULATION

7.1 Selection of Study Population and Diagnosis

The Study will enroll up to approximately 3000 patients in order to obtain up to 1500 patients (in overall development program) with a perceived PSVT episode within 24 months of study enrollment. Patients will be diagnosed with PSVT by a medical professional and will have reported having at least one previous episode of PSVT prior to study screening.

7.2 Study Entry Criteria

7.2.1 Inclusion Criteria

A patient will be eligible for study participation if they meet all of the following criteria:

1) Has been diagnosed with PSVT by a medical professional and reports having at least one previous episode of PSVT. For clarity, PSVT refers to episodic SVT that includes the AV node as a critical part of reentrant circuit. See Section 6.4 for details on diagnostic criteria.
2) Is at least 18 years of age.
3) Signed NODE-303 written informed consent.
4) Women of child-bearing potential must be willing to use at least 1 form of contraception during the trial and must be willing to discontinue from the study should they become or plan to become pregnant. Postmenopausal females are defined as having amenorrhea for at least 12 months prior to Screening without an alternative medical cause.
5) Willing and able to comply with study procedures.

7.2.2 Exclusion Criteria

A patient will be excluded from the study if they meet any of the following criteria:

1) Patients with only a history of atrial arrhythmia that does not involve the atrioventricular (AV) node as part of the tachycardia circuit (*e.g.,* atrial fibrillation, atrial flutter, intra-atrial tachycardia) are not eligible. Patients with a history of these tachycardias who are also diagnosed with PSVT are eligible.
2) History of allergic reaction to verapamil.
3) Current therapy with digoxin, or any Class I or III antiarrhythmic drug. Patients may be eligible if these drugs are stopped at least five half-lives before the administration of etripamil NS. The only exception is oral amiodarone which must be stopped 30 days before enrollment.
4) History or evidence of ventricular pre-excitation, *e.g.,* delta waves, Wolff-Parkinson-White syndrome.
5) History or evidence of a second- or third-degree AV block.
6) History or evidence of severe ventricular arrhythmia (*e.g.*, torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia).
7) Symptoms of congestive heart failure New York Heart Association Class II to IV.
8) SBP < 90 mmHg at Screening, Baseline or any Follow-up Visit.
9) Severe symptoms of hypotension experienced during PSVT episodes.
10) Significant physical or psychiatric condition including alcoholism or drug abuse, which, in the opinion of the Investigator, could jeopardize the safety of the patient, or impede the patient's capacity to follow the study procedures.
11) History of syncope due to an arrhythmic etiology at any time, or history in last 5 years of unexplained syncope.
12) Is pregnant or breastfeeding.
13) Previously enrolled in a clinical trial for etripamil and received study drug or participation in any clinical trial for other investigational products or medical devices within 30 days of Screening.
14) History of ACS or stroke within 6 months of Screening.
15) Evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the Screening Visit as follows:
    a) <60mL/min/1.73m^2 for patients <60 years of age
    b) <40mL/min/1.73m^2 for patients ≥60 and <70 years of age
    c) <35mL/min/1.73m^2 for patients ≥70 years of age.

7.3 Patient Discontinuation/Withdrawal

All patients will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable

attempt to keep patients in the study; however, patients must be withdrawn from the study if they withdraw consent to participate.

After a patient self-administers a dose of etripamil NS to treat the fourth perceived PSVT episode in this study, they should return for a Final Study Visit within 14 days of the episode, not a Follow-up Visit, and they may be eligible for the early drug access program as per the local guidelines.

Investigators must attempt to contact patients who fail to attend scheduled visits to verify continued participation in the study, or if the patient is withdrawing from the study. If a patient withdraws, the reason for withdrawal should be determined, and if an AE was the cause of withdrawal, the AE must be documented, reported, and followed as described in Section 10.2.

Milestone reserves the right to request the withdrawal of a patient because of protocol violations or other reasons.

The investigator also has the right to withdraw patients from the study or discontinue study drug treatment at any time for apparent lack of therapeutic effect, or drug treatment that is intolerable or otherwise unacceptable to the patient, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the patient's best interest.

If a patient is withdrawn or discontinues treatment, the reason and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at a Final Study Visit should be performed at the time a patient withdraws from the study. Common reasons expected to lead to discontinuation for patients in this study include;

- Patient goes on to receive ablation therapy. See Section 8.7 for more information regarding ablations
- Patient does not want to continue to additional Treatment Periods

8. TREATMENTS

8.1 Identification of Investigational Product

The formulation of etripamil is for IN administration and will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid (EDTA), and sulfuric acid.

8.2 Labeling and Packaging

Clinical labeling and packaging of the study drug will be performed by Catalent.

8.2.1 Labeling

Study drug will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practice (GMP) and International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. In compliance with these regulations and guidelines, the label may include information such as the study protocol number, administration sequence, lot number, storage conditions, expiry date, Sponsor identification, or appropriate cautionary language for investigative material. Proof labels, detailing actual label text, will be available in the study files.

8.2.2 Packaging

Study drug will be packaged according to current GMP and ICH GCP guidelines. The study drug distributor will package the study drug. Study drug will be identified with a kit identifier. Each kit will contain one 70 mg nasal spray device, patients will receive two kits. The kit identifiers for each patient will be recorded in the Cenduit clinical supply tracking system for the study.

8.3 Treatments Administered

The treatment regimen of etripamil is an initial dose of etripamil NS 70 mg (one spray of 100 µL in each nostril), to be followed by a second dose (one spray of 100 µL in each nostril) 10 minutes later (not to exceed 15 minutes) if the patient continues to experience PSVT symptoms. Patients who are symptom-free within 10 minutes after the first dose do not repeat the dose.

The devices will be prefilled and packaged. Instructions for its use will be provided to the patient.

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.

If the BDS does not deploy, it will be considered a missed dose. If only one spray, per dosing session, of the BDS is administered for any reason, it will be considered a partial dose. Missed and partial doses will be recorded in the eCRF.

8.4 Additional Medical Intervention

During an episode, if the symptoms of PSVT have not resolved within 30 minutes after initial study drug administration, the patient may seek appropriate medical care as needed. If the patient goes to a medical facility for PSVT treatment, they must give the study identification card included in the study kit to the on-site medical personnel. This study identification card will contain a brief description of the study, a description of study drug, and the Investigator (study physician) contact information.

Sites will enter all concomitant medications taken and concomitant procedures conducted during any medical facility visit in the EDC.

8.5 Drug Storage and Accountability

Study drug will be stored at the clinical site at ambient room temperature (15°C to 30°C [59°F to 86°F]) and will be protected from light in a secure area with access limited to authorized personnel.

During the study, the patient will be instructed to keep and return used and unused BDS devices to the site at each Follow-up Visit for drug accountability. Patients will be instructed to maintain the study drug in an ambient temperature environment at all times. At the conclusion of the study, patients will return unused study drug to the site for drug accountability during their Final Study Visit.

Records will be maintained at each clinical site indicating the receipt and dispensation of all study drug supplies. The responsible pharmacist or designee at the investigational site must keep an accurate inventory of study drug shipments received and the amount of study drug used or not used by each patient. A full reconciliation of drug inventory will be performed at the end of the study, and the results of the inventory will be recorded in the drug accountability log.

The final accountability of study drug (both used and unused kits) will be performed by the Clinical Research Associate (CRA) at the sites. The sites will be allowed to destroy study drug after CRA accountability. If sites are not able to destroy drug, they should return drug for destruction. The details about drug return are outlined in the Pharmacy Manual provided to the sites. If no study drug remains at a site, this will be indicated in the drug accountability log.

8.6 Treatment Compliance

All doses of the study drug will be administered by the patient in an at-home setting. Patients will report whether they took study drug, and at what date and time they took study drug.

Dosing details will be recorded in the patient's eCRF.

8.7 Prior and Concomitant Therapies

All concomitant medications and treatments used within 30 days of the Screening Visit (including over-the-counter medications and herbal supplements) until the Final Study Visit will be recorded in the source document and on the appropriate eCRF.

Current therapy with digoxin, or any Class I or III antiarrhythmic drug is not allowed during the study. Patients may be eligible to participate if these drugs are stopped at least five half-lives before the study drug is dispensed. The only exception is oral amiodarone which must be stopped 30 days before study drug is dispensed. The 30-day maximum duration between Screening and Baseline Visits allows patients to wash-out amiodarone.

Class I or III Antiarrhythmic drugs used on an acute basis (*e.g.*, lidocaine) for a procedure or treatment will NOT require a patient be withdrawn from the study. These patients will be instructed not to take etripamil NS for at least 5 half-lives of the concomitant antiarrhythmic drug, unless the drug is amiodarone. Amiodarone use during the study is prohibited.

The use of any drugs of abuse which, in the opinion of the Investigator, would impact the validity of the study results is prohibited.

Ablation: Patients who plan to have an ablation for the treatment of their PSVT are eligible to enroll in the study so long as they are deemed highly likely to have a PSVT event prior to the ablation Enrolled patients who are scheduled to receive an ablation procedure for the treatment of PSVT in a time frame which makes it unlikely they will have an at-home episode of PSVT treated with etripamil NS, should withdraw from the study and complete a final Follow-up Visit prior to the ablation procedure. Patients who have previously had an ablation for the treatment of PSVT that is determined to be unsuccessful are eligible to enroll in the study if they experience PSVT episodes after the ablation is completed and should have evidence (electrocardiographic and repeated clear symptoms) of PSVT occurring after the ablation.

If a patient starts or plans to start any prohibited medication or treatment, they should withdraw from the study and complete a Final Study Visit.

9. STUDY PROCEDURES

Prospective study patients will be asked to sign the informed consent form (ICF) before the commencement of any study-related assessments or procedures, including the cessation of prohibited concomitant therapy. Patients who have previously consented will be asked to sign a new ICF in the event that its contents have been updated, at the time of their next scheduled study visit.

For a summary of assessments and procedures throughout the study, refer to the schedule of assessments (Section 17.1).

9.1 Study Periods, Visits, and Procedures

9.1.1 Screening Visit (Days -30 to -1)

Prospective study patients will be asked to sign the informed consent form before the commencement of any study-related assessments or procedures.

If a patient meets at least 1 exclusion criterion, the patient will be considered a screening failure. Re-screening may be allowed after consultation between the Investigator and Medical Monitor, or should the inclusion/exclusion change.

The Screening Visit will include at least one visit to the clinic, during which the Investigator or designee will verify that the patient meets the eligibility criteria of the NODE-303 study, will obtain the signed informed consent, and conduct screening procedures. The informed consent for NODE-303 will be applicable for the duration of the study period; ICF should be signed again at the following scheduled study visit in the event its contents are updated during the study.

The Screening Visit may occur up to 30 days prior to Baseline to allow time for safety laboratory parameters, review of the safety ECG, and any washout of background medications. Screening ends when the patient is dispensed study drug or screen fails.

The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Assign a patient number via IRT system.
3. Review inclusion/exclusion criteria.
4. Record demographics and detailed medical history, including review of medications taken within 30 days before Screening.
5. Record concomitant medications. Patients on prohibited therapies may participate in the study if these drugs are stopped at least five half-lives before study drug is dispensed. The only exception is oral amiodarone which must be stopped 30 days before study drug is dispensed.
6. Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems (See Section 9.3.2.3.3 for systems).
7. Record vital signs (blood pressure, heart rate) after the patient has been in a seated position for at least 5 minutes.
8. Measure height and weight.
9. Collect blood and urine samples for clinical laboratory tests (hematology, serum chemistry, pregnancy test, and urinalysis); see Section 9.3.2.2.1 for a complete list of required laboratory tests.

10. Conduct a 12-lead ECG reading, upload results to the archive. A previous 12-lead ECG (taken within 1 month prior to the Screening Visit) of sufficient quality to fully assess patient safety and eligibility may be used by the site as long as there has been no significant change in the patient's underlying condition or general health (such as having an ablation, or other cardiac event). Previous ECGs should also be uploaded to the archive.
11. Receive results of clinical laboratory tests, review the ECG, and confirm patient eligibility.

9.1.2 Baseline Visit

The Baseline Visit will occur after screening procedures are completed.

To ensure the safety of trial participants in NODE-303, and to reduce the risks associated with the COVID-19 pandemic by reducing the number of visits the patient is required to make to the investigative site, it is permitted that all Screening Visit procedures and Baseline Visit procedures be conducted on the same day. In this case, duplicate Screening Visit blood and urine samples will be collected, one set will be sent to the central laboratory, and the second set will be analyzed by a local laboratory. If there are no exclusionary results from the local laboratory, the patient will be permitted to continue with the Baseline Visit procedures. If the patient successfully completes all Screening and Baseline Visit procedures, and is preliminarily enrolled (pending receipt of results from the central laboratory), they will be dispensed study medication and all study materials, but instructed not to use the study medication until they are informed by the investigative site that the results have been received from the central laboratory, there are no exclusionary results and the patient has been successfully enrolled. The official date of enrollment of the patient into the study will be the date the site receives the results from the central laboratory. If there are exclusionary results from the central laboratory, the patient will return to the site, be withdrawn from the study and complete a Final Study Visit.

The local laboratory will not be certified for use in the study, and the local laboratory results will not be entered into the study database but will be retained in the patient's site study file.

The following procedures will be performed at the Baseline Visit:

1. Charge the patient's CMS Device prior to the visit.
2. Confirm patient remains eligible for the study.
3. Record any changes in concomitant medications.
4. Train patients on how to use the PRO (See Section 9.3.1.1 for full details on the PRO), the CMS, and the etripamil nasal spray device,
5. Provide patient with patient instructions and other materials.
6. Have the patient complete a baseline PRO survey while on-site, but may complete the validated scales (BIPQ, CAQ, SF-36) up to 48 hours after the Baseline Visit.
7. Determine how much CMS material a patient is likely to need (patients with frequent short episodes for which they may not use etripamil NS may require additional materials).
8. Once all other Screening and Baseline procedures are complete, dispense two study drug kits and CMS materials.

9.1.3 Treatment Period (Until patient withdrawal, completion, or discontinuation)

The Treatment Period refers to the duration of the study after a patient has been given study drug and sent home until they have a perceived episode, discontinue from the study, or the overall study is completed. After a patient has a perceived episode AND takes study drug, they should return to

the clinic for a Follow-up Visit (see Section 9.1.4 below). If the patient does not take study drug for a perceived PSVT episode, they may continue in the Treatment Period. Patients may continue in the study until they have treated a total of 4 perceived PSVT episodes with etripamil NS, after which they will complete the study and may be eligible for the early drug access program as per local guidelines.

During the Treatment Period, patients will complete a monthly survey regarding their quality of life and PSVT. Patients may receive reminders regarding study participation and how to use etripamil NS and the CMS during the Treatment Period. During this period, the patient should self-identify symptoms of PSVT. When an episode occurs, they will perform a VM, and self-administer etripamil NS if the symptoms do not resolve during or after the VM. Patients will complete the TSMQ-9 questionnaire (if they administer etripamil NS) and other specified questions related to an episode within 24 hours after each episode resolves.

If the symptoms of PSVT have not resolved within 30 minutes after initial study drug administration, the patient may seek appropriate medical care as needed. If the patient goes to a medical facility for PSVT treatment, they must give the study identification card included in the study kit to the on-site medical personnel. This study identification card will contain a brief description of the study, a description of study drug, and the Investigator (study physician) contact information.

Full details on the CMS can be found in Section 9.3.2.4. Details on the patient reported outcome system can be found in Section 9.3.1.1.

The following procedures will be performed by the Site during a Treatment Period:

1. Follow up via phone with patients who have failed to complete two consecutive monthly surveys.
2. Contact patients who have had a perceived episode as identified by the patient reported outcome system and schedule a Follow-up Visit if they took study drug.
3. If a patient runs out of CMS materials but has not taken study drug, provide additional materials to the patient.

The following procedures will be performed by the patient during a Treatment Period:

1. Patients will complete the monthly PRO survey throughout the Treatment Period.
2. When a patient self-identifies that a PSVT episode is occurring they should;
    a. If possible, log in to the PRO system for step by step guidance on procedures.
    b. Apply the CMS.
    c. Perform a VM. If symptoms resolve after this VM, patients should NOT take drug. They should remove the CMS Device from its connection, and switch it off, complete the other episode survey questions on the PRO, and continue in the Treatment Period. If symptoms do not resolve, they should proceed with the procedures below.
    d. Self-administer etripamil NS.
    e. Mark the time etripamil NS was taken by pressing on the CMS Device as trained by site staff.

f. If symptoms persist after 10 minutes have passed since taking etripamil NS, the patient should self-administer a second dose of etripamil NS. If symptoms persist 30 minutes after the initial administration the patient may seek additional medical care as needed.
g. Keep the CMS Device on for at least 1 hour after taking etripamil NS.

3. After a PSVT episode occurs during which study drug was taken, the patient should;
   a. As soon as possible after an episode has resolved, complete the TSQM-9 questionnaire and other episode survey questions on the PRO.
   b. After wearing the CMS for at least 1 hour following the initial administration of the drug, they should switch off the CMS Device and remove the CMS from the chest and the device from the connecting electrodes.
   c. Contact their clinical site to schedule a Follow-up Visit.
   d. Keep the empty etripamil nasal spray device(s) and bring them together with any unused etripamil NS to the Follow-up Visit.
   e. Bring the CMS Device with them to the Follow-up Visit.
   f. If a patient requires additional CMS system materials (patches or training materials), they should contact the site to get the needed materials.

9.1.4 Follow-up Visit (up to 14 days after an episode)

After a patient experiences a perceived PSVT episode AND takes study drug, they should return to the clinic for a Follow-up Visit. If the patient has a perceived episode but did not take study drug, they do not need to schedule a Follow-up Visit. During this visit, the Investigator will evaluate the results of the last usage of etripamil NS, along with the CMS data, and will decide whether the patient can continue in the study.

To continue in the study patients should;

1. Meet the inclusion/exclusion criteria of the most current protocol version
2. Have completed the latest version of the Informed consent form (ICF)
3. Express a willingness and desire to continue in the study
4. Have treated less than 4 perceived episodes of PSVT with etripamil NS in this study.

If the patient treated their fourth perceived PSVT episode in this study, complete a Final Study Visit instead of a Follow-up Visit. If it is determined that a patient should not continue in the study for any reason, the site should conduct a Final Study Visit (Section 9.1.5) instead of a Follow-up Visit.

The following procedures will be performed at a Follow-up Visit:

1. Immediately log in to the CMS online portal. Upload the CMS data. This starts the processing of Holter data by the CMS lab. The data should be processed, and an initial safety report returned to the site within 1.5 hours from data upload.
2. Review inclusion/exclusion criteria to make sure the patient remains eligible for the study.
3. Record concomitant medications.
4. Record vital signs (blood pressure, heart rate) after the patient has been in a seated position for at least 5 minutes.
5. Record weight.

6. Collect the used and unused nasal spray devices from the patient. If the patient does not have the drug devices, confirm they took the drug and record the lost devices in the eCRF.
7. Review the CMS data;
    a. For quality and adherence to the protocol, and
    b. To determine whether there are any safety or eligibility concerns that merit withdrawing the patient from the study, and
    c. To determine whether any AEs are present

    If CMS data is not processed and returned within 1.5 hours from data upload, and no other safety concerns exist, the site may keep the patient in the study and dispense two additional drug kits. When the initial CMS safety report becomes available, sites will review it for any safety issues to determine if the patient needs to be called back for withdrawal and a Final Study Visit.
8. Review the PRO data for quality and adherence, evaluate any additional medical intervention (including vagal maneuvers) the patient received for PSVT episodes during the Treatment Period. Make sure the patient is completing the PRO for any PSVT episodes that occur, regardless of whether or not they took etripamil NS.
9. Collect any adverse event data during the Treatment Period, and the accurate onset date and time.
10. Provide any additional training on study procedures or devices.
11. If the patient remains eligible to continue in the study, two study drug kits and any required CMS materials (or training materials) may be dispensed.

9.1.5 Final Study Visit

Upon completion of the overall study (Common Study End Date), treating 4 perceived PSVT episodes with etripamil NS in this study, discontinuation or withdrawal of a patient, the site should have the patient return for the Final Study Visit procedures below.

1. Record concomitant medications.
2. Record vital signs (blood pressure, heart rate) after the patient has been in a seated position for at least 5 minutes.
3. Record weight.
4. Collect the used and unused nasal spray devices from the patient. If the patient does not have the devices, confirm they took the drug and record the lost devices in the eCRF.
5. Review the CMS data to determine whether any AEs are present.
6. Review the PRO data for quality and adherence, evaluate any additional medical intervention the patient received for PSVT episodes during the Treatment Period. Close out the patient in the PRO system and collect any electronic device provided to the patient.
7. Collect any adverse event data during the Treatment Period, and the accurate onset date and time.
8. Collect the CMS.
9. Collect any reason for discontinuation and complete the patient's End of Study form in the eCRF.

9.1.6 Conduct of NODE-303 Study during COVID-19 pandemic

To ensure the safety of trial participants in NODE-303, new processes or modification of listed processes may be put in place to reduce the risks associated with the COVID-19 pandemic. These potential changes include, but are not limited to, the use of tele-medicine to conduct study visit procedures, conduct of study procedures outside of the clinical site (*i.e.*, at a patient's home) by site personnel or by trained but non-study personnel, and the distribution of investigational products by alternative secure delivery methods. In the event alternative processes are implemented, the process and the reason for the implementation for the contingency measure will be documented by the sponsor and clinical investigators.

9.2 Study Duration

Patients may continue in the study until they treat 4 perceived PSVT episodes with etripamil NS, at which time they will complete the study and may be eligible for the early drug access program in line with local country regulations. The duration of treatment will depend on the frequency of a patient's PSVT episodes.

After each episode of perceived PSVT is treated with the study drug, eligible consenting patients will have the opportunity to continue in NODE-303 and self-manage subsequent episodes of PSVT with etripamil NS. The patient can come back to receive two additional treatment kits after every episode treated with etripamil NS provided that no adverse effect nor any eligibility criteria would preclude another administration of etripamil NS.

9.2.1 Common Study End Date (CSED)

NODE-303 will continue until the end of the development program, *i.e.,* when enough documented self-administrations of etripamil NS are included in the safety database as determined by Sponsor. The CSED will depend on the rate of accrual of the primary endpoint, unique patients with an episode. When the sponsor announced the CSED, sites will be notified, and should schedule all current patients to return to the site as soon as possible for a Final Study Visit. The CSED announcement will contain additional information on study closeout timelines.

Patients who have a perceived episode and take study drug during this period should return for their Final Study Visit within 14 days of when the episode occurred and have any ongoing AEs monitored for resolution for at least 30 days after the last dose of study drug administration.

9.3 Assessments

9.3.1 Efficacy

9.3.1.1 Patient Reported Outcomes – PRO System

At the Baseline Visit, patients will be provided with a phone application which provides a variety of study assessments and information throughout the course of the study. The PRO system will work regardless of device connectivity at the time of use, as data will be uploaded the next time a patient is connected. If a patient does not have a smartphone or device, they may be given a device if available. The PRO system will include the following;

- A general walk-through of procedures to follow during an episode, designed for use during a PSVT episode.

- A baseline survey which captures information about a patients PSVT, and administers validated scales, the BIPQ, CAQ, and SF-36. Patients should complete the baseline survey on-site, and may complete the validated scales within 2 days of the Baseline Visit.
- A per episode survey which includes questions regarding each specific PSVT episode the patient experiences including information on drug administration, symptoms, the episode itself, and medical interventions required. When a patient takes etripamil NS, it will administer the TSQM-9.
- A monthly PRO survey will be administered, including items related to the patient's PSVT, quality of life, and the impact of PSVT on their activities. Validated scales BIPQ, CAQ, and SF-36 will be administered every 6 months.

9.3.1.1.1 Monthly Survey – Brief Illness Perception Questionnaire (BIPQ), Cardiac Anxiety Questionnaire (CAQ), Short Form (36) Health Survey (SF-36) and other questions

Each month patients will be asked to complete the Monthly Survey which pertains to their PSVT specific symptoms and the underlying course of their disease over the last month. At Baseline and every 6 months, patients will be asked to complete the BIPQ, CAQ, and SF-36.

The BIPQ is a 9-item patient reported measure of cognitive and emotional representations of illness. Questions focus on aspects of personal attributions and control of the course of the disease.

The CAQ is an 18-item patient reported measure with three subscales designed to assess cardiac specific anxiety. Individual items are summed and divided by 18 to obtain a CAQ scale.

The SF-36 is a 36-item patient reported survey of general patient health and quality of life. It consists of eight scaled scores, which are weighted sums of the questions in their section. The lower the score, the more disability.

9.3.1.1.2 Per Episode Survey - Treatment Satisfaction Questionnaire for Medication (TSQM-9) and other questions

After each episode, patients will be asked to complete a per-episode survey regarding the episode, drug administration, symptoms, and medical interventions. If the patient takes etripamil NS for the episode, they will also be administered the TSQM-9.

The TSQM-9 is a 9-item patient reported questionnaire on four key dimensions of treatment satisfaction.

9.3.1.2 Additional Medical Intervention Required

The degree to which patients require medical intervention for PSVT episodes will be assessed by collecting information on emergency department visits, hospital admissions, discontinuations to receive ablation, and concomitant medication use. This information will be collected both by the PRO device, and by site personnel through the course of the study.

9.3.1.3 Characteristics of patient PSVT episodes

The characteristics of a patient's PSVT episode will initially be assessed by the investigator, and finally determined by a medical central reviewer based upon data from the CMS and other available information on an episode. Section 9.3.2.4 outlines what data will be assessed.

Based on these assessments, analyses will be conducted on the number of episodes a patient experiences, the frequency of those episodes over time, the number terminated by VM, type of PSVT (including not a true PSVT event), duration of PSVT, time to conversion post etripamil NS administration, and the proportion of patients who convert at 3, 5, 10, 15, 20, 30 and 60 minutes after etripamil NS administration.

9.3.2 Safety

Safety assessments will include the evaluation of AEs; vital sign measurements; CMS recordings, and physical examination findings.

9.3.2.1 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 10.

9.3.2.2 Clinical Laboratory Safety Assessments

9.3.2.2.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time point specified in the schedule of assessments (Section 17.1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count, including differential
Serum Chemistry	Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, and uric acid
Urinalysis	pH, specific gravity, blood, glucose, protein, and ketones
Pregnancy Test	For women of childbearing potential only. A blood test will be performed at Screening and as required throughout the study to confirm any suspected pregnancy
Urine Drug Screen	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol

Blood and urine samples for hematology, serum chemistry, and urinalysis will be sent to a central laboratory for analyses.

9.3.2.3 Clinical Examinations

9.3.2.3.1 Vital Signs

Vital signs will include blood pressure, heart rate, and weight. Blood pressure and heart rate will be measured after the patient has been in a sitting position for 5 minutes.

9.3.2.3.2 12 Lead Safety ECG

A 12 lead Safety ECG will be conducted at Screening to confirm that patient meets inclusion/exclusion criteria. A previous 12-lead ECG (taken within 1 month prior to the Screening Visit) of sufficient quality to fully assess patient safety and eligibility may be used by the site as long as there has been no significant change in the patient's underlying condition or general health (such as having an ablation, or other cardiac event). Previous ECGs should also be uploaded to

the archive. Data from the ECG will be collected at the site and reviewed by site personnel for potential concomitant disorders which would exclude the patient from the trial.

12-Lead Safety ECGs will be uploaded and stored centrally in the study database throughout the study.

9.3.2.3.3 Physical Examination

A complete physical examination (excluding breast and genitourinary examination) will be performed at Screening. Systems examined should include General Appearance/Constitution, Eyes, ENT/Mouth, Respiratory, Cardiovascular, Gastrointestinal, Muscular, Skin, Neurological, Endocrine, Lymph Nodes, Allergy/Immunological, and Psychiatric.

9.3.2.4 Cardiac Monitoring System (CMS)

A portable device will be used as the CMS for this study. The CMS is an at-home ECG monitor which will be applied as soon as possible when an episode of PSVT is perceived by the patient. It is removed after (at least) 1 hour post initial study drug administration.

Patients should be provided with a CMS Device, and sufficient materials to record anticipated perceived PSVT episodes until their next Follow-up Visit. Patients with frequent short PSVT episodes for which they may not use study drug should receive extra CMS materials.

During a perceived PSVT episode, patients will apply the CMS. After the episode they should switch off the CMS Device. If they took drug, they will return to the site for a Follow-up Visit.

Immediately at the start of a Follow-up Visit, the site should log into the online web portal and plug the CMS Device into the docking station to upload the episode data. This data will be processed by the CMS lab, and an initial .pdf formatted CMS safety report will be generated. The data should be processed, and an initial CMS safety report returned to the site within 1.5 hours from data upload. Sites should then review the CMS safety report, See Section 9.1.4 for details.

If CMS data is not processed and returned within 1.5 hours from data upload, and no other safety concerns exist, the site may keep the patient in the study and dispense two additional drug kits. When the initial CMS safety report becomes available, sites will review it for any safety issues to determine if the patient needs to be called back for withdrawal and a Final Study Visit.

Data from the episode will be reviewed centrally by a designated medical expert. This medical expert will review the CMS data for several items:

1. Potential safety or eligibility concerns that may impact the decision whether to continue treating a patient with etripamil NS. All such concerns will be communicated to the site, and the investigator will make the final decision based on a full evaluation of the patient and data.
2. Potential Adverse Events. All data indicating potential AEs will be communicated to the site, and the investigator will make the final decision of whether a finding constitutes an AE based on a full evaluation of the patient and data.
3. Abnormal findings from the CMS Holter recordings. Pre-specified types of abnormal Holter findings will be documented by the medical central reviewer and will be entered in the EDC.
4. Whether an episode was a true PSVT event, or something else. This will be documented in the EDC.

5. The time to conversion, and time to conversion after study drug administration (when determinable). This will be documented in the EDC.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

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

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

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms will be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it will be recorded as a separate AE on the eCRF. In cases requiring medical or surgical procedures, the underlying condition, rather than the procedure itself, will be recorded as an AE(s).

Clinically significant abnormal assessments that are detected during the study or are present at Screening and significantly worsen will be reported as AEs or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal assessment is clinically significant. Any abnormal assessments considered clinically significant by the Investigator must be recorded on the AE page of the eCRF.

Events that occur in patients during Treatment Periods of the study when study drug is not administered are also considered AEs.

10.1.2 Adverse Drug Reaction

All noxious and unintended responses to a study drug related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to a study drug” means that a causal relationship between a study drug and an AE is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a study drug qualify as ADRs.

All AEs for which the judgment of relationship to the study drug is “possible” or higher will be considered ADRs. If a relationship to the study drug is not given, then the AE must be treated as if the relationship to the study drug were “possible.”

10.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For etripamil NS, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

10.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.* ***For clarity, hospitalizations for PSVT related ablations, or conversions of PSVT episodes will not be considered SAEs.***
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a patient who has received a study drug is not considered an SAE unless it is suspected that the study drug(s) interacted with a contraceptive method and led to the pregnancy.*
- Is an important medical event.
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The occurrence of malignant tumors is also to be considered serious.*

10.1.5 Treatment-Emergent Adverse Events

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

10.2 Management of Adverse Events

Adverse events will be collected from the time of signing the ICF until the patient withdraws or discontinues from the study.

10.2.1 Collection of Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

10.2.2 Evaluation of Adverse Events

10.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 10.1.4.

10.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 10.1.4. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations. All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

10.2.2.3 Action(s) Taken

Action(s) taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.

10.2.2.4 Outcome at the Time of Last Observation

The outcome, including Fatal, at the time of last observation will be classified per eCRF completion instructions. Only select fatal as an outcome when the AE results in death. If more than 1 AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

10.2.2.5 Adverse Event Relationship to the Study Drug

The assessment of the relationship of an AE to study drug administration is a clinical decision based on all available information at the time the event is reported.

The relationship of an AE to study drug administration is to be assessed according to the following definitions:

- Not related – An event that is definitely not associated with study drug administration and is judged clearly due to causes other than study drug.
- Unlikely related – An event that follows a temporal sequence from study drug administration, such that a relationship is not likely and could be reasonably explained by the patient's clinical state or other modes of therapy administered to the patient.
- Possibly related – An event that follows a reasonable temporal sequence from study drug administration, but may be due to another cause and could also be reasonably explained by the patient's clinical state or other modes of therapy administered to the patient.
- Probably related – An event that follows a reasonable temporal sequence from study drug administration that is not easily explained by another cause (*e.g.*, known characteristics of the patient's clinical state or other treatment), and is confirmed by improvement on stopping or slowing study drug administration.
- Definitely related – An event that is clearly associated with study drug administration.

An AE/SAE that has been assessed as "possibly related" "probably related" or "definitely related" will be classified as "related" for regulatory reporting purposes. An AE/SAE that has been assessed as "not related" or "unlikely related" will be classified as "unrelated" for regulatory reporting purposes.

The following factors will also be considered:

- The temporal sequence from study drug administration;
  - The event should occur after study drug administration. The length of time from study drug exposure to event will be evaluated in the clinical context of the event.
- Underlying, concomitant, and/or intercurrent diseases;
  - Each report will be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication;
  - The other medications the patient is taking or the treatment the patient receives will be examined to determine whether any might be recognized to cause the event in question.
- Known response pattern for this class of study drug;
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses; and
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug.

The known pharmacological properties (*e.g.*, absorption, distribution, metabolism, and excretion) of the study drug will be considered.

10.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 10.2.)

- AE name or term.
- When the AE first occurred (start date and time).
- When the AE stopped (stop date and time or an indication of "ongoing").
- Severity of the AE.
- Seriousness (*e.g.*, hospitalization or death).
- Actions taken.
- Outcome.
- Investigator opinion regarding the AE relationship to the study drug.

10.2.4 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after the patient's last dose of study drug in the study) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (*i.e.*, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE will be included in the EDC. Patients who do not receive study drug during the study do not need AEs followed after the Final Study Visit. AEs ongoing at the time of database lock should have all available information entered into the database and be followed as described in this section in case the AE eventually meets SAE criteria.

All SAEs should be followed until satisfactory resolution, even after database lock.

10.2.5 SAE Reporting

10.2.5.1 Serious Adverse Events

SAEs will be captured from the time ICF is signed until the Final Study Visit.

The investigator or designee must report all SAEs promptly to IQVIA Biotech safety within 24 hours of first becoming aware of the event by selecting Serious-Yes on the AE page of the eCRF and entering the valid fields as indicated below.

At the time of first notification, the investigator or designee must provide the following information on the AE page of the eCRF for the SAE to be considered valid:

- Adverse event term
- Is the event serious- Selected as Yes
- Seriousness criteria
- Patient's date of birth.
- Patient's gender.

- Initial Causality (Not related, Unlikely related, Possibly related, Probably related, Definitely related)

However, the AE page of the eCRF should be completed in its entirety to ensure that a complete SAE Report can be created by IQVIA Biotech Safety. Additional relevant information and missing information concerning the SAE should be provided on the AE page of the eCRF. Source documentation (*e.g.*, death certificate, autopsy reports) should be provided to IQVIA Biotech Safety via email or fax at Safety-inbox.biotech@iqvia.com/1-866-761-1274 (toll-free) or 919-313-1412 (toll) using Form SM584: Site Fax Cover Sheet Template, when requested.

In the event the EDC system is not working, the SAE must be reported within 24 hours by completing Form SM335: Serious Adverse Event Report Template and submitting to IQVIA Biotech Safety via email or fax at Safety-inbox.biotech@iqvia.com/1-866-761-1274 (toll-free) or 919-313-1412 (toll).

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/Independent Ethics Committee (IEC), principal and coordinating investigators, study investigators, and institutions. The detailed reporting duties and division of responsibilities between Milestone and designated vendors will be provided in a separate document (see the Safety Management Plan). Each investigator is obligated to learn about the reporting requirements for investigators in his or her country. The study monitor may be able to assist with this.

Follow-up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (*e.g.*, persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system and submit any supporting documentation (*e.g.*, patient discharge summary or autopsy reports) via e-mail or fax. If it is not possible to access the EDC system, follow the procedures outlined above for the initial reporting of SAEs.

10.2.5.2 Adverse Drug Reactions

Milestone will report all ADRs related to the study drug to the proper health authorities; serious ADRs will be reported immediately and nonserious ADRs will be reported after completion of the study. Suspected serious adverse drug reactions must be reported to Milestone immediately, regardless of the time that has elapsed since the end of the period of observation.

10.2.5.3 Nonserious Adverse Events

Milestone will review nonserious AEs that are recorded in the eCRF on a regular basis.

10.3 Special Considerations

10.3.1 Adverse Events of Special Interest

Due to the pathophysiology of PSVT, certain arrhythmias may occur as part of the normal course of the disease, particularly during the onset and conversion of PSVT episodes. CMS holter abnormalities should be carefully reviewed for type, duration, relation to underlying disease, and general clinical context when determining if an AE occurred. Investigators should consult with the medical monitor if they have any questions regarding potential CMS holter abnormalities or arrhythmias.

Due to the mechanism of action of etripamil, patients could be at a higher risk of certain adverse events of special interest. Investigators should be on the alert for these events, or for symptoms which indicate an event may be present. An AESI may indicate that a patient should be withdrawn from the study and a careful evaluation of any patients with AESI is merited. Investigators should contact the medical monitor if any safety concerns arise.

Investigators should follow the standard protocol process for AE and SAE reporting for these AESI.

Below is a list of AEs which are of particular interest in this study, if they occur within 24 hours of etripamil NS administration.

List of AESI in the 24 hours after etripamil NS administration;

- Tachyarrhythmias
- Bradyarrhythmias
- AV Block – any degree
- Hypotension and/or syncope

10.3.2 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice at least 1 form of adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected. Women who plan to become pregnant should not enroll, or should discontinue from the study.

Pregnancy testing will be conducted at the Screening Visit on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during study drug treatment or within 30 days of discontinuing the study drug will be immediately discontinued from study participation. The Investigator must report the pregnancy within 24 hours of learning of the pregnancy, on Form SM586: Pregnancy Report Form Template and email or fax to IQVIA Biotech Safety at Safety-inbox.biotech@iqvia.com/1-866-761-1274 (toll-free) or 919-313-1412 (toll). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

Final Study Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. Follow-up findings must be reported on the initial Form SM586: Pregnancy Report Form Template submitted to IQVIA Biotech Safety and forwarded to IQVIA Biotech Safety via email or fax at Safety-inbox.biotech@iqvia.com/1-866-761-1274 (toll-free) or 919-313-1412 (toll). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

10.3.3 Overdose

The maximal dose of etripamil NS should not be exceeded during the study, as study drug is dispensed for single use only.

Overdose that occurs during the study will be treated and documented as an AE /SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, patient identification, study drug, dose,

action taken (*e.g.*, administration of antidote [if available] or supportive measures or therapy), and any comments.

11. STUDY COMMITTEES

NODE-303 will be governed by a steering committee (SC) which will periodically review the safety data from Study 303 and other ongoing studies. The SC will be responsible for reviewing safety data and providing recommendations for alterations to the NODE-303 protocol, study sites, metrics, conduct, inclusion and exclusion criteria, and data. In particular they will review clinical and non-clinical data at the milestones identified in Section 12.4.6. Additional details may be found in the SC charter.

12. STATISTICS

This section briefly describes the statistical methods to be used to analyze efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that will be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

12.1 Study Endpoints

12.1.1 Primary Endpoint

The primary objective of this study is to evaluate the safety of self-administered etripamil NS. Efficacy variables will be collected as secondary or exploratory analyses.

12.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Number of emergency department visits, or other medical intervention.
- Number of hospital admissions (including inpatient and outpatient hospitalizations).
- Characteristics of patients who receive ablation.
- Concomitant PSVT medication usage.
- Improvement in patient quality of life, as measured by the PRO scales.
- Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9).
- Mean and Median time to conversion post etripamil NS administration.
- Proportion of patients who convert at 3, 5, 10, 15, 20, 30, and 60 minutes after etripamil NS administration.

Exploratory endpoints are:

- Frequency of PSVT episodes, and use of etripamil NS for those episodes, as captured by the PRO.
- Number of PSVT episodes a patient experiences.
- Frequency of PSVT episodes.

- Number of PSVT episodes terminated by VM.
- Type of PSVT episodes, number of true PSVT episodes.
- Duration of PSVT episodes.

12.1.3 Safety Endpoints

Safety endpoints include the following:

- Incidence of AEs.
- Vital sign measurements.
- Physical examination findings.
- Holter recordings from the CMS.

12.2 Sample Size Determination

There is no statistical hypothesis in this uncontrolled OL safety study. NODE-303 will continue until the end of the development program, *i.e.,* when enough documented self-administrations of etripamil NS are included in the safety database.

It is anticipated that as many as 3000 patients may need to be enrolled in order to accrue a sufficient number of patients in the Safety Population within 24 months.

12.3 Analysis Populations

The following 4 analysis populations are planned for this study:

- Overall Population: All patients enrolled into the study.
- Safety Population: The Safety Population will be the primary safety analysis population and will include all patients who receive any amount of the study drug.
- Efficacy Population: The Efficacy Population will include all patients who receive at least 1 dose of study drug for an episode determined to be PSVT.

12.4 Statistical Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a P value of less than or equal to 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of patients, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of patients in each category.

12.4.1 Study Patients and Demographics

12.4.1.1 Disposition and Withdrawals

The numbers of patients screened, entering treatment, taking study drug, completing the study, withdrawing from the study, and discontinuing treatment, along with reasons for discontinuation or withdrawal, will be tabulated. The number of patients in each analysis population will be reported.

12.4.1.2 Protocol Deviations

Major protocol deviations will be classified and documented by Milestone before database lock and will be discussed in the CSR.

12.4.1.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, ethnicity, weight, PSVT history, and height) will be summarized. Medical history and clinical laboratory tests will be listed.

Prior and concomitant medications will be summarized by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

12.4.2 Exposure and Compliance

Study drug administration will be summarized in terms of number of unique patients exposed to drug, number of partial doses administered, number of doses taken per episode, and number of doses taken per patient. These quantities, including the mean, SD, minimum, and maximum, and categorical summary of number of doses will be provided.

12.4.3 Handling of Missing Data

Missing data will not be imputed in the trial. A detailed summary of missing data, or variations in data collection across regions or protocol versions will be included in the CSR.

12.4.4 Efficacy Analyses

Efficacy variables will be summarized and analyzed using the Efficacy Population unless otherwise specified. Comparisons of available data from patients in the Safety population versus the Efficacy Population will be done.

Additional details are provided in the Statistical Analysis Plan.

12.4.4.1 Secondary Efficacy Analyses

- The proportion of patients with PSVT episode related ED visits, PSVT related medical interventions, PSVT related hospital admissions, receiving ablations for PSVT, using concomitant PSVT medication, and changing use of concomitant PSVT medication will be reported.
- Improvement in patient quality of life will be analyzed as the change in elements and overall score in the BIPQ, CAQ, SF-36, and other survey questions over time versus baseline.
- Patient satisfaction will be analyzed via the TSQM-9 numeric scoring scale after dosing and over multiple doses.
- Time to conversion of PSVT will be analyzed as median time from start of CMS recording or drug taken marker to PSVT conversion in patients with sufficient CMS data for analysis.
- Proportions of patients with PSVT who convert at 3, 5, 10, 15, 20, 30 and 60 minutes will be analyzed for patients with true PSVT episodes and sufficient CMS data for analysis.

12.4.4.2 Exploratory Efficacy Analyses

- Summaries will be presented for characteristics of PSVT episodes such as the frequency, number terminated by VM, type of PSVT (including true versus not true PSVT), duration of PSVT.

12.4.5 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.3). Data from patients in the Efficacy populations may be presented for comparison of key endpoints.

Safety and tolerability will be assessed through AEs, vital signs measurements, and from the CMS recordings.

No formal statistical comparisons will be performed for safety endpoints.

12.4.5.1 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities reporting system.

The number and percentage of patients with AEs will be displayed for each treatment group by SOC and preferred term. Additionally, AEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of and tabulation of SAEs will be provided.

Adverse Events will also be analyzed by their timing relative to patient episodes and relative to study drug administration. AEs which occur within 24 hours of an episode (regardless of whether study drug is taken) will be referred to as 'Episode Emergent' adverse events. AEs which occur within 24 hours of taking study drug will be referred to as 'Treated Episode Emergent' adverse events.

12.4.5.2 Clinical Laboratory Evaluations

Clinical laboratory parameters are utilized primarily as a screening and eligibility procedure. Parameters will be categorized as low, normal, or high according to laboratory range specifications.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

12.4.5.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values will be reported for systolic blood pressure, diastolic blood pressure, heart rate, and weight.

12.4.5.4 Physical Examination Findings

Physical examination data will be presented in the listings.

12.4.6 Interim Analyses

The study will include regular analyses of safety data in NODE-303 and the overall etripamil NS development program. These analyses will be conducted at:

- The conclusion of the NODE-301 study primary analysis.
- When data is obtained on at least 125 patients who are greater than 70 years of age, or greater than 60 years of age and taking a concomitant PSVT medication across all studies, and
- After every 250 unique patients treated for perceived episodes in NODE-303.

Based on the results of these reviews, inclusion/exclusion criteria and study procedures in NODE-303 will be adapted to broaden or narrow the study population, or to increase/decrease the extent of safety data collected.

As NODE-303 is an open-label safety study, these interim analyses will not have an effect on the overall statistical analysis.

13. INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

13.1 Ethical Conduct of the Study

The ICH GCP guidelines serve as an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

13.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Local regulations and the ICH GCP guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, informed consent forms, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by Milestone or authorized CRO.

13.3 Informed Consent

The informed consent form and any changes to the informed consent form made during the course of the study must be agreed to by Milestone or their designee and the IRB/IEC prior to its use and must be in compliance with ICH GCP guidelines, local regulatory requirements, and legal requirements.

The Investigator or designee must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator or designee will obtain written informed consent from each patient before any study-specific activity is performed and will document in the source documentation that consent was obtained prior to enrollment in the study. If substantial changes are made to the ICF, patients should be re-consented at their next

study visit, unless such changes are deemed to have a major impact on potential patient safety in which case patients may be asked to re-consent as soon as possible. The original signed copy of the informed consent form must be maintained by the Investigator and is subject to inspection by a representative of Milestone, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed informed consent form will be given to the patient.

13.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP guidelines, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, Milestone in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, Milestone or their designee will review with the Investigator and site personnel the following: the study protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, patient training material, and the procedure for reporting SAEs.

The Investigator will permit Milestone or their designee to monitor the study as frequently as deemed necessary to determine if data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents, and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

13.5 Data Collection

Data for the NODE-303 study will be collected at the site and entered into the EDC for inclusion in the database. Data from the CMS, at-home PRO systems, and Central laboratory will be transmitted to the sponsor or designee and integrated into the database prior to official lock. All electronic data collection systems will be designed for 21 CFR Part 11 compliance, with audit trail capability.

This study will be conducted in compliance with applicable regional data privacy and data handling regulations and laws.

13.6 Disclosure of Data

Data generated by this study must be available for inspection by local regulatory authorities, Milestone or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

13.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or Milestone, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records [*e.g.*, eCRFs and hospital records]), all original signed informed consent forms, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records will be retained by the Investigator according to specifications in the ICH GCP guidelines, local law regulations, or as specified in the clinical study agreement, whichever is longer. The Investigator must obtain written permission from Milestone before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, Milestone will be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Milestone.

13.8 Audits and Inspections

Authorized representatives of Milestone, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Milestone audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact Milestone immediately if contacted by a regulatory agency about an inspection.

13.9 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with Milestone before any study data are submitted for publication. Milestone reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication is achieved.

13.10 Financial Disclosure

Investigators are required to provide financial disclosure information to Milestone to permit Milestone to fulfill its obligations under 21 CFR §54 and other appropriate international regulations. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

NODE-303 is sponsored and funded fully by Milestone Pharmaceuticals Inc.

14. STUDY ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by CRO or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety.

Previous Protocol Versions:

Version 1.0, 21 June 2019
Version 2.0, 15 February 2021

14.2 Protocol Authors

NODE-303 protocol was written and finalized by Milestone Pharmaceuticals employees, with external scientific advice provided by the Steering Committee and other experts, consultants, and vendors.

15. FINAL CLINICAL STUDY REPORT

Milestone will retain ownership of the data generated from the study.

The final clinical study report will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

16. REFERENCES

1. Issa ZF, Miller JM, Zipes DP. Clinical arrhythmology and electrophysiology: a companion to Braunwalds's Heart Disease. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2010.
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17. ATTACHMENTS

17.1 Schedule of Assessments

Table 2. Schedule of Procedures

	Screening Visit (within 30 days of baseline)[7]	Baseline Visit[9]	Treatment Period[1]	Follow-Up Visits (within 14 days of treated episode)[10]	Final Study Visit
Informed Consent	X				
Eligibility	X	X		X	
Demographics / medical history	X				
Concomitant Medications	X	X		X	X
Physical Exam	X				
Vital signs[2]	X			X	X
Hematology, chemistry, urinalysis, urine drug screen[8]	X				
Pregnancy test	X				
On-site Safety ECG	X				
Patient Training		X		X[4]	
Dispense study kit[5]		X		X	
Apply and Start CMS			X		
Perform VM			X		
Self-administer drug[11]			X		
PROs[6]		X	X		
TSQM-9			X		
Patient Reminders[3]			X		
Return used study drug to site				X	X
Review CMS data				X	X
Adverse Events		X		X	X
Collect CMS					X
End of Study eCRF Completion					X

Table 2 Schedule of Procedures (Continued)

[1] Treatment Period assessments are done by the patient in an at-home setting.
[2] Vital signs include blood pressure, heart rate, and weight. **Height to be taken at Screening Visit only**.
[3] Sites will call patients who have missed two consecutive PRO surveys to retrain and engage the patient.
[4] At Follow-up Visits, sites will re-train patients who are having issues with their CMS or PRO systems.
[5] Study kit at Baseline will include CMS Device and materials, two study drug kits, study identification card and any paper training or PRO materials required or requested. Study kits at Follow-up will include two study drug kits, additional CMS materials, and any paper training or PRO materials required or requested.
[6] PROs are administered via Phone or Tablet application. PROs include a) Baseline Survey to be done on site at Baseline; b) the BIPQ, CAQ, and SF-36 done within 48 hours of Baseline and every 6 months thereafter; c) a Monthly Survey done each month after Baseline; d) a Per Episode Survey done for each episode regardless of whether or not a patient takes drug; e) the TSQM-9 done after each episode where the patient takes drug.
[7] Screening and Baseline Visits can be incorporated into one visit for purposes of avoiding an extra on-site visit in extenuating circumstances.
[8] Blood / urine samples can be analysed locally for purposes of preliminary enrolment if Screening/Baseline Visits are combined; samples **also** to be sent to Central lab. Central lab results will **allow** enrollment in study.
[9] Baseline Visit can be conducted with Screening Visit for purposes of avoiding an extra on-site visit in extenuating circumstances.
[10] Follow-up Visits can be conducted within **up to 60** days of treated episode in extenuating circumstances.
[11] Patients should self-administer one dose, wait 10 minutes, and self-administer a repeat dose if PSVT symptoms persist.

APPENDICES

A. Address List
B. Regulations and Good Clinical Practice Guidelines

A. Address List

Study personnel and site addresses to be kept in the Trial Master File

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Patients
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives [and applicable regulations/guidances]:

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
http://www.ich.org/LOB/media/MEDIA482.pdf