CLINICAL STUDY PROTOCOL

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

The NODE-302 Trial

(Extension of NODE-301)

Investigational Product: Etripamil (MSP-2017)
Protocol Number: MSP-2017-1158

Sponsor:
Milestone Pharmaceuticals Inc.
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Version Number: 2.0
Original Protocol: 18 May 2018
Amendment 1: 18 October 2018

PROCEDURES IN CASE OF EMERGENCY OR SERIOUS ADVERSE EVENT REPORTING

Emergency Contact Information

Role in Study	Name	Address/Telephone Number
Clinical Study Leader	Douglas Wight	dwight@milestonepharma.com/+1-514-336-0444, ext. 226
Responsible Physician	Francis Plat	fplat@milestonepharma.com/+1-514-336-0444, ext. 225
Medical Monitor	Silvia Shardonofsky	sshardonofsky@milestonepharma.com/+1-514-336-0444, ext. 235

Serious Adverse Event Reporting

Any serious adverse event (SAE) (as defined in Section 8.2) occurring from the time of study drug administration during the Treatment Period(s) through the Final Study Visit or Early Termination Visit (whichever is later) must be reported to Medpace Clinical Safety **within 24 hours** of awareness of the event. Any SAE occurring within a 30-day follow-up period after taking the study drug that the Investigator considers related to study drug administration must be reported in the same manner.

To report an SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically and will retrieve the form.

To report an SAE if the EDC system is not available:

- Send an e-mail to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE Reporting Line (number listed below);
- Fax/e-mail a completed SAE form to Medpace Clinical Safety (number and e-mail address listed below); and
- When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

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 via e-mail or fax.

Medpace Clinical Safety Contact Information

Medpace Clinical Safety
SAE Reporting Line (USA/Canada): +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
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SIGNATURE PAGE

STUDY TITLE: Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia
The NODE-302 Trial (Extension of NODE-301)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Francis Plat, MD Chief Medical Officer Milestone Pharmaceuticals Inc.	19-OCT-2018
Douglas Wight, MSc Vice President, Drug Development Milestone Pharmaceuticals Inc.	18-Oct-2018
Guy Rousseau, PhD Vice President, Regulatory Affairs Milestone Pharmaceuticals Inc.	19-OCT-2018

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 Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia
The NODE-302 Trial (Extension of NODE-301)

SHORT TITLE: Safety Study of Intranasal Etripamil for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia
The NODE-302 Trial (Extension of NODE-301)

PROTOCOL NUMBER: MSP-2017-1158

INVESTIGATIONAL PRODUCT: Etripamil (MSP-2017)

PHASE: 3

INDICATION: Paroxysmal supraventricular tachycardia (PSVT)

OBJECTIVES:

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

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

POPULATION:

The NODE-302 study is designed to obtain safety data to contribute to the etripamil safety database. Only patients randomized in the NODE-301 study are potentially eligible for the NODE-302 study. However, it is expected that among the randomized patients from the NODE-301 study, there will be at least 125 high-risk patients who are defined as follows:

- ≥70 years of age; or
- ≥60 years of age with either first degree atrioventricular (AV) block (PR interval >200 milliseconds) or concomitant use of medication known to affect cardiac conduction (i.e., beta-blockers, diltiazem, verapamil).

If these high-risk patients are underrepresented in the NODE-301 study (i.e., <125 patients), additional high-risk patients will be recruited into the NODE-302 study to reach 125 high-risk patients enrolled. These high-risk patients will receive a test dose of etripamil NS 70 mg and will be evaluated for enrollment in the NODE-302 study according to the same process described in the NODE-301 study.

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients at least 18 years of age;
2. Signed the NODE-302 written informed consent;
3. Previously randomized in the NODE-301 study:
   - Received the study drug to treat symptoms the patient believed were consistent with an episode of PSVT during the NODE-301 study, irrespective of the study drug efficacy;

     OR

   - Did not experience an episode of PSVT or did not use the study drug at the time of the NODE-301 study completion;
4. Willing and able to comply with all aspects of the study;
5. Females of childbearing potential who are sexually active must agree to use an approved highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of study drug. Females of childbearing potential should have a negative urine pregnancy test result at the Qualification Visit and at the Follow-up Visit(s), and must use an approved form of contraception between the 2 visits. Approved forms of contraception include hormonal intrauterine devices and hormonal contraceptives (oral birth control pills, Depo-Provera®, patch, or other injectables) together with supplementary double-barrier methods, such as condoms or diaphragms with spermicidal gel or foam;

   The following categories define females who are NOT considered to be of childbearing potential:

   - Premenopausal females with 1 of the following:
     a. Documented hysterectomy,
     b. Documented bilateral salpingectomy, or
     c. Documented bilateral oophorectomy, or
   - Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause; and
6. Male patients, except those who are surgically sterile, must use an approved highly effective form of contraception during the 3 days after study drug administration.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Evidence of new severe arrhythmia discovered since the NODE-301 Test Dose Randomization Visit, including those reported on the Cardiac Monitoring System (CMS) report of the outpatient PSVT event treated with the study drug in the NODE-301 study, including but not limited to:
   a. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm;

b. Significant symptomatic sinus bradycardia heart rate (HR) ≤40 bpm or sinus pauses (≥3 seconds);

c. Any significant ventricular arrhythmia (premature ventricular beats and couplets [>6 premature ventricular contractions per 45 seconds electrocardiogram (ECG)] are considered significant); or

d. Atrial fibrillation (event lasting longer than 30 seconds) or atrial flutter;

2. Any drug-related or procedure-related serious adverse event (AE) during the NODE-301 study;
3. Any severe AE in the NODE-301 study that was severe enough to preclude administration of etripamil NS 70 mg in the NODE-302 study;
4. Any new drug prescribed after the end of the patient's participation in the NODE-301 study that could lower blood pressure or decrease AV node conduction;
5. Systolic blood pressure <90 mmHg after a 5-minute rest in sitting position at the NODE-302 Qualification Visit;
6. Any symptoms consistent with clinically severe hypotension such as presyncope, medically significant lightheadedness, syncope, nausea, or vomiting;
7. New therapy with digoxin, amiodarone, or any Class I or III antiarrhythmic drug added after the end of the patient's participation in the NODE-301 study;
8. New evidence of ventricular pre-excitation (e.g., delta waves, short PR interval, Wolff-Parkinson-White syndrome) on the ECG since randomization in the NODE-301 study;
9. New symptoms of congestive heart failure defined by the New York Heart Association Class II to IV since randomization in the NODE-301 study;
10. New stroke since randomization in the NODE-301 study;
11. New evidence of a significant physical or psychiatric condition including 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 since randomization in the NODE-301 study;
12. New syncope since randomization in the NODE-301 study, especially if observed during the monitoring of the event treated in the NODE-301 study;
13. New evidence of hepatic dysfunction, defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN, unless due to Gilbert syndrome, observed at the NODE-302 Qualification Visit;
14. New evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the NODE-302 Qualification Visit as follows:

    a. <60 mL/min/1.73 m^2 for patients <60 years of age,

    b. <40 mL/min/1.73 m^2 for patients ≥60 and <70 years of age, or

    c. <35 mL/min/1.73 m^2 for patients ≥70 years of age;

15. Participation in any investigational drug or device study or the use of any investigational drug or device since the Final Study Visit in the NODE-301 study.

Withdrawal Criteria

Patient participation in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- The patient took the study drug in both the NODE-301 and the NODE-302 studies for symptoms not associated with an episode of PSVT;
- Occurrence of any medical condition, AE, or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Requirement of a prohibited concomitant medication and/or change in the use of chronic therapies, such as concomitant beta-blockers, calcium channel blockers, and medications that can lower blood pressure;
- Patient failure to comply with protocol requirements or study-related procedures;
- Termination of the study by Milestone or a regulatory authority; or
- The patient self-administered a total of 11 doses of etripamil NS 70 mg in the NODE-302 study.

Patients who withdraw from the study after taking etripamil NS 70 mg and had a Follow-up Visit will be required to undergo an Early Termination Visit.

Patients who withdraw from the study and did not take etripamil NS 70 mg will be required to undergo an Early Termination Visit.

Patients who withdraw after taking the study drug but did not have a Follow-up Visit will be required to undergo a Final Study Visit.

STUDY DESIGN AND DURATION:

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

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

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

The study will include the following:

Qualification Visit

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

Treatment Period(s)

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

Follow-up Visit(s)

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

Final Study Visit

A complete assessment will be performed by the Investigator.

Early Termination Visit

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Investigational Product and Dosage: The formulation of etripamil is for intranasal administration and will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid, and sulfuric acid. The dose of etripamil to be evaluated in the NODE-302 study is 70 mg.

Mode of Administration: All patients will receive a total of 200 µL of etripamil NS 70 mg (i.e., 100 µL in each nostril via the Aptar Pharma Nasal Spray Bidose System) each time they self-administer study drug. The devices will be prefilled and packaged into child-resistant boxes. Instructions for its use are provided in the Manual of Operations and Procedures and will be provided in the study drug box.

DURATION OF TREATMENT:

The NODE-302 study will be operational until the end of the development program (i.e., when a sufficient number of documented study drug administrations have been achieved for inclusion in the etripamil safety database).

SAFETY VARIABLES:

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

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

EFFICACY VARIABLES:

Efficacy assessments will be based on the data derived from CMS recordings. The Adjudication Committee will evaluate the complete CMS ECG data recorded from patients to determine if a true PSVT episode occurred. If the event is related to a confirmed episode of PSVT, the primary endpoint, conversion to sinus rhythm (SR) after study drug administration, will be adjudicated and the primary variable, the time to conversion, will be adjudicated for the primary efficacy analysis.

STATISTICAL ANALYSES:

Analysis Populations

The Safety Population will include all patients who take the study drug.

The Efficacy Population will include all patients who use the study drug to treat a positively adjudicated episode of PSVT. This population will not include patients who take the study drug for symptoms not associated with an episode of PSVT.

Analysis of Efficacy

The efficacy analyses will be performed on the Efficacy Population. The primary efficacy variable is the time to conversion of an episode of PSVT to SR after study drug administration.

Analysis of Safety

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

SAMPLE SIZE DETERMINATION:

There is no statistical hypothesis in this uncontrolled open-label safety study. Based on the anticipated randomization of 500 patients in the NODE-301 study, it is estimated that 300 to 500 patients will be eligible for the NODE-302 study. The final number of episodes of PSVT in the NODE-302 study will depend on the frequency and timing of episodes of PSVT during the study. The NODE-302 study will be operational until the end of the development program (i.e., when a sufficient number of documented study drug administrations have been achieved for inclusion in the etripamil safety database).

If the population includes fewer than 125 high-risk patients at the end of the NODE-301 study, new patients meeting the high-risk categories will be eligible to enroll in the NODE-302 study to ensure the following:

- 125 high-risk patients being enrolled (i.e., having received a test dose); and
- 75 of the enrolled high-risk patients having subsequently self-administered etripamil NS 70 mg during an episode of PSVT, with 20 of them being ≥70 years of age.

MONITORING COMMITTEES:

Steering Committee

A single Steering Committee will be responsible for the scientific oversight of both the NODE-301 and NODE-302 studies. The Steering Committee Chair will review the original protocol and potential amendments.

Data and Safety Monitoring Committee

A single Data and Safety Monitoring Committee (DSMC) will operate for both the NODE-301 and NODE-302 studies. The DSMC will review the accumulating safety data on a regular basis to detect any safety issue that could be related to the study drug or the protocol procedures involved in the patient's management of an episode of PSVT.

Adjudication Committee

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

The EPs will adjudicate the following:

1. The presence of PSVT (AV nodal reentrant tachycardia or AV reentrant tachycardia determination if possible);

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

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

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

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

The Adjudication Committee will review the secondary ECG safety endpoints (i.e., arrhythmia and conduction disorders).

SITES: This study will be conducted at the same sites as the NODE-301 study.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
BDS	Aptar Pharma Nasal Spray Bidose System
CFR	Code of Federal Regulations
CMS	Cardiac Monitoring System
CMS safety report	Analysis of the ECG tracing by a core laboratory for cardiac safety
CRA	Clinical Research Associate
CSR	Clinical Study Report
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
E_{max}	Maximal efficacy
EP	Electrophysiologist
EPL	Electrophysiology laboratory
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Heart rate
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IN	Intranasal(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
MFD	Maximum feasible dose
MoOP	Manual of Operations and Procedures
NS	Nasal spray
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PSVT	Paroxysmal supraventricular tachycardia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SR	Sinus rhythm

Abbreviation	Definition
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
VM	Vagal Maneuver
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION AND BACKGROUND INFORMATION

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 milliseconds.[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.

1.1 Phase 1 Study

A Phase 1 study 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 healthy, adult male patients. 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 (i.e., 2 sprays of 100 µL of solution of 35 mg of etripamil in each nostril). 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. The 4 doses selected to be studied in a Phase 2 study were 35, 70, 105, and 140 mg.

1.2 Phase 2 Study

NODE-1, 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 an outpatient 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				

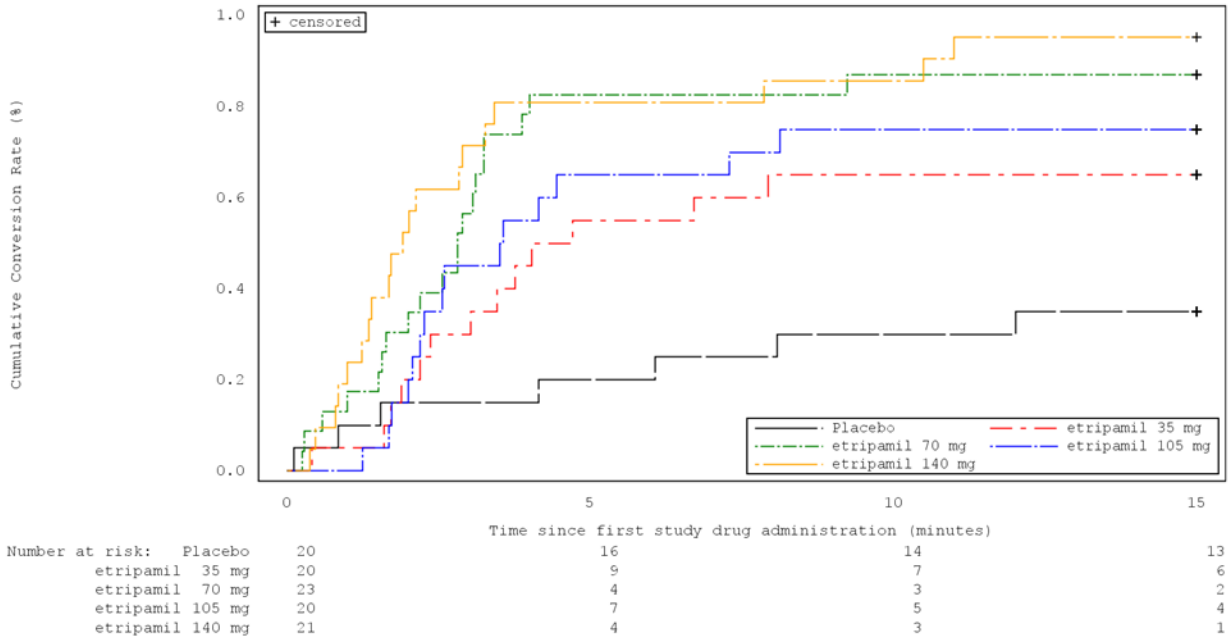
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = the number of patients in the Evaluable Population in the given group; NA = not available; vs. = versus.
Source: Clinical Study Report MSP-2017-1109

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



Number at risk:					
Placebo	20	16	14	13
etripamil 35 mg	20	9	7	6
etripamil 70 mg	23	4	3	2
etripamil 105 mg	20	7	5	4
etripamil 140 mg	21	4	3	1

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 AEs were severe and 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.

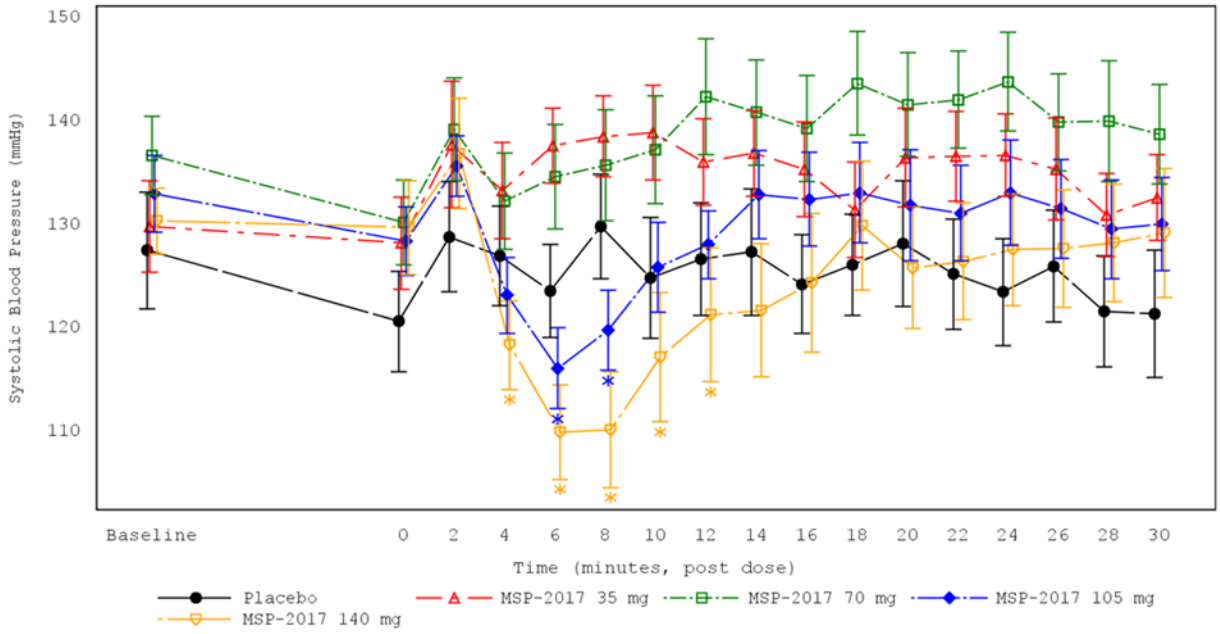
Of note, 1 patient had an episode of second-degree AV block with hypotension beginning 5 minutes after conversion to SR immediately following administration of etripamil NS 140 mg. Atrioventricular block resolved after 43 minutes, and ablation was subsequently performed.

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 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 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.

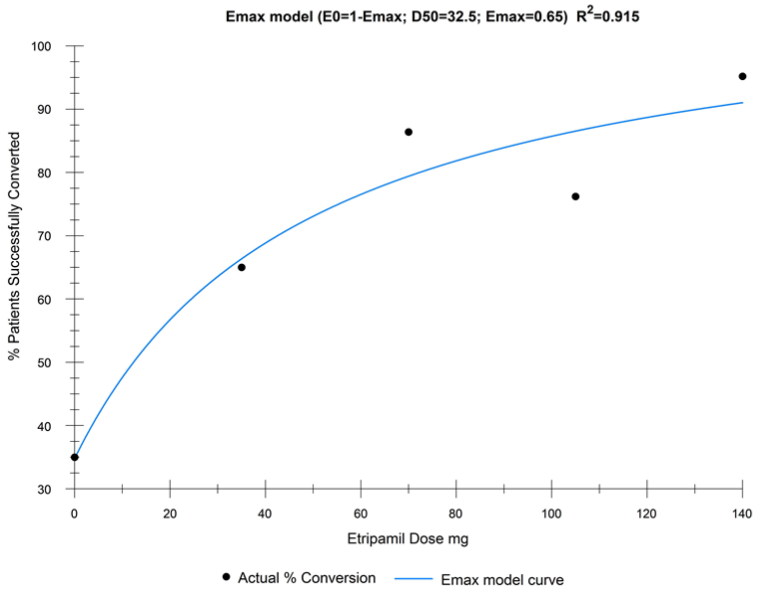
Figure 2. Mean (Standard Error) Systolic Blood Pressure (mmHg) Over Time



Note: Asterisks (*) indicate statistically significant as $p<0.05$ versus baseline. 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.
PSVT = paroxysmal supraventricular tachycardia.
Source: Clinical Study Report MSP-2017-1109

The Cochran-Armitage test for trend showed the presence of an association between conversion rate and the etripamil treatment groups ($p<0.0001$). The maximal efficacy (E_{max}) asymptotic model best fits the dose response relationship showing a plateau starting at or before 70 mg (Figure 3).

Figure 3. Dose Response Maximal Efficacy Model



D50 = dose (mg) related to 50% of the maximal effect; E0 = fitted efficacy at time 0 (placebo effects); E_{max} = maximal efficiency; R^2 = coefficient of determination.
Source: Clinical Study Report MSP-2017-1109

The observed balance between efficacy and safety in the etripamil NS 70 mg group makes this dose a good candidate for future studies.

1.3 Rationale

Etripamil addresses an unmet medical need since there are currently no short-acting products available for patient self-administered treatment of acute 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 acute PSVT would give patients the option to safely terminate acute episodes of PSVT without the need for a hospital visit. An episodic treatment option would 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 70 mg as a viable alternative treatment option.

The goal of this open-label extension study of the Phase 3 NODE-301 study is to demonstrate the safety of etripamil NS 70 mg in the treatment of spontaneous episodes of PSVT when self-administered by patients in an outpatient setting.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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

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

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

The study will include the following:

- A Qualification Visit,
- Treatment Period(s),
- Follow-up Visit(s), and
- A Final Study Visit or an Early Termination Visit.

3.2 Study Visits

3.2.1 Qualification Visit

The Qualification Visit may coincide with the NODE-301 Final Study Visit, or it may be conducted at a future time. During the Qualification Visit, the Investigator will review the patient's recent medical status and verify the patient's eligibility for the NODE-302 study (see Sections 4.1 and 4.2). Patients will be asked to sign the NODE-302 informed consent form before commencement of any study-related assessments or procedures, and the signed informed consent form will be applicable for the initial and all subsequent episodes of PSVT.

Although patients in the NODE-301 study signed the informed consent form and qualify for the NODE-302 study, mandatory assessments must be carried out to confirm ongoing eligibility and inclusion in the NODE-302 study.

The results of the safety laboratory testing (hematology, chemistry, and urinalysis) performed either at the NODE-301 Final Study Visit or specifically for the NODE-302 Qualification Visit, will not be available to the Investigator at the Qualification Visit, but this will not prevent the Investigator from enrolling patients in the NODE-302 study. However, if there is an exclusionary safety laboratory result upon availability of these results, the patient will be asked to return to the site and be withdrawn from the NODE-302 study.

If the patient is entering the NODE-302 study after taking the study drug to treat an episode of PSVT in the NODE-301 study, the CMS safety report (see List of Abbreviations for definition) for the treated episode must be available for evaluation at the Qualification Visit.

Patients will each have a unique identification number during the study.

Patients will be trained on how to report AEs to the sites during the study for evaluation and on specific procedures to be followed when they experience an episode of PSVT, including how to identify and report PSVT symptoms, contact the Telephone Coach (if possible), set up and use the CMS, perform a Vagal Maneuver (VM), and administer study drug. Patients will be trained to complete a patient diary (PSVT symptoms and Treatment Satisfaction Questionnaire for Medication [TSQM]) after each PSVT episode treated with study drug. Standardized training will be described in the Manual of Operations and Procedures (MoOP).

3.2.2 Treatment Period(s)

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

A caregiver may help the patient with these procedures, and this should be annotated in the electronic case report form (eCRF).

The steps of the procedures are the following:

1. Contact the Telephone Coach (if possible) who will guide the patient through the study procedures. If the patient is unable to reach the Telephone Coach, he/she may proceed with the procedures using the printed and electronic guides provided;
2. Apply the CMS to record cardiac activity. The CMS recording should continue for at least 5 hours regardless of treatment outcome;
3. Perform a VM. If the VM is successful in relieving symptoms, the patient will not self-administer the study drug but will keep the CMS device on for 5 hours. The episode of PSVT and the results of the VM will be analyzed by the cardiac monitoring core laboratory. The patient will remain in the study for a subsequent episode of PSVT;
4. Administer etripamil NS 70 mg if the symptoms do not resolve after completion of the VM. The patient will push the CMS event marker button to record the time of dosing immediately prior to self-administering etripamil NS 70 mg IN as instructed. The CMS should not be removed, and the recording should continue for at least 5 hours after study drug administration;
5. Report and rate the symptoms of PSVT and their evolution, as well as overall treatment satisfaction, in a patient diary and TSQM;

6. If the symptoms of PSVT have not resolved within 20 minutes after study drug administration, the patient may seek appropriate medical care and follow these steps:
    a. When the patient reaches a medical care facility to seek treatment for the episode of PSVT, the patient must give the study identification card included in the study kit to the on-site medical personnel. The study identification card contains a brief description of the etripamil study; the Investigator and Medical Monitor contact information; and a short questionnaire to be filled out by the on-site physician to document the diagnosis of the episode, the treatment administered, and the outcome; and
    b. The CMS should not be removed, and recording should continue for at least 5 hours after study drug administration; and
7. Schedule a Follow-up Visit within 7 days of study drug administration and/or episode of PSVT.

The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site. The operational aspects are described in the MoOP. These reports will be sent to the site and the Medical Monitor.

The presence of an episode of PSVT and termination will be evaluated by an independent Adjudication Committee. The Adjudication Committee's evaluations will be done using the complete CMS ECG recorded during the patient's PSVT episode.

3.2.3 Follow-up Visit(s)

Every time the patient self-administers study drug (up to a maximum of 11 doses of etripamil NS 70 mg in the NODE-302 study), the patient will be instructed to return to the site within 7 days after study drug administration for a complete assessment by the Investigator and will receive another study kit including 1 dose of study drug, if the patient does not meet any withdrawal criteria (see Section 4.3). This assessment will include a review of the CMS safety report for the treated episode of PSVT, so this report must be available for evaluation at the Follow-up Visit(s). The CMS safety report must be reviewed before an additional drug kit is dispensed.

If the patient used the CMS for an episode of PSVT that subsequently was terminated by a successful VM (i.e., the patient did not use the study drug), the patient will be instructed to return to the site within 7 days after the episode to ensure that all data has been downloaded from the CMS.

3.2.4 Final Study Visit

The Final Study Visit will occur under the following circumstances:

- The required number of episodes of PSVT are observed in the study and the study is completed,
- The patient has started treatment with a prohibited medication,
- The Sponsor decides to terminate the study for any reason,
- The patient self-administers 11 doses of the study drug in the NODE-302 study,
- The patient is deemed to have completed participation in the study for any other reason, or
- The patient withdraws after taking etripamil NS 70 mg but did not have a Follow-up Visit yet.

A complete assessment will be performed by the Investigator (see Section 6.4).

3.2.5 Early Termination Visit

The Early Termination Visit will occur under the following circumstances:

- The patient withdraws from the study after taking etripamil NS 70 mg and had a Follow-up Visit; or
- The patient withdraws from the study and did not take etripamil NS 70 mg.

In these cases, the patient should come to the site to return the study kit and the Investigator should close the case with Interactive Response Technology (IRT) (see Section 6.5).

4 SELECTION AND WITHDRAWAL OF PATIENTS

The NODE-302 study is designed to obtain safety data to contribute to the etripamil safety database. Only patients randomized in the NODE-301 study are potentially eligible for the NODE-302 study. However, it is expected that among the randomized patients from the NODE-301 study, there will be at least 125 high-risk patients who are defined as follows:

- ≥70 years of age; or
- ≥60 years of age with either first degree AV block (PR interval >200 milliseconds) or concomitant use of medication known to affect cardiac conduction (i.e., beta-blockers, diltiazem, verapamil).

If these high-risk patients are underrepresented in the NODE-301 study (i.e., <125 patients), additional high-risk patients will be recruited into the NODE-302 study to reach 125 high-risk patients enrolled (see Section 9.2.5). These high-risk patients will receive a test dose of etripamil NS 70 mg and will be evaluated for enrollment in the NODE-302 study according to the same process described in the NODE-301 study.

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients at least 18 years of age;
2. Signed the NODE-302 written informed consent;
3. Previously randomized in the NODE-301 study:
   - Received the study drug to treat symptoms the patient believed were consistent with an episode of PSVT during the NODE-301 study, irrespective of the study drug efficacy;

     OR

   - Did not experience an episode of PSVT or did not use the study drug at the time of the NODE-301 study completion;
4. Willing and able to comply with all aspects of the study;
5. Females of childbearing potential who are sexually active must agree to use an approved highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of study drug. Females of childbearing potential should have a negative urine pregnancy test result at the Qualification Visit and at the Follow-up Visit(s), and must use an approved form of contraception between the 2 visits. Approved forms of contraception include hormonal intrauterine devices and hormonal contraceptives (oral birth control pills, Depo-Provera®, patch, or other injectables) together with supplementary double-barrier methods, such as condoms or diaphragms with spermicidal gel or foam;

The following categories define females who are NOT considered to be of childbearing potential:

- Premenopausal females with 1 of the following:
  a. Documented hysterectomy,
  b. Documented bilateral salpingectomy, or
  c. Documented bilateral oophorectomy, or
- Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause; and

6. Male patients, except those who are surgically sterile, must use an approved highly effective form of contraception during the 3 days after study drug administration.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Evidence of new severe arrhythmia discovered since the NODE-301 Test Dose Randomization Visit, including those reported on the CMS report of the outpatient PSVT event treated with the study drug in the NODE-301 study, including but not limited to:
   a. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm;
   b. Significant symptomatic sinus bradycardia HR ≤40 bpm or sinus pauses (≥3 seconds);
   c. Any significant ventricular arrhythmia (premature ventricular beats and couplets [>6 premature ventricular contractions per 45 seconds ECG] are considered significant); or
   d. Atrial fibrillation (event lasting longer than 30 seconds) or atrial flutter;
2. Any drug-related or procedure-related SAE during the NODE-301 study;
3. Any severe AE in the NODE-301 study that was severe enough to preclude administration of etripamil NS 70 mg in the NODE-302 study;
4. Any new drug prescribed after the end of the patient's participation in the NODE-301 study that could lower blood pressure or decrease AV node conduction;
5. Systolic blood pressure <90 mmHg after a 5-minute rest in sitting position at the NODE-302 Qualification Visit;
6. Any symptoms consistent with clinically severe hypotension such as presyncope, medically significant lightheadedness, syncope, nausea, or vomiting;
7. New therapy with digoxin, amiodarone, or any Class I or III antiarrhythmic drug added after the end of the patient's participation in the NODE-301 study;
8. New evidence of ventricular pre-excitation (e.g., delta waves, short PR interval, Wolff-Parkinson-White syndrome) on the ECG since randomization in the NODE-301 study;

9. New symptoms of congestive heart failure defined by the New York Heart Association Class II to IV since randomization in the NODE-301 study;
10. New stroke since randomization in the NODE-301 study;
11. New evidence of a significant physical or psychiatric condition including 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 since randomization in the NODE-301 study;
12. New syncope since randomization in the NODE-301 study, especially if observed during the monitoring of the event treated in the NODE-301 study;
13. New evidence of hepatic dysfunction, defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN, unless due to Gilbert syndrome, observed at the NODE-302 Qualification Visit;
14. New evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the NODE-302 Qualification Visit as follows:
    a. <60 mL/min/1.73 m^2 for patients <60 years of age,
    b. <40 mL/min/1.73 m^2 for patients ≥60 and <70 years of age, or
    c. <35 mL/min/1.73 m^2 for patients ≥70 years of age;
15. Participation in any investigational drug or device study or the use of any investigational drug or device since the Final Study Visit in the NODE-301 study.

4.3 Withdrawal Criteria

Patient participation in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- The patient took the study drug in both the NODE-301 and the NODE-302 studies for symptoms not associated with an episode of PSVT;
- Occurrence of any medical condition, AE, or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Requirement of a prohibited concomitant medication and/or change in the use of chronic therapies, such as concomitant beta-blockers, calcium channel blockers, and medications that can lower blood pressure;
- Patient failure to comply with protocol requirements or study-related procedures;
- Termination of the study by Milestone or a regulatory authority; or
- The patient self-administered a total of 11 doses of etripamil NS 70 mg in the NODE-302 study.

Patients who withdraw from the study after taking etripamil NS 70 mg and had a Follow-up Visit will be required to undergo an Early Termination Visit.

Patients who withdraw from the study and did not take etripamil NS 70 mg will be required to undergo an Early Termination Visit.

Patients who withdraw after taking the study drug but did not have a Follow-up Visit will be required to undergo a Final Study Visit.

5 STUDY TREATMENTS

5.1 Rationale for Study Dose

The choice of the etripamil NS 70 mg dose has been made according to the data obtained in the etripamil Phase 1 and Phase 2 studies.

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 1.1).

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 1.2).

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. Mean SBP did not drop following administration of etripamil 35 and 70 mg.

Etripamil 35 mg had an overall success rate of 65% at 15 minutes compared to 35% with the placebo. The treatment effect of 30%, compared to the high efficacy rates of existing therapies, renders the 35 mg dose inadequate as a development candidate.

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 in contrast to the 2 higher doses.

For these reasons, etripamil NS 70 mg has been selected as the only dose for the NODE-302 study.

5.2 Randomization and Blinding

This is an open-label study and no randomization will be performed.

5.3 Drug Supplies

Milestone will provide sufficient quantities of etripamil NS 70 mg for the study. The lot numbers of supplied study drug will be recorded in the final Clinical Study Report (CSR).

5.3.1 Formulation and Packaging

The formulation of etripamil is for IN administration and will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid, and sulfuric acid. The dose of etripamil to be evaluated in the NODE-302 study is 70 mg.

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 Harmonisation (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.

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 uniquely identified with a generated kit identifier. The kit identifier for each patient will be recorded in the electronic data capture (EDC) system for the study.

Bellwyck Pharma Services is the study drug distributor and will facilitate the delivery and resupply of study drug to the investigational sites. The Investigator or designee must contact the IRT when any unscheduled replacements of study drug are required.

5.3.2 Study Drug Administration

All patients will receive a total of 200 μL of etripamil NS 70 mg (i.e., 100 μL in each nostril via the Aptar Pharma Nasal Spray Bidose System [BDS]) each time they self-administer study drug. The devices will be prefilled and packaged into child-resistant boxes. Instructions for its use are provided in the MoOP and will be provided in the study drug box.

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 drug administration, patients are to remain in a seated position with their head upright, breathe normally, and refrain from blowing their nose.

5.3.3 Treatment Compliance

For this study, study drug will be self-administered or administered with the help of a caregiver. Patients will be required to return the used BDS, the CMS, and the study identification card to the site at their Follow-up Visit(s) and Final Study Visit or Early Termination Visit. The patient will be questioned about the study drug administration, including any issues related to the use of the device such as failure in deployment of the BDS, to confirm drug compliance and accountability.

5.3.4 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 BDS devices to the site for final 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 final drug accountability during their Final Study Visit or Early Termination 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.

5.3.5 Study Drug Handling and Disposal

The final accountability of study drug 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 no study drug remains, this will be indicated in the drug accountability log.

5.4 Prior and Concomitant Medications and/or Procedures

5.4.1 Excluded Medications and/or Procedures

Current participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the Qualification Visit is prohibited (except participation in the NODE-301 study).

The use of digoxin, amiodarone, or any Class I or III antiarrhythmic drug is prohibited in the NODE-302 study.

The effects of concomitant beta-blockers, calcium channel blockers, and medications that can lower blood pressure will be evaluated for each patient in the NODE-301 study. The use of these chronic drugs that were shown to be well tolerated by patients in the NODE-301 study (i.e., during the test dose and during an episode of PSVT if applicable) should not be modified in the NODE-302 study. No new test dose will be performed in the NODE-302 study; therefore, if a change in the use of these chronic therapies is necessary, the patient should be withdrawn from the study.

Drugs commonly used for the chronic prophylactic treatment of episodes of PSVT (e.g., beta-blockers, verapamil, and diltiazem) cannot be started after inclusion of the patient in the NODE-302 study. If the patient requires a prohibited medication during the NODE-302 study for a medical diagnosis other than PSVT, the Investigator should consider withdrawing the patient from the study unless the medical condition(s) may be appropriately stabilized with alternatives.

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

5.4.2 Documentation of Prior and Concomitant Medication Use

The use of any concomitant medications or devices will be recorded in the eCRF by the Investigator and documented in the final CSR.

6 SITE STUDY PROCEDURES

6.1 Qualification Visit

The Qualification Visit may coincide with the NODE-301 Final Study Visit, or it may be conducted at a future time. The following procedures are mandatory for inclusion in the NODE-302 study:

- Obtain informed consent for the NODE-302 study;
- Confirm eligibility based on inclusion/exclusion criteria;
- Review any post-dose AEs that occurred in the NODE-301 study;
- Evaluate any medical intervention that occurred during the Treatment Period in the NODE-301 study;
- Record concomitant medications;
- Evaluate the patient's current medical status since the NODE-301 study;
- Perform physical examination (including height and weight);
- Obtain and record vital signs (blood pressure and HR);
- Perform a 12-lead ECG;
- Collect urine sample for central laboratory urinalysis;
- Collect blood sample for safety laboratory testing (hematology, chemistry, and serum pregnancy test for females of childbearing potential) by the central laboratory;
- Review the CMS safety report, if the patient took the study drug in the NODE-301 study;
- Collect urine samples for on-site pregnancy test for females of childbearing potential; and
- Each eligible patient will receive a study kit, which includes the study drug (etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material.

If the Qualification Visit occurs within 48 hours of the NODE-301 Final Study Visit, the results from the NODE-301 Final Study Visit procedures may be reviewed and used to confirm other inclusion/exclusion criteria and/or procedures in the NODE-302 Qualification Visit, as applicable. If the Qualification Visit occurs after 48 hours of the NODE-301 Final Study Visit, the study procedures performed at the NODE-301 Final Study Visit cannot be used and must be repeated. See the MoOP for further details.

6.2 Treatment Period(s)

During the Treatment Period(s), the patient will perform a sequence of steps described in Section 3.2.2, including etripamil NS 70 mg administration when the patient identifies symptoms of an episode of PSVT. Each patient will have the option to manage multiple episodes of PSVT (up to a maximum of 11 doses of etripamil NS 70 mg) in the NODE-302 study.

The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site. The operational aspects are described in the MoOP. These reports will be sent to the site and the Medical Monitor.

The presence of an episode of PSVT and termination will be evaluated by an independent Adjudication Committee. The Adjudication Committee's evaluations will be done using the complete CMS ECG recorded during the patient's PSVT episode.

In all cases, the presence of an episode of PSVT and termination will be reported to the Investigator by the cardiac monitoring core laboratory as well as potential arrhythmia or conduction issues identified on the 5-hour recording.

6.3 Follow-up Visit(s)

All patients who experience an episode of PSVT and self-administer the study drug will be instructed to return to the site within 7 days after each episode. The following procedures will be performed:

- Evaluate the patient's medical status;
- Review/have patient complete the patient diary entries of scoring scales;
- Record any AEs;
- Collect/return the study kit, if applicable:
    a. Used study drug, and
    b. Used study identification card;
- Record concomitant medications;
- Obtain and record vital signs (blood pressure and HR);
- Collect urine sample for central laboratory urinalysis, only at the first Follow-up Visit for which the patient took the study drug;
- Collect blood sample for safety laboratory testing (hematology, chemistry, and serum pregnancy test for females of childbearing potential) by the central laboratory, only at the first Follow-up Visit for which the patient took the study drug;
- Collect urine samples on-site for pregnancy test for females of childbearing potential;
- Review the CMS safety report;
- Evaluate any medical intervention during the Treatment Period(s); and
- Ensure the patient continues to be eligible for the study.

If the patient decides to continue in the NODE-302 study, a new study kit, which will contain a new study drug and a study identification card (if previous one was used), will be dispensed to the patient. The patient will be provided with a new diary (TSQM and relief of symptoms numeric scoring scales). The CMS will be checked to ensure that all data was downloaded and transmitted to the core laboratory at the Follow-up Visit prior to being given back to the patient.

In addition, an on-site Follow-up Visit must occur due to the following:

- If patients experience an episode of PSVT for which they apply the CMS and the episode is subsequently terminated by a VM. In this case, the CMS will be checked to ensure that all data was downloaded and transmitted to the core laboratory and patients should remain in the study for subsequent episodes of PSVT.

6.4 Final Study Visit

At the Final Study Visit, the following procedures will be performed:

- Identify reason(s) for study completion;
- Evaluate the patient's current medical status;
- Review/have patient complete the patient diary entries of scoring scales, only if the patient took the study drug;
- Record any AEs;
- Evaluate any medical intervention since the last Treatment Period;
- Collect/return the study kit, including:
    a. Used or unused study drug,
    b. Used or unused CMS, and
    c. Study identification card;
- Perform physical examination (including height and weight);
- Obtain and record vital signs (blood pressure and HR);
- Record concomitant medications;
- Review the CMS safety report;
- Collect urine sample for central laboratory urinalysis, only if the patient took the study drug;
- Collect blood sample for safety laboratory testing (hematology, chemistry, and serum pregnancy test for females of childbearing potential) by the central laboratory, only if the patient took the study drug; and
- Close the case with IRT.

6.5 Early Termination Visit

The following procedures will be performed for patients that withdraw from the study:

- Identify the reason(s) for withdrawal;
- Collect the study kit, including:
    a. Used or unused study drug,
    b. Used or unused CMS, and
    c. Study identification card;
- Obtain the signed withdrawal form; and
- Close the case with IRT.

7 EFFICACY ASSESSMENTS

Efficacy assessments will be based on the data derived from CMS recordings. The Adjudication Committee will evaluate the complete CMS ECG data recorded from patients to determine if a true PSVT episode occurred. If the event is related to a confirmed episode of PSVT, the primary endpoint, conversion to SR after study drug administration, will be adjudicated and the primary variable, the time to conversion, will be adjudicated for the primary efficacy analysis.

Following each PSVT episode treated with study drug, the patient will report and rate symptoms of the episode of PSVT and its evolution, as well as overall treatment satisfaction, in a patient diary and TSQM.

7.1 Adjudication Process

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

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

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

The EPs will adjudicate the following:

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

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

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

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

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

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

8 SAFETY ASSESSMENTS

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

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

8.1 Adverse Events

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

Adverse events, which include clinical laboratory test variables, will be monitored from the time of study drug administration during the Treatment Period(s) through the Final Study Visit or Early Termination Visit (whichever is later). Patients will be instructed to report any AE they experience to the Investigator. Investigators will assess for AEs at each visit and record event(s) on the appropriate AE eCRF.

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).

Any medical condition that is present when a patient is qualified or present at baseline that does not deteriorate will not be reported as an AE. However, medical conditions or signs or symptoms present at baseline that change in severity or seriousness beginning at the Treatment Period will be reported as an AE(s).

Clinically significant abnormal assessments that are detected during the study (i.e., beginning at the Treatment Period) or are present at baseline 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. Clinically significant abnormal assessments occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

The Investigator will rate the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of not related, unlikely related, possibly related, probably related, or definitely related (see Section 8.1.3).

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

8.1.2 Unexpected 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, 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.

8.1.3 Assessment of Adverse Events by the Investigator

Assessment of Severity

Mild – An event that is usually transient in nature and generally does not interfere with normal activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating, causing an inability to work or perform normal activities.

Causality Assessment

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 SAE that has been assessed as "possibly related," "probably related," or "definitely related" will be classified as "related" for regulatory reporting purposes. An 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.

In the event of death, a single cause of death will be recorded as an AE. Death is an outcome and is not considered an AE. An exception is sudden death, when the cause is unknown.

8.2 Serious Adverse Events

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

- Death;
- A life-threatening AE;
  - NOTE: An AE or adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Milestone, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- An event that requires hospitalization or prolongation of existing hospitalizations;
  - Any hospital admission will be considered an inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled prior to study

drug administration. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery will be recorded as AEs and assessed for seriousness;

- Admission to the hospital for social or situational reason (e.g., no place to stay or live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
  - Important medical events that may not result in death, a life-threatening situation, or hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

Any SAE (as defined in Section 8.2) occurring from the time of study drug administration during the Treatment Period(s) through the Final Study Visit or Early Termination Visit (whichever is later) must be reported to Medpace Clinical Safety **within 24 hours** of awareness of the event. Any SAE occurring within a 30-day follow-up period after taking the study drug that the Investigator considers related to study drug administration must be reported in the same manner.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically and will retrieve the form.

To report an SAE if the EDC system is not available:

- Send an e-mail to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE Reporting Line (number listed below);
- Fax/e-mail a completed SAE form to Medpace Clinical Safety (number and e-mail address listed below); and
- When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

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 via e-mail or fax.

Medpace Clinical Safety Contact Information

Medpace Clinical Safety
SAE Reporting Line (USA/Canada): +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax (USA/Canada): +1-866-336-5320 or +1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

Medical Monitor
Silvia Shardonofsky, MD
Telephone: +1-514-336-0444, ext. 235
E-mail: sshardonofsky@milestonepharma.com

The Investigator is required to submit SAE reports to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) in accordance with local requirements. All Investigators involved in clinical studies using the same study drug will receive any safety alert notifications for onward submission to their local IRB/IEC as required. This is an open-label study; therefore, all reports sent to Investigators will be unblinded.

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.

8.4 Pregnancy Reporting

Patients are requested to report to the Investigator any pregnancies of themselves or their partner(s) (informed consent is required for partner[s] prior to collecting any information) that occur within 30 days of study drug administration. The Investigator should report the pregnancy to Medpace Clinical Safety (see Section 8.3) within 24 hours of notification.

After the pregnancy is reported, Medpace Clinical Safety personnel will forward the exposure in utero form to the Investigator for completion. The Investigator should monitor the patient/partner until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow reporting procedures for an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the United States Food and Drug Administration (FDA), Health Canada, and applicable competent authorities in all the Member States concerned, and in any case no later than 7 days after knowledge by the Sponsor of such a

case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, Health Canada, and applicable competent authorities concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.6 Medical Device Complaints

Medical device complaints will be reported according to the requirements of local law and legislation.

In the United States, medical device complaints or product problems with the spray device may be voluntarily reported by the Investigator to FDA through MedWatch, the FDA Safety Information and Adverse Event Reporting Program.

8.7 Clinical Laboratory Evaluations

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

8.8 Vital Signs

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

8.9 Electrocardiograms

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

Safety assessments will be based on the data derived from CMS recordings. The cardiac monitoring core laboratory will review the CMS records for each patient and will send an ECG strip and report to the Investigator.

8.10 Physical Examinations

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

9 STATISTICS

A separate Statistical Analysis Plan (SAP) will be prepared to provide a full description of the analyses to be performed for this study.

9.1 Analysis Populations

The Safety Population will include all patients who take the study drug.

The Efficacy Population will include all patients who use the study drug to treat a positively adjudicated episode of PSVT. This population will not include patients who take the study drug for symptoms not associated with an episode of PSVT.

9.2 Statistical Methods

9.2.1 Patient Disposition and Demographic/Baseline Characteristics

The numbers and percentages of patients will be provided for patient disposition and for each study population. For patients who discontinue from the study, the primary reason for discontinuation will be listed and summarized.

Summary statistics will be provided for demographic characteristics (e.g., age, gender, race, and ethnicity) and for baseline disease variables.

The number of etripamil administrations per patient will be reported.

9.2.2 Study Drug Administration and Concomitant Medications

Log entries detailing the IN administration of the study drug to patients will be listed.

Verbatim terms for concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHODD). The numbers and percentages of patients taking concomitant medications will be summarized by anatomical therapeutic chemical classification and preferred term.

9.2.3 Analysis of Efficacy

The efficacy analyses will be performed on the Efficacy Population. The primary efficacy variable is the time to conversion of an episode of PSVT to SR after study drug administration.

9.2.3.1 Primary efficacy analysis

Patients who did not convert after 5 hours following study drug administration or who converted following medical assistance will be censored at 5 hours or at the time of medical assistance (whichever is earliest).

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

9.2.3.2 Secondary efficacy analyses

The TSQM will be reported.

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

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

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

All analyses will be described in detail in the SAP.

9.2.4 Analysis of Safety

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

9.2.5 Sample Size Determination

There is no statistical hypothesis in this uncontrolled open-label safety study. Based on the anticipated randomization of 500 patients in the NODE-301 study, it is estimated that 300 to 500 patients will be eligible for the NODE-302 study. The final number of episodes of PSVT in the NODE-302 study will depend on the frequency and timing of episodes of PSVT during the study. The NODE-302 study will be operational until the end of the development program (i.e., when a sufficient number of documented study drug administrations have been achieved for inclusion in the etripamil safety database).

If the population includes fewer than 125 high-risk patients at the end of the NODE-301 study, new patients meeting the high-risk categories (see Section 4) will be eligible to enroll in the NODE-302 study to ensure the following:

- 125 high-risk patients being enrolled (i.e., having received a test dose); and
- 75 of the enrolled high-risk patients having subsequently self-administered etripamil NS 70 mg during an episode of PSVT, with 20 of them being ≥70 years of age.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by CRAs during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for and electronically signed by the Investigator.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) §11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the latest versions of the following thesauri will be used:

- The Medical Dictionary for Regulatory Activities for medical history and AEs, and
- The WHODD for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs should be reviewed and electronically signed by the Investigator who signed the protocol.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, CMS data, inventory of study drug kits, regulatory documents, and other Milestone correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (i.e., original records or certified copies). These records will be retained in a secure file for the period set forth in the clinical study agreement or as required by the local law. Prior to transfer or destruction of these records, Milestone must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 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.

11.2 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.

11.3 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 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 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. 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.

11.4 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, MoOP, 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.

11.5 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.

11.6 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.

11.7 Monitoring Committees

11.7.1 Steering Committee

A single Steering Committee will be responsible for the scientific oversight of both the NODE-301 and NODE-302 studies. The Steering Committee Chair will review the original protocol and potential amendments.

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

11.7.2 Data and Safety Monitoring Committee

A single DSMC will operate for both the NODE-301 and NODE-302 studies. The DSMC will review the accumulating safety data on a regular basis to detect any safety issue that could be related to the study drug or the protocol procedures involved in the patient's management of an episode of PSVT.

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

11.7.3 Adjudication Committee

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

The EPs will adjudicate the following:

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

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

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

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

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

The Adjudication Committee will review the secondary ECG safety endpoints (i.e., arrhythmia and conduction disorders).

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

11.8 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.

11.9 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.

11.10 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.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace 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, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 Address List

12.2.1 Sponsor

Milestone Pharmaceuticals Inc.
1111 Dr. Frederik-Philips Blvd., Suite 420
Saint-Laurent, QC H4M 2X6, Canada
Telephone: +1-514-336-0444

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227, USA
Telephone (USA): +1-800-730-5779

12.2.3 ECG Core Laboratory for CMS Safety Reports

Preventice Solutions, Inc.
1717 N Sam Houston Parkway West, Suite 100
Houston, TX 77038, USA
Telephone: +1-888-747-1442

12.2.4 ECG Core Laboratory for Primary Endpoint Adjudication

Cardiovascular Research Foundation
1700 Broadway, 9th Floor
New York, NY 10019, USA
Telephone: +1-646-434-4595

12.2.5 Study Drug Distribution and Accountability

Bellwyck Pharma Services
8946 Global Way
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Telephone: +1-513-874-1200
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12.2.7 Biological Specimens

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 2. Schedule of Procedures

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

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

1. The Qualification Visit of this study may coincide with the NODE-301 Final Study Visit or it may be conducted at a future time. Some procedures listed in the NODE-302 Schedule of Procedures Qualification Visit may refer to procedures conducted specifically for the NODE-301 study. If the Qualification Visit occurs within 48 hours of the NODE-301 Final Study Visit, the results from the NODE-301 Final Study Visit procedures may be reviewed and used to confirm other inclusion/exclusion criteria and/or procedures in the NODE-302 Qualification Visit, as applicable. If the Qualification Visit occurs after 48 hours of the NODE-301 Final Study Visit, the study procedures performed at the NODE-301 Final Study Visit cannot be used and must be repeated. See the MoOP for further details.
2. The Treatment Period will begin immediately following the Qualification Visit. Eligible patients will perform a sequence of steps, including etripamil NS 70 mg self-administration when patients identify symptoms of PSVT.
3. All patients who experience an episode of PSVT and self-administer the study drug will be instructed to return to the site within 7 days after each episode. Patients may continue to use study drug up to a maximum of 11 doses of etripamil NS

70 mg in the NODE-302 study. If the patient used the CMS for an episode of PSVT that subsequently was terminated by a successful VM (i.e., the patient did not use the study drug), the patient will be instructed to return to the site within 7 days after the episode to ensure that all data has been downloaded from the CMS.

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

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

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

Hematology

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

Additional Hematology

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

Urinalysis

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

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

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