CLINICAL STUDY PROTOCOL

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

The NODE-301 Trial

Investigational Product: Etripamil (MSP-2017)
Protocol Number: MSP-2017-1138

Sponsor:
Milestone Pharmaceuticals Inc.
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Amendment 2: 20 February 2018
Amendment 3: 04 October 2018
Amendment 4: 09 July 2019

involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to Milestone Pharmaceuticals Inc. and that it may not be further disclosed to third parties.

PROCEDURES IN CASE OF EMERGENCY OR SERIOUS ADVERSE EVENT REPORTING

Emergency Contact Information

Role in Study	Name	Address and 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 at the Test Dose Randomization Visit through the Final Study Visit 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, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia. The NODE-301 Trial

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.	
Douglas Wight, MSc Vice President, Drug Development Milestone Pharmaceuticals Inc.	
Guy Rousseau, PhD Vice President, Regulatory Affairs Milestone Pharmaceuticals Inc.	

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, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia. The NODE-301 Trial

SHORT TITLE: Efficacy and Safety of Etripamil for the Termination of Spontaneous PSVT. NODE-301

PROTOCOL NUMBER: MSP-2017-1138

INVESTIGATIONAL PRODUCT: Etripamil (MSP-2017)

PHASE: 3

INDICATION: Paroxysmal supraventricular tachycardia (PSVT)

OBJECTIVES:

The primary objective of this study is to determine whether etripamil nasal spray (NS) 70 mg self-administered by patients is superior to placebo at terminating episodes of PSVT in an outpatient setting.

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

The exploratory objectives of the study are:

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

POPULATION:

The population for this study is patients at least 18 years of age who have electrographically documented history of PSVT with a history of sustained episodes (i.e., typically lasting approximately 20 minutes or longer).

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. Electrographically documented history of PSVT (e.g., electrocardiogram [ECG] obtained during an episode of PSVT, Holter monitoring, loop recorder, etc.). If patient had a prior ablation for PSVT, patient must have documented ECG evidence of PSVT post-ablation;

3. History of sustained episodes of PSVT (i.e., typically lasting approximately 20 minutes or longer);
4. 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 serum pregnancy test result at the Screening Visit and at the Final Study Visit, a negative urine pregnancy test at the Test Dose Randomization Visit and must use an approved form of contraception between the visits. Approved forms of contraception include hormonal intrauterine devices or 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;

5. Male patients, except those who are surgically sterile, must use an approved highly effective form of contraception during the 3 days after any study drug administration; and
6. Signed written informed consent.

Exclusion criteria

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

1. Systolic blood pressure (SBP) <90 mmHg after a 5-minute rest in sitting position at the Screening Visit or before the test dose. In patients treated with a chronic prophylactic drug for PSVT (e.g., beta-blockers, verapamil, and diltiazem), the drug may be stopped for at least the equivalent of 5 half-lives and patients may be rescreened once;
2. History of severe symptoms of hypotension, especially syncope, during episodes of PSVT;
3. History of atrial arrhythmia that does not involve the atrioventricular (AV) node as part of the tachycardia circuit (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia);
4. History of allergic reaction to verapamil;
5. Current therapy with digoxin or any Class I or III antiarrhythmic drug, except if these drugs are stopped at least the equivalent of 5 half-lives before the Test Dose Randomization Visit;
6. Current therapy with amiodarone, or have taken amiodarone within 30 days prior to the Test Dose Randomization Visit;
7. Evidence of ventricular pre-excitation (e.g., delta waves, short PR interval <100 msec, Wolff-Parkinson-White syndrome) on the ECG performed at the Screening Visit or before the test dose administration;

8. Evidence of a second- or third-degree AV block on the ECG performed at the Screening Visit or before the test dose administration;
9. History or evidence of severe ventricular arrhythmia (e.g., torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia);
10. Current congestive heart failure defined by the New York Heart Association Class II to IV;
11. Stroke in the last 6 months;
12. Evidence of hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN at the Screening Visit, unless due to Gilbert syndrome;
13. Evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the Screening 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;
14. Females who are pregnant or lactating;
15. Evidence or history of any significant physical or psychiatric condition including drug abuse, which, in the opinion of the Investigator, could jeopardize the safety of patients or affect their participation in the study. Additionally, the Investigator has the ability to exclude a patient if for any reason the Investigator judges the patient is not a good candidate for the study or will not be able to follow study procedures; or
16. Participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the Screening Visit.

Before randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients on the study procedures. A failure of the test dose is considered if patients meet any of the following criteria occurring after administration of the etripamil NS 70 mg test dose:

1. Any symptoms consistent with clinically severe hypotension such as pre-syncope, medically significant lightheadedness, syncope, nausea, or vomiting;
2. For patients with a pre-test dose SBP above 100 mmHg:
    a. Decrease in SBP ≥40 mmHg after test dose; or
    b. Post-test dose SBP <80 mmHg;
3. For patients with a pre-test dose SBP between 90 mmHg and 100 mmHg (inclusive):
    a. Post-test dose SBP <75 mmHg;
4. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm;

5. New, significant sinus bradycardia heart rate (HR) ≤40 bpm or sinus pauses (≥3 seconds), if considered by the Investigator to put the patient's safety at risk if either were to occur while not under medical supervision;
6. Any new significant ventricular arrhythmia (premature ventricular beats and couplets [>6 premature ventricular contractions per 45 seconds ECG] are considered significant); or
7. Atrial fibrillation or atrial flutter (event lasting longer than 30 seconds).

Patients who fail the test dose will proceed in the study as follows:

- If the Investigator identifies a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as beta-blocker), a re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients may be randomized if they pass the second test dose, and the cause of the test dose failure is eliminated for the duration of the study; or
- If the Investigator cannot identify a reversible cause of the initial test dose failure, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population, including all patients who received at least 1 test dose of etripamil NS 70 mg.

During each patient's Test Dose Randomization Visit, the test dose Cardiac Monitoring System (CMS) ECG data will be reviewed by the cardiac monitoring core laboratory, and a report will be sent to the site. The operational aspects are described in the manual of operations and procedures (MoOP).

STUDY DESIGN AND DURATION:

NODE-301 is a multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etripamil NS 70 mg self-administered by patients who experience an episode of PSVT in an outpatient setting. Each episode will be documented by an ambulatory CMS that will be placed on the chest by the patient or caregiver when symptoms begin and will record at least 5 hours of continuous ECG. Each CMS will be identified by a unique number.

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

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

Part 2 will consist of patients that will not be included in Part 1, i.e., Part 2 will consist of patients who were not dosed with the double-blind study drug or have not discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode. The data from patients in Part 2 will be combined with that from Part 1 and will be included in exploratory analyses. Exploratory analyses will include safety; and primary, secondary, and exploratory efficacy

analyses for Parts 1 and 2 combined. Patients in Part 2 will be unblinded at the end of the study. Part 2 will end when one of the following criteria is met:

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

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

The study will include a Screening Visit, a Test Dose Randomization Visit, Follow-up Visits, a Treatment Period, and a Final Study Visit.

Screening Visit

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

Test Dose Randomization Visit

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

Follow-up Visits

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

Treatment Period

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

Final Study Visit

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Investigational Product and Dosage: The formulation of etripamil will consist of MSP-2017 (etripamil), water, acetic acid, disodium ethylene-diamine-tetra-acetic acid (EDTA), and sulfuric acid. The dose of etripamil to be evaluated in the NODE-301 study is 70 mg. The same formulation will be used for the Test Dose Randomization Visit and for the Treatment Period.

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

Mode of Administration: All patients will receive a total of 200 μL of etripamil NS 70 mg or placebo (i.e., 100 μL in each nostril via the Aptar Pharma Nasal Spray Bidose System). 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.

DURATION OF TREATMENT:

This is an event-driven study; approximately 150 randomized patients presenting with a positively adjudicated episode of PSVT and treated with the study drug are required to control the type I error rate at the desired alpha = 0.01 and to get an adequate power. Since the time from enrollment to when patients experience their first positively adjudicated episode of PSVT treated with study drug is unknown, the study is projected to randomize up to 500 patients. The final number of randomized patients and of adjudicated episodes of PSVT will depend on the frequency and timing of episodes of PSVT during the study. Enrollment into the study will stop on the date of the adjudication of the 150th positively adjudicated PSVT episode.

EFFICACY VARIABLES:

The primary efficacy endpoint is defined as an adjudicated termination of a positively adjudicated episode of PSVT (AV nodal reentrant tachycardia [AVNRT] or AV reentrant tachycardia [AVRT] determination if possible) and conversion to sinus rhythm (SR) for at least 30 seconds.

The primary efficacy endpoint will be evaluated using the time to conversion of an episode of PSVT to SR after study drug administration as the primary efficacy variable.

The secondary efficacy endpoints will include:

- Relief of specific symptoms (i.e., heart palpitations, rapid pulse feeling, chest pain, anxiety, shortness of breath, dizziness, and fainting) potentially associated with an episode of PSVT; and
- Rating of Treatment Satisfaction Questionnaire for Medication (TSQM).

The exploratory efficacy endpoints will include:

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

SAFETY VARIABLES:

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

During the etripamil test dose period, vital signs, SBP, diastolic blood pressure, HR measurements, arrhythmia, conduction disorders on the ECGs, and clinical AEs will be recorded. These data will be reported in the Overall Safety Population. These variables will be reported in the pre-identified relevant subgroups of patients (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction) for pre-defined subgroup analyses.

During the Treatment Period, safety variables will be recorded.

STATISTICAL ANALYSES:

Analysis populations

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

The modified Intent to Treat (mITT) Population includes all randomized patients who take the randomized study drug, not during a test dose visit. The subjects will be included in the treatment arm (placebo or double-blind study drug) in which they were randomized.

The Test Dose Only Population includes all patients who receive the test dose of etripamil NS 70 mg, but do not receive randomized drug (Overall Safety Population, minus the Safety Population). The Test Dose Only Population will also include pre-identified relevant subgroups of patients (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction) for pre-defined subgroup analyses.

The Safety Population includes all randomized patients who take the study drug, not during a test dose visit. The subjects will be included in the treatment arm (placebo or double-blind study drug) according to actual received treatment.

The Overall Safety Population includes the Safety Population and the Test Dose Only Population.

Efficacy analyses

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

The data from patients in Part 1 will be included in pivotal analyses. Pivotal analyses will include safety; and primary, secondary, and exploratory efficacy analyses for Part 1 only.

The data from patients in Part 2 will be combined with that from Part 1 and will be included in exploratory analyses. Exploratory analyses will include safety; and primary, secondary, and exploratory efficacy analyses for Parts 1 and 2 combined.

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

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

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

In addition to the primary analysis of the primary endpoint, Kaplan-Meier estimates of time to conversion will be calculated and reported as a Kaplan-Meier plot. Conversion rates at 3, 5, 10, 15, 20, 30, 60, and 90 minutes after study drug administration will be reported for the etripamil group and the placebo group. The odds ratio (OR), and the CI for the OR, will be calculated. The Kaplan-Meier estimate of the time at which 25%, 50%, and 75% of episodes of PSVT conversions occur will be calculated.

A sensitivity analysis for the primary efficacy endpoint will be performed on the mITT Population. In this analysis, the time to PSVT episode conversion will include "misidentification of PSVT by the patient." All of these patients will be censored at the conversion of the non-reentry supraventricular tachycardia to SR or at 5 hours if conversion is not observed or if there were no tachycardia observed at all.

For the secondary efficacy endpoint analyses, relief of specific symptoms associated with the termination of an episode of PSVT by the study drug will be analyzed by comparing the numeric scoring scale scores in the 2 treatment groups, and treatment satisfaction will be analyzed by comparing the rating of TSQM in the 2 treatment groups.

Exploratory efficacy endpoint analyses will include descriptive statistics of the number of patients requiring additional medical intervention to terminate an episode of PSVT and descriptive statistics of the number of positively adjudicated episodes of PSVT converted by performing a VM.

The primary, secondary, and subgroup analyses (e.g., concomitant medications) for efficacy may be repeated in all patients (Parts 1 and 2).

Safety analyses

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.

Safety summaries will be presented for patients in Part 1 of the study. Additional safety analyses will be conducted for all patients (Parts 1 and 2).

SAMPLE SIZE DETERMINATION:

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

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

However, since patients will be randomized before they have a qualifying episode of PSVT, it is unlikely that the 2:1 etripamil:placebo PSVT episodes ratio will match the 2:1 randomization ratio. In such a case, it is preferable to target a higher sample size to cover for the worst-case scenarios in terms of unbalance.

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

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

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

MONITORING COMMITTEES:

Steering Committee

The Steering Committee will be responsible for the scientific oversight of the study. The Steering Committee Chair will review the original protocol and potential amendments.

Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (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. The committee will be entitled to request a review of unblinded safety data.

Adjudication Committee

The Adjudication Committee will comprise at least 5 members, all cardiac electrophysiologists, 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 intravenous adenosine in a medical care facility).

The conclusion of the Adjudication Committee will be used in the primary and secondary analyses.

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

SITES:

This study will be conducted at up to 75 sites.

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
CI	Confidence interval
CMS	Cardiac Monitoring System
CRA	Clinical Research Associate
CSR	Clinical study report
DBP	Diastolic blood pressure
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylene-diamine-tetra-acetic acid
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
OR	Odds ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PSVT	Paroxysmal supraventricular tachycardia
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SR	Sinus rhythm
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 msec.[1] Etripamil is directed towards the 2 most common subtypes of PSVT, atrioventricular (AV) nodal reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT), together accounting for approximately 90% of PSVT cases.[1] In both conditions, a pharmaceutical agent capable of transiently prolonging AV conduction time can result in arrhythmia termination and restoration of normal sinus rhythm (SR).

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

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 subjects. All etripamil doses were generally well tolerated, and there was no difference in the safety profile and PK between the 2 etripamil formulations (MSP-2017A and MSP-2017B). The study of formulation A was stopped at 60 mg, and formulation B was studied at 105 mg and 140 mg. Pharmacokinetic analyses demonstrated rapid absorption and elimination following IN administration of etripamil (across the dose range tested), and a dose proportional systemic exposure (area under the curve and maximum plasma concentration for MSP-2017 and its inactive metabolite [MSP-2030]) following administration of up to 140 mg of MSP-2017 (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 a clinical setting.

During a pre-study visit, patients were randomly assigned to 1 of the 5 following study groups in a 1:1:1:1:1 ratio: placebo, or etripamil nasal spray (NS) at 35, 70, 105, or 140 mg. Induction of PSVT was attempted using standard pacing and programmed stimulation methods. If PSVT could not be induced after a reasonable number of attempts, or could be induced but did not sustain for 5 minutes, IV isoproterenol was infused. After a minimum of 5 minutes in induced, sustained PSVT, patients were administered double-blind study drug NS via 4 pre-filled Aptar Pharma Unit dose spray devices by EPL personnel using a double-dummy, multiple-dose design. Each device delivered 100 µL of either placebo or 35 mg of etripamil. The appropriate combination of active and placebo devices was used to deliver etripamil according to the dose (0, 35, 70, 105, or 140 mg) assigned at randomization and arranged so that all the active medication was administered prior to any placebo.

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

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

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

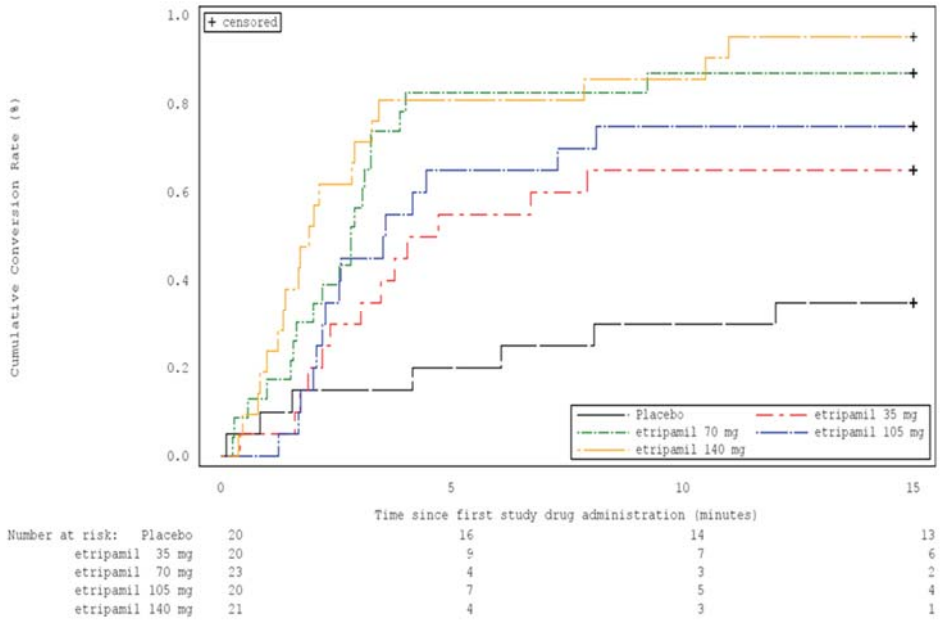
	Placebo (N = 20)	**MSP-2017 35 mg (N = 20)**	**MSP-2017 70 mg (N = 23)**	**MSP-2017 105 mg (N = 20)**	**MSP-2017 140 mg (N = 21)**
Number (%) of patients converted to sinus rhythm within 15 minutes after study drug	7 (35.0)	13 (65.0)	20 (87.0)	15 (75.0)	20 (95.2)
Treatment comparisons					
Odds ratio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

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

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

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

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



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

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

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

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

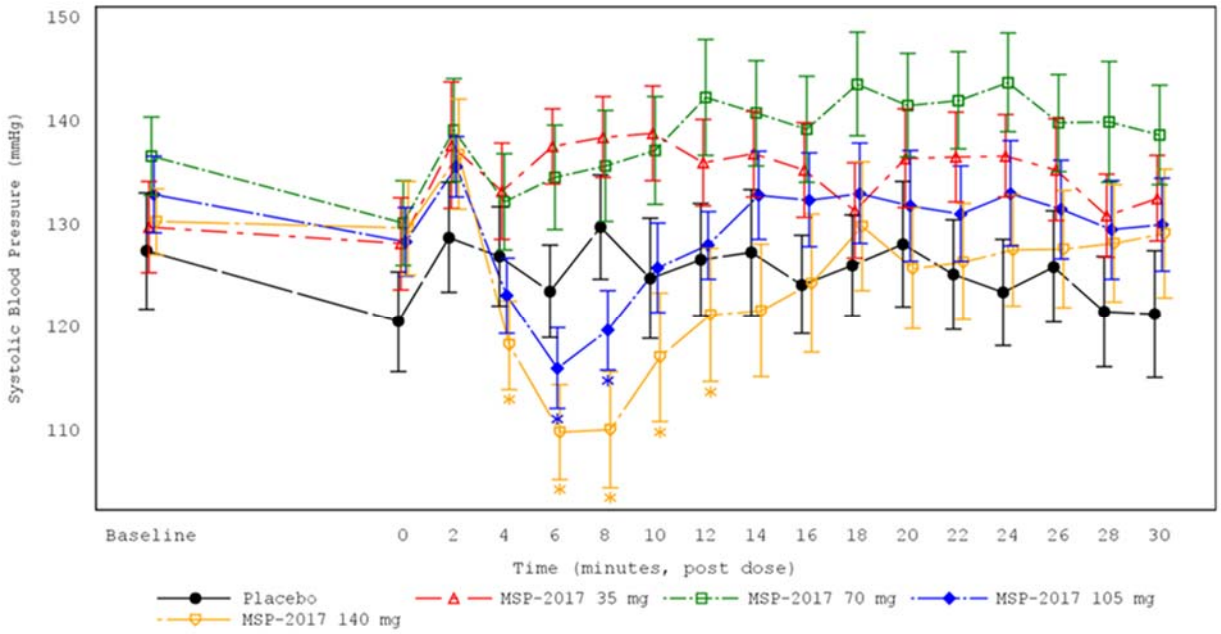
Of note, 1 patient had an episode of second-degree AV block with hypotension beginning 5 minutes after conversion to SR immediately following administration of etripamil NS 140 mg. Atrioventricular block resolved after 43 minutes, and ablation was subsequently performed.

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

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

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

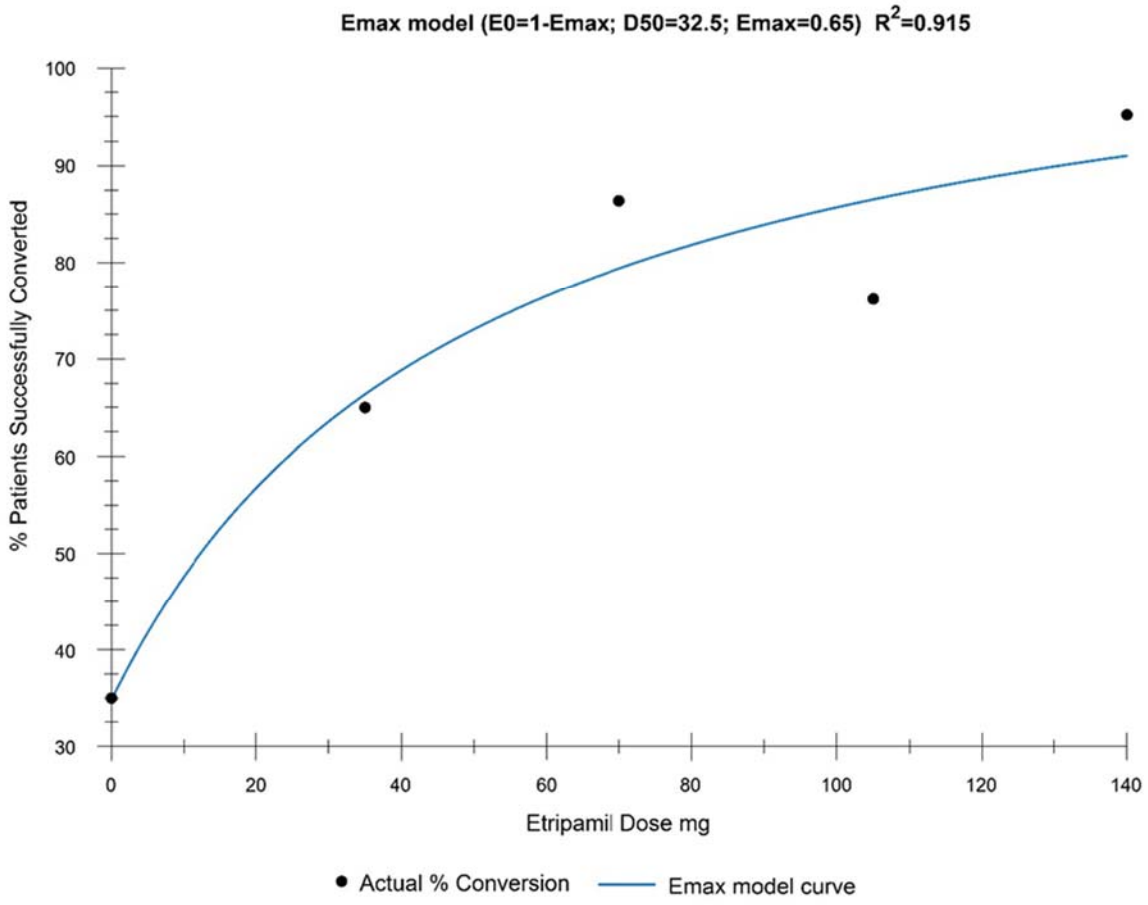
Figure 2. Mean (±Standard Error) Systolic Blood Pressure (mmHg) Over Time



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 (see 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

The primary objective of this study is to determine whether etripamil NS 70 mg is superior to placebo at terminating acute episodes of PSVT in an outpatient setting. Therefore, a double-blind, placebo-controlled, parallel design study is the most appropriate to reach the objective.

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 as a viable alternative treatment option.

The goal of this double-blind Phase 3 NODE-301 study is to demonstrate the safety and effectiveness 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 determine whether etripamil NS 70 mg self-administered by patients is superior to placebo at terminating episodes of PSVT in an outpatient setting.

2.2 Secondary Objective

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

2.3 Exploratory Objectives

The exploratory objectives of the study are:

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

3 STUDY DESCRIPTION

3.1 Summary of Study Design

NODE-301 is a multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etripamil NS 70 mg self-administered by patients who experience an episode of PSVT in an outpatient setting. Each episode will be documented by an ambulatory Cardiac Monitoring System (CMS) that will be placed on the chest by the patient or caregiver when symptoms begin and will record at least 5 hours of continuous electrocardiogram (ECG). Each CMS will be identified by a unique number. This study will be conducted at up to 75 sites.

This is an event-driven study; approximately 150 randomized patients presenting with a positively adjudicated episode of PSVT and treated with the study drug are required to control the type I error rate at the desired alpha = 0.01 and to get an adequate power. Since the time from enrollment to when patients experience their first positively adjudicated episode of PSVT treated with study drug is unknown, the study is projected to randomize up to 500 patients. The final number of randomized patients and of adjudicated episodes of PSVT will depend on the frequency and timing of episodes of PSVT during the study. Enrollment into the study will stop on the date of the adjudication of the 150th positively adjudicated PSVT episode. See the sample size determination section (Section 9.2.5) for additional details.

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

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

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

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

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

The study will include the following:

- A Screening Visit,
- A Test Dose Randomization Visit,

- Follow-up Visits,
- A Treatment Period, and
- A Final Study Visit.

3.2 Study Visits

3.2.1 Screening Visit

During the Screening Visit, the Investigator will review the patient's medical history and complete assessments to confirm eligibility, including confirmation of PSVT.

Investigators will be provided with a manual of operations and procedures (MoOP) that will define acceptable source documents required to confirm the PSVT diagnosis.

The Investigators will enroll patients who have a history of sustained episodes of PSVT (i.e., typically lasting approximately 20 minutes or longer).

Females of childbearing potential and male patients, except those who are surgically sterile, who are sexually active must agree to use an approved highly effective form of contraception.

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

If an enrolled patient meets at least 1 exclusion criterion, the patient will be considered a screening failure. Re-screening may be allowed after consultation with the Investigator and Medical Monitor.

3.2.2 Test Dose Randomization Visit

The initial Test Dose Randomization Visit must occur within 28 days after the Screening Visit. Before randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients on the study procedures. The test dose administration will take place at the study site under medical supervision while the patient is in SR. Any post-dose AEs will be recorded. The test dose procedures are detailed in the MoOP. The test dose failure criteria are listed in the protocol exclusion criteria (Section 4.2).

- Patients who pass the test dose will be randomized in a 2:1 ratio to etripamil or placebo using an Interactive Response Technology (IRT) system. If the CMS ECG test dose report is delayed for any unforeseen reason, patients will be allowed to leave and return to the site another day for randomization.
- Patients who fail the test dose will proceed in the study as follows:
    - If the Investigator identifies a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as beta-blocker), a re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients may be randomized if they pass the second test dose, and the cause of the test dose failure is eliminated for the duration of the study; or

- If the Investigator cannot identify a reversible cause of the initial test dose failure, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population, including all patients who received at least 1 test dose of etripamil NS 70 mg.

The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site in a report based on the mobile system's proprietary arrhythmia detection algorithms and automatic ECG collection. During each patient's Test Dose Randomization Visit, the cardiac monitoring core laboratory will generate a summary test dose report within approximately 1 to 2 hours of the receipt of the ECG data. This report will be used by the site to determine if the patient passes or fails the test dose and if the eligibility criteria to be randomized in the study have been met. The operational aspects of the use of the CMS during the test dose are described in the MoOP.

Randomized 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 self-administer study drug. A caregiver may help the patient with these procedures. Each randomized patient will receive a study kit, which includes the blinded study drug (placebo or etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material. Randomized patients will also be provided with a patient diary to be completed after experiencing a PSVT episode. The patient diary collects information about symptoms of the patient's PSVT episode and includes a Treatment Satisfaction Questionnaire for Medication (TSQM). Standardized training will be described in the MoOP.

3.2.3 Follow-up Visits

Follow-up Visits will occur approximately monthly from the time of randomization and can be conducted by patients returning to the investigative site (preferred) or by the site personnel contacting patients by telephone. During this visit, inclusion/exclusion criteria will be reviewed to ensure patients are eligible to continue in the study, and patients will be re-trained on the procedures they will need to follow when they experience the symptoms of an episode of PSVT. Routine monthly Follow-up Visits are highly recommended but are not mandatory. A missing Follow-up Visit will not be considered a deviation of the protocol, and patients will not be excluded from the study for missing their monthly Follow-up Visits.

A Follow-up Visit will also occur 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, it is mandatory for patients to be on-site for the Follow-up Visit so that site personnel can ensure that all data has been downloaded from the CMS device. Patients will retain their CMS and remain in the study for subsequent episodes of PSVT.

3.2.4 Treatment Period

All randomized patients will perform a sequence of steps, including study drug self-administration when patients identify symptoms of an episode of PSVT. A caregiver may help the patient with these procedures, and this should be annotated in the electronic case report form (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;
3. Perform a VM. If the VM is successful in relieving symptoms, the patient will not self-administer study drug but will keep the CMS device on for 5 hours. The episode of PSVT and the results of the VM will be adjudicated, and the patient will remain in the study for a subsequent episode of PSVT;
4. Administer study drug 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 the study drug 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 symptoms of PSVT 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, patients 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 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;
    b. The CMS should not be removed, and recording should continue for at least 5 hours after study drug administration;
    c. If unblinding is judged necessary by the on-site treating physician, a 24/7 assistance telephone number will be provided on the study identification card so that the situation can be discussed with the Medical Monitor. It is recommended to contact the study Medical Monitor before any unblinding occurs; and
7. Schedule a Final Study Visit within 7 days of study drug administration.

The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site in a report based on the mobile system's proprietary arrhythmia detection algorithms and automatic ECG collection. The cardiac monitoring core laboratory will generate a summary report within 48 hours of the receipt of ECG data. The operational aspects are described in the MoOP. These reports will be sent to the site and the Medical Monitor.

In all cases, 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.

3.2.5 Final Study Visit

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

This visit will occur under the following circumstances:

- The patient fails the test dose,
- The patient self-administers study drug (or with the help of a caregiver) for an episode of PSVT whether or not the episode is subsequently adjudicated as a true episode of PSVT,
- The patient has started treatment with a prohibited medication before experiencing an episode of PSVT,
- The patient withdraws consent from the study for any reason,
- The Sponsor decides to terminate the study for any reason, or
- The patient is deemed to have completed participation in the study for any other reason.

4 SELECTION AND WITHDRAWAL OF PATIENTS

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. Electrographically documented history of PSVT (e.g., ECG obtained during an episode of PSVT, Holter monitoring, loop recorder, etc.). If patient had a prior ablation for PSVT, patient must have documented ECG evidence of PSVT post-ablation;
3. History of sustained episodes of PSVT (i.e., typically lasting approximately 20 minutes or longer);
4. 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 serum pregnancy test result at the Screening Visit and at the Final Study Visit, a negative urine pregnancy test at the Test Dose Randomization Visit and must use an approved form of contraception between the visits. Approved forms of contraception include hormonal intrauterine devices or 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;

5. Male patients, except those who are surgically sterile, must use an approved highly effective form of contraception during the 3 days after any study drug administration; and
6. Signed written informed consent.

4.2 Exclusion Criteria

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

1. Systolic blood pressure <90 mmHg after a 5-minute rest in sitting position at the Screening Visit or before the test dose. In patients treated with a chronic prophylactic drug for PSVT (e.g., beta-blockers, verapamil, and diltiazem), the drug may be stopped for at least the equivalent of 5 half-lives and patients may be rescreened once;
2. History of severe symptoms of hypotension, especially syncope, during episodes of PSVT;
3. History of atrial arrhythmia that does not involve the AV node as part of the tachycardia circuit (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia);

4. History of allergic reaction to verapamil;
5. Current therapy with digoxin or any Class I or III antiarrhythmic drug, except if these drugs are stopped at least the equivalent of 5 half-lives before the Test Dose Randomization Visit;
6. Current therapy with amiodarone, or have taken amiodarone within 30 days prior to the Test Dose Randomization Visit;
7. Evidence of ventricular pre-excitation (e.g., delta waves, short PR interval <100 msec, Wolff-Parkinson-White syndrome) on the ECG performed at the Screening Visit or before the test dose administration;
8. Evidence of a second- or third-degree AV block on the ECG performed at the Screening Visit or before the test dose administration;
9. History or evidence of severe ventricular arrhythmia (e.g., torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia);
10. Current congestive heart failure defined by the New York Heart Association Class II to IV;
11. Stroke in the last 6 months;
12. Evidence of hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN at the Screening Visit, unless due to Gilbert syndrome;
13. Evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the Screening 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;
14. Females who are pregnant or lactating;
15. Evidence or history of any significant physical or psychiatric condition including drug abuse, which, in the opinion of the Investigator, could jeopardize the safety of patients or affect their participation in the study. Additionally, the Investigator has the ability to exclude a patient if for any reason the Investigator judges the patient is not a good candidate for the study or will not be able to follow study procedures; or
16. Participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the Screening Visit.

Before randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients on the study procedures. A failure of the test dose is considered if patients meet any of the following criteria occurring after administration of the etripamil NS 70 mg test dose:

1. Any symptoms consistent with clinically severe hypotension such as pre-syncope, medically significant lightheadedness, syncope, nausea, or vomiting;
2. For patients with a pre-test dose SBP above 100 mmHg:
    a. Decrease in SBP ≥40 mmHg after test dose; or
    b. Post-test dose SBP <80 mmHg;
3. For patients with a pre-test dose SBP between 90 mmHg and 100 mmHg (inclusive):
    a. Post-test dose SBP <75 mmHg;
4. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm;
5. New, significant sinus bradycardia HR ≤40 bpm or sinus pauses (≥3 seconds), if considered by the Investigator to put the patient's safety at risk if either were to occur while not under medical supervision;
6. Any new significant ventricular arrhythmia (premature ventricular beats and couplets [>6 premature ventricular contractions per 45 seconds ECG] are considered significant); or
7. Atrial fibrillation or atrial flutter (event lasting longer than 30 seconds).

Patients who fail the test dose will proceed in the study as follows:

- If the Investigator identifies a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as beta-blocker), a re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients may be randomized if they pass the second test dose, and the cause of the test dose failure is eliminated for the duration of the study; or
- If the Investigator cannot identify a reversible cause of the initial test dose failure, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population, including all patients who received at least 1 test dose of etripamil NS 70 mg (see Section 9.1).

During each patient's Test Dose Randomization Visit, the test dose CMS ECG data will be reviewed by the cardiac monitoring core laboratory, and a report will be sent to the site. The operational aspects are described in the MoOP.

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;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by Milestone or a regulatory authority.

If a patient withdraws consent after the test dose and before an episode of PSVT, he/she will be required to undergo the Final Study Visit procedures and will still be considered evaluable in the Test Dose Only Population and Safety Population (see Section 9.1).

5 STUDY TREATMENTS

5.1 Treatment Groups

Before randomization, all patients will receive a test dose of etripamil NS 70 mg to evaluate tolerability and to train patients on the study procedures. The test dose administration will take place at the study site under medical supervision while the patient is in SR. Patients who pass the test dose will be randomized in a 2:1 ratio to etripamil NS 70 mg or placebo using IRT.

5.2 Rationale for Dosing

The choice of the dose level of etripamil NS was made according to the data obtained in 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 NODE-301.

5.3 Randomization and Blinding

At the Screening Visit, a unique patient identification number will be established for each patient at the investigational site. This patient identification number will be used for patient identification throughout the study and in all study-related documentation. This will be a 6 digit hyphenated number of the following format: XXX-YYY, where XXX is the unique site identification number and YYY is a sequential unique number assigned to the patient at that site. Each patient number will be assigned only once and will not be reassigned to another patient if a patient fails during the

Screening Visit. The IRT will not allow repeat of numbers. This unique identifier is used in all study documentation for that patient from first to last contact.

The Investigator or designee must electronically contact the IRT to acquire a treatment assignment for each patient.

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

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

5.4 Unblinding

In the event of an emergency, it will be possible to determine to which treatment the patient has been allocated by calling a 24/7 assistance telephone number provided on the patient's study identification card. The Medical Monitor should be consulted prior to unblinding whenever possible. Any unblinding performed by the Investigator or medical personnel must be recorded in the source documents.

5.5 Drug Supplies

Milestone will provide sufficient quantities of etripamil and placebo NS for the study. The lot numbers of supplied study drug will be recorded in the final clinical study report (CSR).

5.5.1 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 (EDTA), and sulfuric acid. The dose of etripamil to be evaluated in the NODE-301 study is 70 mg. The same formulation will be used for the Test Dose Randomization Visit and for the Treatment Period.

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

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. Double-blind study drug will be uniquely identified with a randomly 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 site. The Investigator or designee must contact the IRT when any unscheduled replacements of study drug are required.

5.5.2 Study Drug Administration

All patients will receive a total of 200 μL of etripamil NS 70 mg or placebo (i.e., 100 μL in each nostril via the Aptar Pharma Nasal Spray Bidose System [BDS]). The devices will be prefilled and packaged into child-resistant boxes. Instructions for its use are provided in the MoOP and will be provided in the study drug 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. Patients will receive study drug (randomized in a 2:1 ratio to etripamil:placebo) as determined by their treatment group assignment.

If the BDS does not deploy, it will be considered a missed dose.

5.5.3 Treatment Compliance

The patient will administer the test dose of study drug at the clinical site with the guidance of study personnel. The date, dosing initiation time, and dose completion time will be recorded. For the double-blind portion of the 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 Final Study Visit. The patient will be questioned about the 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.

5.5.4 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.

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.

5.5.5 Study Drug Handling and Disposal

The final accountability of study drug will be performed by the Clinical Research Associate (CRA) at the sites. Sites will not be allowed to destroy study drug. All study drug kits will be returned to Milestone's designee at study closeout after CRA accountability is completed. If no study drug remains, this will be indicated in the drug accountability log.

5.6 Prior and Concomitant Medications and/or Devices

5.6.1 Excluded Medications and/or Devices

Current participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the Screening Visit is prohibited.

The use of digoxin or any Class I or III antiarrhythmic drug with less than the equivalent of 5 half-lives of this drug prior to the Test Dose Randomization Visit is prohibited. The use of amiodarone within 30 days prior to the Test Dose Randomization Visit is prohibited.

Drugs for chronic prophylactic treatment of episodes of PSVT (e.g., beta-blockers, verapamil, and diltiazem) cannot be started after randomization.

If the treatment with antihypertensive drugs (monotherapy or combinations) is modified after the randomization, a new test dose may be conducted, after consultation with the Medical Monitor.

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

5.6.2 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 Screening Visit

The following procedures will be performed at the Screening Visit. See also Table 2 (Schedule of Procedures):

- Obtain informed consent. The patient is considered enrolled in the study when informed consent is obtained;
- Record demographics and medical/surgical history;
- Evaluate and record concomitant medications;
- Perform physical examination (including height and weight);
- Obtain and record vital signs (blood pressure and HR);
- 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;
- Perform 12-lead ECG; and
- Confirm eligibility based on inclusion/exclusion criteria (including confirmation of PSVT diagnosis per the MoOP).

6.2 Test Dose Randomization Visit

The Test Dose Randomization Visit must occur within 28 days after the Screening Visit. The following procedures will occur at the Test Dose Randomization Visit:

- Confirm eligibility (additional eligibility criteria apply to pass the test dose at the Test Dose Randomization Visit only);
- Record the CMS identifier number in the EDC system for the test dose;
- Train the patient on:
    - Symptom identification, assessment, and reporting;
    - Contacting the Telephone Coach (if possible) who will guide the patient through the study procedures. For the Test Dose Randomization Visit only, the Telephone Coach should be contacted once the 10 minutes of baseline recording with the CMS is complete. If the patient is unable to reach the Telephone Coach, he/she may proceed with the procedures using the printed and electronic guides provided;
    - Set up and use of the CMS;
    - Performance of VMs;
    - Recording of time of administration of study drug;
    - Administration of etripamil NS (as described in the MoOP);

  - Use of patient diary; and
  - Reporting of AEs to the sites during the study for evaluation;
- Record concomitant medications;
- Record any post-dose AEs;
- Collect urine sample for pregnancy test for females of childbearing potential;
- All patients will receive a test dose of etripamil NS 70 mg before randomization. Patients should be placed in a comfortable sitting position for a minimum of 5 minutes before starting the test dose administration procedure. The procedure must not be carried out in the standing or fully supine position:
  - Apply the CMS to record cardiac activity at least 10 minutes pre-test dose. The CMS recording should continue for at least 30 minutes post-test dose. A caregiver may assist with this procedure;
  - Perform a 12-lead ECG recording for 10 seconds within approximately 30 minutes pre-test dose and 30 minutes post-test dose. The paper speed for these recordings should be 25 mm/sec. A continuous on-screen ECG monitoring (at least 2-leads) is required from the beginning until the end of the test dose;
  - Vital signs (SBP, diastolic blood pressure [DBP], and HR) will be obtained within 10 minutes pre-test dose and every 5 minutes (±1 minute) for 30 minutes post-test dose;
  - Additional vital signs and ECGs should also be performed in the event of patient symptoms, and the time and nature of those symptoms as well as potential medical interventions should be reported in the EDC; in this case, ECG and vital sign monitoring should continue until symptoms disappear;
  - Perform a VM;
  - Push the CMS event marker button;
  - Administer etripamil NS 70 mg;
  - In case of AE, bradycardia, hypotension, arrhythmia or AV block, the patient will stay under medical surveillance until the symptoms and anomalies disappear; and
- Send (transmit) the CMS ECG to the cardiac monitoring core laboratory.

Patients who pass the test dose will be randomized using the IRT to obtain the study kit assignment. Each randomized patient will receive a study kit, which includes the blinded study drug (placebo or etripamil NS), a CMS (the CMS identifier number will be recorded in the EDC system for the test dose), a study identification card, patient's study instructions, and other study-related material. Randomized patients will also be provided with a patient diary to be completed after experiencing a PSVT episode. The patient diary collects information about symptoms of the patient's PSVT episode and includes a TSQM. If the CMS ECG test dose report is delayed for any unforeseen reason, patients will be allowed to leave and return to the site another day for randomization.

Patients who fail the test dose will proceed in the study as follows:

- If the Investigator identifies a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as beta-blocker), a re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients may be randomized if they pass the second test dose, and the cause of the test dose failure is eliminated for the duration of the study; or
- If the Investigator cannot identify a reversible cause of the initial test dose failure, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population, including all patients who received at least 1 test dose of etripamil NS 70 mg (see Section 9.1).

6.3 Follow-up Visits

Follow-up Visits will occur approximately monthly from the time of randomization and can be conducted by patients returning to the investigative site (preferred) or by the site personnel contacting patients by telephone. A missing Follow-up Visit will not be considered a deviation of the protocol, and patients will not be excluded from the study for missing their monthly Follow-up Visits.

The following procedures will occur at this visit:

- Ensure the patient continues to be eligible for the study;
- Re-train the patient on (re-training procedures are described in the MoOP):
    - Symptom identification, assessment, and reporting;
    - Contacting 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;
    - Set up and use of the CMS;
    - Performance of VMs;
    - Recording of time of administration of study drug;
    - Use of patient diary;
    - Reporting of AEs to the sites during the study for evaluation; and
    - Administration of study drug (etripamil or placebo) with BDS (as described in the MoOP);
- Record concomitant medications. If the patient has started any medication that could interact unfavorably with etripamil (e.g., blood pressure, AV conduction), the Investigator may conduct an additional test dose. The Medical Monitor may be consulted when deciding if an additional test dose is required. If an additional test dose is required, the same procedures as described in the Test Dose Randomization Visit will be followed; and
- Record any AEs.

An on-site Follow-up Visit must occur 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, it is mandatory for patients to be on-site for the Follow-up Visit so that site personnel can ensure that all data has been downloaded from the CMS device. Patients will retain their CMS and remain in the study for subsequent episodes of PSVT.

6.4 Treatment Period

All randomized patients will be instructed to perform the steps described in Section 3.2.4 after they have identified the symptoms they consider to be consistent with an episode of PSVT. A caregiver may help the patient with these procedures, and this should be annotated in the eCRF.

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

6.5 Final Study Visit

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

This visit will occur under the following circumstances:

- The patient fails the test dose;
- The patient self-administers study drug (or with the help of a caregiver) for an episode of PSVT whether or not the episode is subsequently adjudicated as a true episode of PSVT;
- The patient has started treatment with a prohibited medication before experiencing an episode of PSVT;
- The patient withdraws consent from the study for any reason;
- The Sponsor decides to terminate the study for any reason; or
- The patient is deemed to have completed participation in the study for any other reason.

For patients who failed the test dose, the following procedures will be performed:

- Identify the reason for failure (predefined list is provided in the MoOP);
- Evaluate the patient's medical status before discharge;
- Review the cardiac core laboratory CMS test dose report; and
- Close the case with IRT.

For all other patients, the following assessments will be conducted during this visit:

- Identify reason for study completion;
- Evaluate the patient's medical status;
- Review the patient's diary entries of scoring scales;
- Record any post-dose AEs;

- Collect/return the study kit, including:
  - Used or unused study drug;
  - Study identification card; and
  - Used or unused CMS;
- Evaluate any medical intervention during the Treatment Period;
- Perform physical examination;
- Obtain and record vital signs (blood pressure and HR);
- Record concomitant medications;
- Ensure that all data from the patient's CMS has been downloaded and sent to the cardiac monitoring core laboratory;
- 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;
- Assess eligibility for the open-label extension study; 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 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.

The patient will report and rate symptoms of the episode of PSVT and its evolution as well as overall treatment satisfaction in the patient diary and TSQM.

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as an adjudicated termination of a positively adjudicated episode of PSVT (AVNRT or AVRT determination if possible) and conversion to SR for at least 30 seconds.

The primary efficacy endpoint will be evaluated using the time to conversion of an episode of PSVT to SR after study drug administration as the primary efficacy variable.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will include:

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

7.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will include:

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

7.4 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 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 full disclosure of the 5-hour CMS recording and will report arrhythmias and AV blocks in the eCRF.

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

During the Treatment Period, 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 test dose administration (i.e., Test Dose Randomization Visit) until study participation is complete (i.e., after the Final Study Visit). 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 screened 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 at any time during the study will be reported as an AE(s).

Clinically significant abnormal assessments that are detected during the study 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

8.1.3.1 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.

8.1.3.2 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 Event

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

- Death,
- A life-threatening AE,
  - NOTE: An AE or suspected 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 Ablation for treatment of PSVT will not be considered as an SAE. 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 at the Test Dose Randomization Visit through the Final Study Visit 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. All reports sent to Investigators will be blinded.

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. If a patient becomes pregnant during the study, the patient should be withdrawn from the study and Final Study Visit procedures should be performed.

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 the 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 Screening Visit and at the Final Study Visit. Serum pregnancy tests will be performed on female patients of childbearing potential at the Screening Visit and at the Final Study Visit, and a urine pregnancy test will be performed at the Test Dose Randomization Visit. See Appendix B for a list of clinical laboratory analytes.

8.8 Vital Signs

Vital signs (i.e., SBP, DBP, and HR) will be obtained at the Screening Visit, at the Test Dose Randomization Visit, and at the Final Study Visit. At the Test Dose Randomization Visit, vital signs will be obtained after at least a 5-minute rest in a seated position and within 10 minutes before test dose administration. Following etripamil administration, vital signs will be obtained every 5 minutes (±1 minute) for 30 minutes. Vital signs will be obtained if the patient reports any symptom potentially related to drop in blood pressure.

8.9 Electrocardiograms

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

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

8.10 Physical Examinations

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

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

The modified Intent-to-Treat (mITT) Population includes all randomized patients who take the randomized study drug, not during a test dose visit. The subjects will be included in the treatment arm (placebo or double-blind study drug) in which they were randomized.

The Test Dose Only Population includes all patients who receive the test dose of etripamil NS 70 mg, but do not receive randomized drug (Overall Safety Population, minus the Safety Population). The Test Dose Only Population will also include pre-identified relevant subgroups of patients (e.g., those receiving concomitant beta-blockers, calcium channel blockers, or other drugs known to reduce blood pressure or alter AV conduction) for pre-defined subgroup analyses.

The Safety Population includes all randomized patients who take the study drug, not during a test dose visit. The subjects will be included in the treatment arm (placebo or double-blind study drug) according to actual received treatment.

The Overall Safety Population includes the Safety Population and the Test Dose Only Population.

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

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

9.2.2 Study Drug Administration and Concomitant Medications

Log entries detailing the IN administration of the test dose and the administration of the study drug (etripamil or placebo) to randomized 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 in each treatment group 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. Additional sensitivity efficacy analyses and exploratory efficacy analyses will be performed on the mITT Population.

The data from patients in Part 1 will be included in pivotal analyses. Pivotal analyses will include safety; and primary, secondary, and exploratory efficacy analyses for Part 1 only.

The data from patients in Part 2 will be combined with that from Part 1 and will be included in exploratory analyses. Exploratory analyses will include safety; and primary, secondary, and exploratory efficacy analyses for Parts 1 and 2 combined.

9.2.3.1 Primary efficacy analysis

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

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

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

In addition to the primary analysis of the primary endpoint, Kaplan-Meier estimates of time to conversion will be calculated and reported as a Kaplan-Meier plot. Conversion rates at 3, 5, 10, 15, 20, 30, 60, and 90 minutes after study drug administration will be reported for the etripamil group and the placebo group. The odds ratio (OR), and the CI for the OR, will be calculated. The Kaplan-Meier estimate of the time at which 25%, 50%, and 75% of episodes of PSVT conversions occur will be calculated.

A sensitivity analysis for the primary efficacy endpoint will be performed on the mITT Population. In this analysis, the time to PSVT episode conversion will include “misidentification of PSVT by the patient.” All of these patients will be censored at the conversion of the non-reentry supraventricular tachycardia to SR or at 5 hours if conversion is not observed or if there were no tachycardia observed at all.

9.2.3.2 Secondary efficacy analysis

For the secondary efficacy endpoint analyses, relief of specific symptoms associated with the termination of an episode of PSVT by the study drug will be analyzed by comparing the numeric scoring scale scores in the 2 treatment groups, and treatment satisfaction will be analyzed by comparing the rating of TSQM in the 2 treatment groups.

9.2.3.3 Exploratory efficacy analyses

Exploratory efficacy endpoint analyses will include descriptive statistics of the number of patients requiring additional medical intervention to terminate an episode of PSVT and descriptive statistics of the number of positively adjudicated episodes of PSVT converted by performing a VM.

The primary, secondary, and subgroup analyses (e.g., concomitant medications) for efficacy may be repeated in all patients (Parts 1 and 2).

All statistical 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.

Safety summaries will be presented for patients in Part 1 of the study. Additional safety analyses will be conducted for all patients (Parts 1 and 2).

9.2.5 Sample Size Determination

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

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

However, since patients will be randomized before they have a qualifying episode of PSVT, it is unlikely that the 2:1 etripamil:placebo PSVT episodes ratio will match the 2:1 randomization ratio. In such a case, it is preferable to target a higher sample size to cover for the worst-case scenarios in terms of unbalance.

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

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

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

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 ECG summary reports, inventory of study kits and test doses, 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 Committees

The Steering Committee will be responsible for the scientific oversight of the study. The Steering Committee Chair will review the original protocol and potential amendments.

Further details are provided in the NODE-301 study Steering Committee Charter.

11.7.2 Data and Safety Monitoring Committee

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. The committee will be entitled to request a review of unblinded safety data.

Further details are provided in the NODE-301 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 conclusion of the Adjudication Committee will be used in the primary and secondary analyses.

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

The adjudication process is described in Section 7.4.

Further details are provided in the NODE-301 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/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC 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: +1-800-730-5779

12.2.3 ECG Core Laboratory for Test Dose CMS Data and CMS Monitoring

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
West Chester, OH 45069, USA
Telephone: +1-513-874-1200
Fax: +1-513-874-1201

12.2.6 Medpace Clinical Safety

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227, USA
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

12.2.7 Biological Specimens

Medpace Reference Laboratories LLC
5365 Medpace Way
Cincinnati, OH 45227, USA
Telephone: +1-800-749-1737
Fax: +1-800-705-2177

13 REFERENCES

1. Issa ZF, Miller JM, Zipes DP. Clinical arrhythmology and electrophysiology: a companion to Braunwalds's Heart Disease. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2010.
2. Krikler DM, Spurrell RA. Verapamil in the treatment of paroxysmal supraventricular tachycardia. Postgrad Med J. 1974;50(585):447-453.
3. Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. Circulation. 2003;107(8):1096-1099.
4. DiMarco JP, Sellers TD, Berne RM, West GA, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation. 1983;68(6):1254-1263.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 2. Schedule of Procedures

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

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

1. The Test Dose Randomization Visit must occur within 28 days after the Screening Visit. The CMS identifier number will be recorded in the EDC system for the test dose. A re-challenge with a new test dose of etripamil NS 70 mg within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period).
2. Follow-up Visits to occur approximately monthly via site visit (preferred) or telephone (site visit required for patients who have an episode of PSVT terminated by VM).

3. Treatment Period occurs from randomization until patient has an episode of PSVT treated with study drug.
4. Final Study Visit to occur within 7 days after the final Treatment Period day for patients who fail the test dose or have an episode of PSVT treated with study drug. For patients who failed the test dose, the reason for failure will be identified (predefined list is in the MoOP), the patient's medical status will be evaluated before discharge, the CMS ECG summary report will be reviewed, and the case will be closed with IRT. For all other patients, the reason for study completion will be identified, the patient's medical status will be evaluated, the patient diary entries of scoring scales will be reviewed, and the case will be closed with IRT.
5. Confirmation of eligibility at Screening includes confirmation of PSVT diagnosis. Acceptable source documents to confirm the PSVT diagnosis are provided in the MoOP.
6. Additional eligibility criteria apply to pass the test dose at the Test Dose Randomization Visit only.
7. Eligibility assessments at Follow-up Visits based on review of patient's concomitant medications or changes in health status.
8. If possible. The Telephone Coach will guide the patient through the study procedures. For the Test Dose Randomization Visit only, the Telephone Coach should be contacted once the 10 minutes of baseline recording with the CMS is complete. If the patient is unable to reach the Telephone Coach, he/she may proceed with the procedures using the printed and electronic guides.
9. Including height and weight.
10. Vital signs will be obtained within 10 minutes pre-test dose and every 5 minutes (±1 minute) for 30 minutes post-test dose.
11. Blood and urine tests will be performed on all patients who pass the test dose and are randomized.
12. For females of childbearing potential. Serum pregnancy test required at the Screening Visit and at the Final Study Visit, and a urine test required at the Test Dose Randomization Visit.
13. The paper speed for these recordings should be 25 mm/sec. A continuous on-screen ECG monitoring (at least 2-leads) is required from the beginning until the end of the test dose for the Test Dose Randomization Visit.
14. A 12-lead ECG will be performed on all patients who pass the test dose and are randomized.
15. Before randomization, all patients will be trained on VMs and will receive a test dose of etripamil NS 70 mg to evaluate tolerability. The test dose procedures are described in the MoOP. Patients who pass the test dose will be randomized. If the patient fails the first test dose and the Investigator can identify a potential reversible cause for the failure, a second test dose may be administered within a 14-day window from the initial test dose. If the Investigator cannot identify a reversible cause, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population. During each patient's Test Dose Randomization Visit, the test dose CMS ECG data will be reviewed by the cardiac monitoring core laboratory, and a report will be sent to the site. The operational aspects of the use of the CMS during the test dose are described in the MoOP.
16. Randomized patients will be trained on how to identify and report symptoms, use of the Telephone Coach, set up and use of the CMS, performance of VMs, self-administration of study drug (as described in the MoOP), recording time of study drug administration, use of patient diary, and reporting AEs to the sites during the study for evaluation. A caregiver may assist in these procedures.
17. The study kit will include the blinded study drug (placebo or etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material. Randomized patients will also be provided with a patient diary to be completed after experiencing a PSVT episode.
18. The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site in a report based on the mobile system's proprietary arrhythmia detection algorithms and automatic ECG collection. During each patient's Test Dose Randomization Visit, the cardiac monitoring core laboratory will generate a summary test dose report within approximately 1 to 2 hours of the receipt of the ECG data. This report will be used by the site to determine if the patient passes or fails the test dose and if the eligibility criteria to be randomized in the study have been met. During the Treatment Period, the cardiac monitoring core laboratory will generate a summary report within 48 hours of the receipt of ECG data. The operational aspects are described in the MoOP. These reports will be sent to the site and the Medical Monitor.
19. The CMS recording during an episode of PSVT should continue for at least 5 hours, regardless of treatment outcome.
20. During the Treatment Period, study drug should only be administered if the VM does not resolve the patient's symptoms. The patient will push the CMS event marker button to record the time of dosing immediately prior to self-administering the study drug intranasally as instructed. If symptoms of the PSVT episode have not resolved within 20 minutes after study drug administration, patients may seek appropriate medical care.

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

APPENDIX B: 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)