CLINICAL STUDY PROTOCOL

Multi-Centre, Placebo-Controlled, Phase 2 Study of Etripamil Nasal Spray (NS) for the Reduction of Ventricular Rate in Patients with Atrial Fibrillation

The ReVeRA-201 Trial

Investigational Product: Etripamil (MSP-2017)
Protocol Number: MSP-2017-5001
EudraCT Number: 2022-001854-49

Version Number:	1.0	Original Protocol : 28 JUNE 2019
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	5.0	Amendment 4 : 09 SEPTEMBER 2021
	6.0	**Amendment 5 : 06 JULY 2022**

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Confidentiality Statement

STUDY PROTOCOL

COMPOUND NAME/NUMBER:	Etripamil (MSP-2017)
PROTOCOL NUMBER:	MSP-2017-5001
EUDRACT NUMBER	2022-001854-49
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	Multi-Centre, Placebo-Controlled, Phase 2 Study of Etripamil Nasal Spray (NS) for the Reduction of Ventricular Rate in Patients with Atrial Fibrillation
SHORT TITLE :	ReVeRA-201: Etripamil in Atrial Fibrillation Phase 2
PROTOCOL VERSION:	FINAL Version 6.0
PROTOCOL DATE:	06 JULY 2022
CONTRACT RESEARCH ORGANIZATIONS:	Montreal Health Innovation Coordinating Centre (MHICC) 5000 Bélanger St. Montreal, Quebec H1T 1C8, Canada JSS Medical Research Inc. 9400 Henri-Bourassa Boulevard West Montreal, Quebec, H4S 1N8, Canada

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

APPROVAL SIGNATURES

PROTOCOL NUMBER:	MSP-2017-5001
PROTOCOL VERSION:	FINAL 6.0, 06 JULY 2022
PROTOCOL TITLE:	Multi-Centre, Placebo-Controlled, Phase 2 Study of Etripamil Nasal Spray (NS) for the Reduction of Ventricular Rate in Patients with Atrial Fibrillation (The ReVeRA-201 Trial)

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

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

INVESTIGATOR AGREEMENT

By signing below, I agree that:

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

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

_____

Site Name/City/Country

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

List of Tables

List of Figures

1. SYNOPSIS

PRODUCT NAME/NUMBER	Etripamil (MSP-2017)
PROTOCOL NUMBER	MSP-2017-5001
DEVELOPMENT PHASE	Phase 2
PROTOCOL TITLE	Multi-Centre, Placebo-Controlled, Phase 2 Study of Etripamil Nasal Spray (NS) for the Reduction of Ventricular Rate in Patients with Atrial Fibrillation
SHORT TITLE	ReVeRA-201: Etripamil in Atrial Fibrillation Phase 2
INDICATION	Atrial Fibrillation
OBJECTIVES	Ventricular rate control without conversion of atrial fibrillation (AF) into sinus rhythm is one treatment option recommended in the guidelines.[1] Many patients with AF experience persistent tachycardia with episodes of rapid ventricular rate despite chronic treatment to reduce ventricular rate. Primary: 1. The primary objective of this study is to demonstrate the superiority of etripamil NS over placebo in reducing ventricular rate in patients with AF. Secondary: 1. The secondary objective is to evaluate the safety and efficacy of etripamil NS in patients with AF.
STUDY POPULATION	The study will randomize approximately 50 evaluable patients with AF in the Efficacy Population. Enrollment will continue until the target sample size is reached.
STUDY ENTRY CRITERIA	**Inclusion Criteria:** A patient will be eligible for study participation if they meet all of the following criteria: 1. Aged 18 years and over 2. Has provided written informed consent

[1] January, CT et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, *Journal of the American College of Cardiology* (2014)

	3. Patients with episodes of paroxysmal, persistent or permanent AF, presenting with AF and a ventricular rate ≥110 bpm measured over 1 minute 4. Patients should receive appropriate antithrombotic therapy as per the applicable guidelines for AF management (e.g. Canadian Cardiovascular Society (CCS) / European Society of Cardiology (ESC) guidelines). a. Etripamil (a calcium channel blocker) is intended for acute rate control only.[2] If rhythm control is desired (outside of the present protocol), anticoagulation as per guidelines may start after the administration of study drug. **Exclusion criteria:** A patient will be excluded from the study if they meet any of the following criteria: 1. Has evidence of atrial flutter (ECG) at presentation 2. Has a history of stroke, transient ischemic attack or peripheral embolism within the last 3 months 3. Has received by IV route any of the following within one hour before study drug administration: flecainide, procainamide, digoxin, beta-blocker, or calcium channel blocker 4. Has signs and symptoms of severe congestive heart failure at presentation (e.g. tachypnea, oxygen desaturation <90% unless due to known pulmonary disease, pulmonary rales, sign of peripheral hypoperfusion) 5. Hemodynamic instability, with systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg 6. Known uncorrected severe aortic or mitral stenosis 7. Hypertrophic cardiomyopathy with outflow tract obstruction 8. Has a history of second- or third-degree atrioventricular block 9. Regular rhythm suggesting a complete AV block

[2] Andrade, JG et al., The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Canadian Journal of Cardiology* 2020 Dec; 36(12): 1847-1948. See Section *9.1.1 Acute Rate Control.*

	10. Has a history or evidence of torsades de pointes, sick sinus syndrome, or Brugada syndrome 11. Evidence of Acute Coronary Syndrome within the last 12 months except if patient was successfully revascularized 12. Positive pregnancy test result at screening, and females of childbearing potential who do not agree to use adequate method of contraception for the duration of the study. 13. Has evidence of any clinically significant acute or chronic condition of the nasal cavity (e.g., rhinitis or deviated septum) which could interfere with administration of the study drug in either or both nasal cavities 14. Has a history of sensitivity to verapamil 15. Has previously participated in a clinical study for etripamil 16. Has a history of sensitivity to any components of the investigational product 17. Signs of alcohol or drug intoxication at the time of presentation which, in the opinion of the Investigator, would impact the validity of study results 18. Is currently participating in another drug or device study, or has received an investigational drug or device within 30 days of Screening 19. Has evidence of clinically significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, or renal disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of study results
STUDY DESIGN	This is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the effects of etripamil NS in patients with AF. This study includes Screening, the Treatment Period and Follow-up procedures. Each patient will receive Placebo or 70 mg etripamil NS; treatment will be randomized in a 1:1 ratio, to yield 50 evaluable patients with AF in 2 groups of 25 (Efficacy Population). Screening and treatment procedures should be done at the same visit. Informed consent must be obtained prior to any study procedures.

	Screening Procedures: Patients with AF will be selected by the Investigator. The screening procedures will include obtaining informed consent, a review of inclusion/exclusion criteria, a complete physical examination, and recording of any concomitant medications. **Treatment Procedures:** After screening procedures are complete, eligible patients will be randomized to receive etripamil NS or placebo. Heart rate will be measured via Holter ECG 10 minutes prior to and immediately before drug administration; patients must exhibit a rapid ventricular rate (≥110 bpm measured during 1 minute) prior to drug administration in order to be dosed. Blinded study drug will be administered during Holter ECG monitoring, which will be conducted for at least 10 minutes prior to and for 6 hours after administration. Investigators will record adverse events and concomitant medications. Study drug will be administered by clinical site staff. Patient must be seated for drug administration and should not perform any physical activity within 1-hour post-dose. Patient will be asked to complete the TSQM-9 questionnaire. Patient can be discharged 1 hour after drug administration. **Follow-up Procedures:** Patients will undergo a safety follow-up assessment and return the Holter device approximately 24 hours post-dose. The use of telemedicine is encouraged. Patients will also be contacted by phone 7 days post-dosing for safety follow-up.
INVESTIGATIONAL PRODUCT	The formulation of etripamil NS 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 this study is 70 mg.
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.
TREATMENT REGIMENS	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. Instructions on device usage are provided in Appendix B.
PRINCIPAL INVESTIGATOR	Denis Roy, MD
PLANNED STUDY SITES	This study will be conducted at approximately 20 sites in Canada and in the Netherlands

EFFICACY ENDPOINT	Ventricular rate reduction
CRITERIA FOR EVALUATION	**Efficacy Variables:** Efficacy variables will be obtained from the Holter recordings measured by a central core laboratory. In case of conversion to sinus rhythm, only heart rate measurements prior to sinus conversion will be used to derive efficacy variables. The primary efficacy variable will be: • The maximum reduction in ventricular rate, measured on Holter monitoring, within 60 minutes from drug administration. The secondary efficacy variables will include: • Elapsed time from drug administration to nadir (lowest average heart rate) in the 60 minutes post drug administration. • Percentage of patients achieving ventricular rate of <100 bpm in the 60 minutes post drug administration. o Elapsed time from drug administration to ventricular rate <100 bpm o Duration of ventricular rate <100 bpm in the 60 minutes post drug administration • Percentage of patients with 10% reduction from baseline ventricular rate in the 60 minutes post drug administration. o Elapsed time from drug administration to 10% reduction from baseline ventricular rate o Duration of 10% reduction from baseline ventricular rate in the 60 minutes post drug administration • Percentage of patients with 20% reduction from baseline ventricular rate in the 60 minutes post drug administration. o Elapsed time from drug administration to 20% reduction from baseline ventricular rate o Duration of 20% reduction from baseline ventricular rate in the 60 minutes post drug administration • Percentage of patients cardioverting into sinus rhythm in the 60 minutes post drug administration. o Elapsed time from drug administration to cardioversion into sinus rhythm • Area under the curve (AUC) of heart rate over the 60 minutes and the 360 minutes post drug administration

	• Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9). **Safety Variables:** • Safety variables will include clinical adverse events (AEs), vital signs, and findings from electrocardiographic analysis (ventricular arrhythmia such as premature ventricular contractions, non sustained ventricular tachycardia any AV block)
STATISTICAL METHODS	**Efficacy analyses:** The efficacy analyses will compare placebo-treated patients versus etripamil-treated patients. Efficacy endpoint analyses will include summaries, both over time and as comparisons between placebo and etripamil. Continuous efficacy data will be presented with n, minimum, maximum, median, mean, and standard deviation, whereas discrete efficacy data will be summarized with frequency counts and percentages. *Primary efficacy analysis* The primary efficacy analysis will compare the maximum reduction in ventricular rate in placebo-treated patients versus etripamil-treated patients. This comparison will be done using an analysis of covariance (ANCOVA) adjusting for baseline ventricular rate. *Secondary efficacy analyses* The secondary efficacy analyses performed on the secondary efficacy parameters will use ANCOVA methods for continuous variable, Chi-Square or Fisher exact tests for percentages and Kaplan-Meier methods for elapsed times. **Safety analyses:** Safety data will be summarized with descriptive statistics. Continuous safety data will be presented with n, minimum, Q1, Q3, maximum, median, mean, and standard deviation, whereas discrete safety data will be summarized with frequency counts and percentages.
SAMPLE SIZE DETERMINATION	The primary efficacy variable for this study is the maximal reduction of ventricular rate after study drug administration. Accounting for a two-sided test with a type I error rate of α=0.05, 25 patients per group will provide 93% power to detect a 20 bpm absolute difference in ventricular rate from baseline value between active drug and placebo, assuming a standard deviation of 20 bpm.

STUDY AND TREATMENT DURATION	Patients will receive a single dose of either etripamil NS 70 mg or Placebo. Screening and Treatment procedures should occur at the same visit. Safety follow-up will be performed on the next day, preferably via telemedicine. Patients will also be contacted by phone 7 days after dosing. Total duration of participation is 1 week. Enrollment in the study will continue until enough patients are randomized to provide at least 50 patients in the Efficacy Population, including at least 25 patients in each treatment arm.

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AE	Adverse Event
ANCOVA	Analysis of Covariance
AV	Atrioventricular
BDS	Bidose System
BPM	Beat Per Minute
CCS	Canadian Cardiovascular Society
CFR	Code of Federal Regulations
CMS	Cardiac Monitoring System
CRA	Clinical Research Associate
CRO	Clinical Research Organization
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylene-Diamine Tetra-Acetic Acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Intranasal
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Randomization System
MFD	Maximum Feasible Dose
MHICC	Montreal Health Innovations Coordinating Centre

mITT	Modified Intent to Treat
NS	Nasal Spray
NSVT	Non-Sustained Ventricular Tachycardia
OAC	Oral Anticoagulant
PAF	Paroxysmal Atrial Fibrillation
PD	Pharmacodynamics
PK	Pharmacokinetics
PSVT	Paroxysmal Supraventricular Tachycardia
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SR	Sinus Rhythm
TEAE	Treatment-Emergent Adverse Event
TSQM-9	Treatment Satisfaction Questionnaire for Medication

3. INTRODUCTION

3.1 Background

Etripamil (also referred to as MSP-2017 in study documents), an L-type calcium channel antagonist and short-acting verapamil analog, is currently being developed by Milestone Pharmaceuticals Inc. (hereinafter Milestone) for the treatment of paroxysmal supraventricular tachycardia (PSVT), and other arrhythmias.

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans, with an irregular and often rapid heart rate that increases the risk of stroke and heart failure.

Prevalence estimates range from four to six million patients suffering from atrial fibrillation in the United States. Approximately 25% of these have Paroxysmal Atrial Fibrillation (PAF), another 25% have persistent atrial fibrillation, and 50% have permanent atrial fibrillation.

For most patients, current treatment for AF consists of anti-coagulant therapy, either warfarin or novel oral anti-coagulants (e.g., Pradaxa®, Xarelto®, Eloquis®) to reduce the risk of blood clot embolization and stroke; those who cannot take these stronger blood thinners may be prescribed aspirin at 325 mg a day, but aspirin has only been shown to be somewhat efficacious in a very small and specific population. With regard to the abnormal heart rate that occurs during AF, there are two strategies. One strategy focuses on controlling the heart rate during AF to reduce or eliminate symptoms, while the other takes aim at terminating AF and maintaining sinus rhythm. Multiple clinical studies have demonstrated that there is no difference in outcome whether a rate or rhythm control strategy is pursued (e.g., AF-CHF [1] AFFIRM [2]). The major unmet needs are for more efficacious and safer rhythm-control drugs as well as rate-control drugs with a faster onset of action to bring down the heart rate.

Rhythm control drugs such as amiodarone, dronedarone, flecainide, ibutilide are modestly effective in converting atrial fibrillation into normal sinus rhythm but are often associated with toxicity and can cause life-threatening pro-arrhythmic effects.[3] Rate-control drugs include calcium channel blockers (diltiazem and verapamil) and beta blockers (e.g., metoprolol, atenolol), and their goal is to minimize symptoms associated with an increased ventricular rate, improve cardiac output, and prevent tachycardia-associated cardiomyopathy.[4] Based on data from both the Phase 1 and Phase 2 studies, etripamil has demonstrated its ability to prolong conduction through the atrioventricular (AV) node, which is key to reducing the ventricular rate during AF. This makes etripamil an excellent candidate for use in controlling the ventricular rate in a subset of patients with AF.

Patients who present to the emergency room in AF with a rapid heart rate are almost universally treated with an intravenous calcium channel blocker or beta blocker to provide a rapid reduction in ventricular rate to control symptoms and improve cardiac output.[5] Intravenous (IV) rate-control drugs for immediate rate-control, however, are limited to use in the acute setting and therefore cannot be self-administered by patients in the outpatient setting when symptoms begin. Oral rate-control drugs can be taken at home, but do not provide immediate ventricular rate-control due to the delayed 30 to 90-minute onset of action by the oral route.

3.2 Clinical Experience

3.2.1 Phase 1 Pharmacokinetics Studies

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

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

A maximum of 24 participants, 12 Japanese and 12 non-Japanese, were planned and enrolled in the study and 23 completed the study (1 Japanese subject discontinued prematurely due to the development of an adverse event). After signing the informed consent form (ICF), potential participants underwent screening procedures within 28 days of Day 1. Participants were admitted to the clinical unit on Day -1 and screening procedures were repeated to confirm their eligibility. Participants fasted overnight for at least 10 hours. On Day 1, participants were randomized to 1 of 3 treatment sequences (Placebo-70 mg-35 mg, 35 mg-Placebo-70 mg, or 70 mg-35 mg-Placebo) and received either a single intranasal dose of etripamil or placebo followed by a 2-week washout period between doses. Etripamil NS up to 105 mg was administered using the Phase 3 formulation Aptar Bi-dose nasal spray device (i.e., up to 3 sprays of 100 μL of 350 mg/mL etripamil formulation in each nostril). After the third period, all participants received a dose of 105 mg etripamil. The total study duration was approximately 3 months, including the screening and follow-up. Blood for PK assessments was collected before each dose and at 0.5, 1.5, 3, 5, 7, 10, 15, 25, 50, 90, 360, 720, and 1440 minutes after dosing. Urine for PK analysis was collected before dosing and over the intervals of 0-2 hours, 2-4 hours, 4-6 hours, 6-12 hours, and 12-24 hours after dosing. Vital signs and electrocardiograms (ECGs) were measured at the corresponding PK time points.

Slightly more Japanese participants experienced a Treatment-Emergent Adverse Event (TEAE) compared with non-Japanese participants and there were more TEAEs at the 105 mg dose compared with the 35 mg and 70 mg doses. However, at the 35 mg and 70 mg doses, the percentage of participants with TEAEs was within the range of values associated with placebo treatment. The most frequent TEAEs (>10%) were increased lacrimation, burning nose sensation, and rhinorrhea,

occurring at all doses (including placebo). Each of these was considered by the investigator as related to treatment. Most TEAEs were mild or moderate in intensity, except 1 instance of burning nose sensation (non-Japanese participant at 105 mg etripamil dose) which was severe. There were no serious adverse events. One Japanese participant discontinued due to TEAEs (tearing, facial burning sensation, rhinorrhea). There were no trends in clinical laboratory changes and there were no TEAEs due to changes in clinical laboratory values. There were no meaningful changes in vital signs. Changes in ECGs were generally transient and judged to be not clinically significant by the Investigator.

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

3.2.2 Phase 2 Proof of Concept Study in PSVT

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

During a pre-study visit, patients were randomly assigned to 1 of the 5 following study groups in a 1:1:1:1:1 ratio: placebo, or etripamil 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 heart rate (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 atrioventricular nodal reentry tachycardia.

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 sinus rhythm (SR) within 15 minutes after study drug administration and in whom SR was maintained for at least 30 seconds (primary efficacy endpoint) was 35%, 65%, 87%, 75%, and 95% in the placebo and etripamil NS 35, 70, 105, and 140 mg groups, respectively. Applying the pre-specified hierarchy for determining significance, the 3 highest etripamil doses of 140, 105, and 70 mg showed statistically significantly greater conversion rates compared with placebo (see Table 1).

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

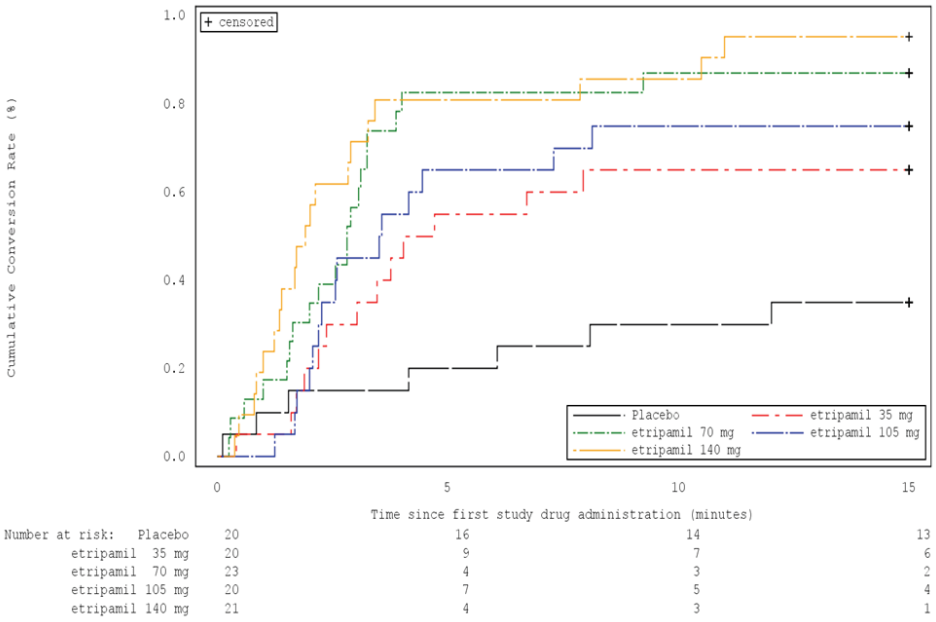
	Placebo (N = 20)	**MSP-2017 35 mg (N = 20)**	**MSP-2017 70 mg (N = 23)**	**MSP-2017 105 mg (N = 20)**	**MSP-2017 140 mg (N = 21)**
Number (%) of patients converted to sinus rhythm within 15 minutes after study drug	7 (35.0)	13 (65.0)	20 (87.0)	15 (75.0)	20 (95.2)
Treatment comparisons					
Odds ratio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

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

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

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

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



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

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

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

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

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

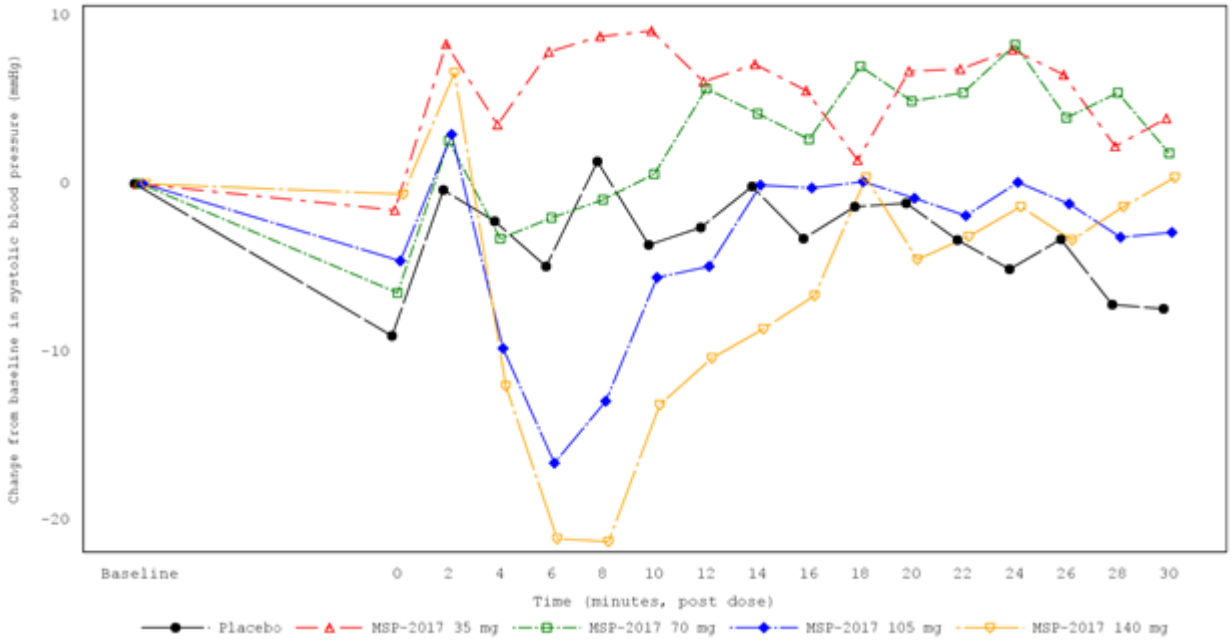
The mean systolic blood pressure (SBP) was decreased from the baseline measurements (before PSVT induction) to measurements done in PSVT before study drug administration (time 0). A decrease of 7 mmHg was statistically significant in the placebo group only (Figure 2).

Compared with baseline, SBP measurements taken from 2 minutes to 16 minutes post-study drug administration demonstrated no decrease in mean SBP in the placebo and the etripamil NS 35 mg group, a minor change of 2 mmHg at 4 minutes post-dose in the etripamil NS 70 mg group, and

decreases of 17 mmHg ($p<0.05$ versus baseline) 6 minutes post-dose in the etripamil NS 105 mg group, and 20 mmHg at 6 minutes and 8 minutes post-dose ($p<0.05$ versus baseline) in the etripamil NS 140 mg group.

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

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



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

3.2.3 NODE-301 Part 1 Phase 3 Efficacy and Safety Study

NODE-301 (MSP-2017-1138), was a Randomized, Double-Blind, Placebo-Controlled Phase 3 safety and efficacy study of etripamil NS in patients with PSVT receiving the drug in an at-home setting. The study was conducted in the United States and Canada. Patients first received etripamil NS at the clinical site while in normal sinus rhythm during a Test Dose Visit. Patients who showed an acceptable safety and tolerability profile in the Test Dose Visit were randomized in a 2:1 ratio to receive either etripamil NS or matching placebo. They returned home and waited for a PSVT episode to occur, at which time they may have taken etripamil NS or placebo. Each episode was documented by an ambulatory Cardiac Monitoring System (CMS) that was placed on the chest by the patient or caregiver when symptoms began and recorded at least 5 hours of continuous ECG. After taking etripamil NS or placebo for the treatment of one PSVT episode, a patient completed the NODE-301 study and was eligible for the open label extension study NODE-302.

The NODE-301 Part 1 trial was an event-driven Phase 3 trial designed to evaluate the efficacy of self-administered etripamil for terminating PSVT episodes in the at-home setting. A total of 431 subjects received a test dose of etripamil 70 mg NS while in sinus rhythm and 198 subjects received study drug (138 etripamil 70 mg; 60 placebo) during a perceived episode of PSVT. A

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

There were no new or clinically relevant safety findings seen in NODE-301 Part 1 study. A total of 308 subjects had at least one AE. The maximum severity was mild (49.8%) or moderate (17.6%). The most commonly reported TEAEs occurring after study drug administration were nasal discomfort, nasal congestion, rhinorrhea, throat irritation and lacrimation. Severe TEAEs included throat irritation, drug hypersensitivity, rhinorrhea, epistaxis and hypotension, each reported in one subject. Fourteen serious adverse events were reported and were assessed by the Investigator as not related to the study treatment.

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

3.2.4 NODE-302 Phase 3 Open Label Extension Study

NODE-302 (MSP-2017-1158) was an open label extension study for NODE-301. This study is now closed and enrolled PSVT patients who had previously completed NODE-301, and followed them for multiple at-home administrations of 70 mg etripamil NS. Each episode was documented by an ambulatory CMS. This study is currently in the reporting phase.

One-hundred and sisty-nine patients were enrolled in the study and 105 patients received at least one dose of etrupamil 70 mg NS. There were no new or clinically relevant safety findings seen in the NODE-302 study. A total of 67 (63.8%) patients have had at least one AE. The maximum severity of TEAEs for most patients was mild (34.3%) or moderate (6.7%). Severe TEAEs were reported in 2 (1.9%) patients (rhinorrhea in 1 patient, and two episodes of epistaxis in 1 patient). There were 34 (32.4%) subjects who experienced an AE that was considered related to the study treatment by the Investigator.

Ten SAEs were reported in 8 (7.6%) subjects. The most frequently reported SAE was supraventricular tachycardia (3 [2.9%] subjects), with all other SAEs reported by 1 (1.0%) subject each, including bradycardia, syncope, ataxia, troponin increased, and pancreatitis. All these SAEs were assessed by the Investigator as not related to the study treatment. The SAEs of syncope and ataxia occurred 50 days and 53 days following the most recent etripamil dose, respectively.

The most commonly reported TEAEs (regardless of relationship to study drug) were nasal discomfort, nasal congestion, and rhinorrhea.

3.2.5 NODE-301 Part 2, the RAPID study

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

- NODE-301 Part 1 consisted of patients that were dosed with the double-blind study drug or had discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode.
- NODE-301 Part 2 (the RAPID Study, ongoing) consists of patients randomized into Part 1 who were not dosed with the double-blind study drug or had not discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode, and new patients enrolled into the study following the completion of Part 1.

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

3.2.6 NODE-303 Phase 3 Open Label Safety Study

The ongoing NODE-303 study is a multi-center, multi-national, open-label study designed to evaluate the safety of etripamil when self-administered by patients for spontaneous episodes of PSVT outside of the clinical setting. The NODE-303 design is intended to provide an assessment of etripamil NS safety in a use setting which closely mimics a real-world setting. Secondary objectives are to evaluate the efficacy of self-administered etripamil NS outside of the clinical setting, to evaluate the impact of etripamil NS on PSVT disease burden, and to evaluate the safety and efficacy of etripamil NS when used for multiple PSVT episodes.

The study will enroll up to approximately 3000 patients to obtain a sufficient number of patients (in the overall development program) with a PSVT episode. Patients are diagnosed with PSVT by a medical professional and have reported having at least one previous episode of PSVT prior to study screening. Patients are provided with an ambulatory CMS to help document PSVT episodes. The CMS is self-applied by the patient when they feel the onset of PSVT symptoms. Patients then self-administer etripamil NS if a vagal maneuver is ineffective to resolve their symptoms. The treatment regimen of etripamil to be evaluated is an initial dose of etripamil NS 70 mg to be followed by a second dose 10 minutes later if the patient continues to experience PSVT symptoms. After each episode of PSVT for which etripamil NS was administered, the patient returns to the investigative site and has the option to continue in NODE-303 and manage subsequent episodes of PSVT with etripamil NS (treatment for up to a maximum of 4 perceived PSVT episodes).

As of the cut-off date (10 December 2021), 369 subjects had self-administered at least one dose of Etripamil NS 70 mg of which 350 subjects took a single dose of etripamil NS 70 mg for all PSVT episodes and 19 subjects took 2x70 mg for at least one PSVT episode. As of the cut-off date, 207 subjects were ongoing, 107 subjects discontinued from the study, and 55 subjects had completed the study after treating 4 PSVT episodes (the maximum in this study).

Of these 350 patients who took a single dose of etripamil NS 70 mg for all PSVT episodes, 205 (59%) had at least one AE and 147 (42%) had at least one TEAE (defined as AEs occurring <24

hours after the administration of etripamil). The maximum severity of these TEAEs for most of the patients was mild (30%) or moderate (9%). Severe AEs were reported in 9 (3%) subjects. The most reported AEs were under Respiratory, thoracic and mediastinal disorder system organ class (SOC) followed by Nervous system disorders SOC. The most commonly reported TEAEs to date (regardless of relationship to study drug) were nasal discomfort (26%) and nasal congestion (11%). There were 11 (3.1%) subjects who reported SAEs that occurred at any time following the first dose of etripamil (death [unknown cause], acute coronary syndrome, coronavirus infection, papillary serous endometrial carcinoma, stress cardiomyopathy (Takotsubo cardiomyopathy), appendicitis, breast cancer, aortic valve stenosis, in 1 subject each, and acute myocardial infarction in 2 subjects, and sepsis and Crohn's disease that were both reported in the same subject, of which only 1 SAE (stress cardiomyopathy) was treatment emergent. None of the SAEs were considered related to the study drug.

3.3 Rationale for the Study

The primary objective of this study is to demonstrate the superiority of etripamil NS over placebo in reducing ventricular rate in patients with AF.

The secondary objective of the study is to further evaluate the safety and efficacy of etripamil NS 70 mg in patients with AF.

Ventricular rate control without conversion of AF into sinus rhythm is one treatment option recommended in the guidelines for the management of AF.[6] Many patients experience persistent tachycardia with episodes of rapid ventricular rate despite chronic treatment to reduce ventricular rate.

Etripamil addresses an unmet medical need since there are currently no short-acting products available for patient self-administered treatment of episodes of atrial fibrillation.

We believe that etripamil NS will provide symptomatic relief in patients who experience rapid ventricular rates during AF. This is a treatment option that patients will be able to self-administer in a non-acute setting to provide immediate ventricular rate control. The rapid onset of action and duration of effect afforded by etripamil nasal spray should provide patients with immediate symptom relief while waiting for AF to spontaneously resolve or waiting for adjunctive oral medications to take effect.

3.4 Summary of Potential Risks and Benefits

The primary benefit of this study is that etripamil nasal spray may provide rapid symptom relief to patients with atrial fibrillation by decreasing the ventricular response rate.

The potential risks of study participation include those associated with exposure to etripamil and the risks of medical evaluation. AEs associated with etripamil include nasal irritation, nasal discomfort, and throat irritation. Potential adverse events which have been rare or not observed in studies to date include other cardiac arrhythmias, or AEs associated with drops in blood pressure (dizziness, headache).

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

4. OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to demonstrate the superiority of etripamil NS over placebo in reducing ventricular rate in patients with AF.

4.2 Secondary Objectives

The secondary objective is to evaluate the safety and efficacy of etripamil NS in patients with AF.

5. STUDY DESIGN

5.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the effects of etripamil NS in patients with AF. This study includes screening procedures, treatment procedures, and a follow-up period. Patients will be randomized in a double-blind fashion to yield at least 50 evaluable patients in 2 groups of at least 25 patients each (Efficacy Population). Each patient will receive a single dose of Placebo or 70 mg etripamil intranasally.

Screening and treatment procedures should be performed at the same visit. Informed consent must be obtained prior to any study-specific procedures being completed. Patients will be contacted by phone (or other available telemedicine application) for follow-up the next day and 7 days after dosing (on-site follow-up visits may be performed as necessary) Total duration of participation is 1 week.

See Section 8 for a full description of the study procedures.

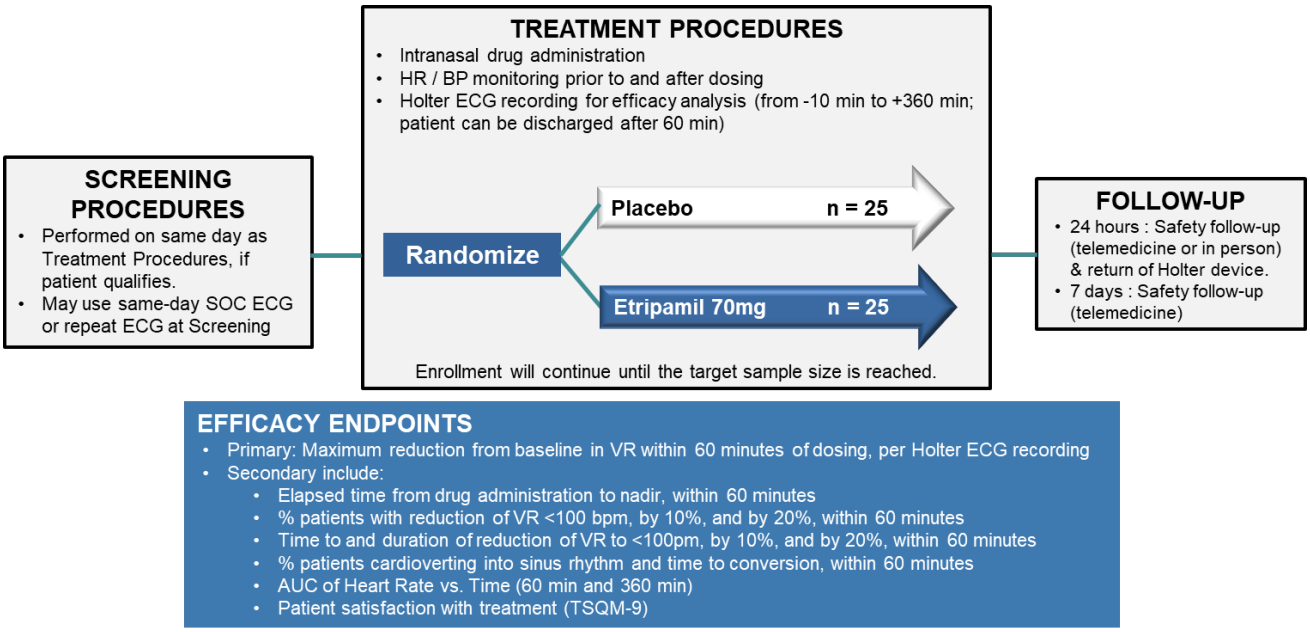
5.2 Discussion of Study Design

In Phase 2 studies, etripamil has been shown to decrease heart rate and convert patients with PSVT to sinus rhythm. A fast-acting calcium channel blocker such as etripamil is likely to reduce ventricular rate in patients with AF as well. As ventricular rate control is one recommended option for treatment of patients with AF, etripamil could provide benefit to this patient population.

This study is designed as a two-arm, double-blind, randomized, placebo-controlled, proof of concept study to evaluate if etripamil decreases ventricular rate in an AF population.

The study design is depicted in Figure 3:

Figure 3. Study Design Schematic



5.3 Rationale for Dosing

The choice of the dose level of etripamil NS (70mg) was made according to the data obtained in Phase 1 and Phase 2 studies. The selected dose is also being studied in the Phase 3 PSVT program, NODE-301 Part 1 and NODE-302 studies and in the ongoing Phase 3 NODE-301 Part 2 (RAPID) and NODE-303 studies that allow a second 70 mg dose if symptoms persist at 10 minutes after the first dose.

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 3.2).

Four doses (35, 70, 105, and 140 mg) were tested in the NODE-1 Phase 2 study. The 3 highest doses (70, 105, and 140 mg) were statistically significantly superior compared with placebo for terminating induced PSVT in the EPL within 15 minutes of dosing; in addition, the time to conversion of PSVT to SR was shorter with these doses compared with placebo. The E_{max} model of dose response indicates that these 3 doses are at the plateau of the dose response, whereas the 35 mg dose is in the ascending portion of the curve (see Section 3.2.2).

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

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

SBP. Currently the 70 mg dose has the greatest amount of safety data available, with strong evidence that it is biologically active.

For these reasons, etripamil NS 70 mg has been selected as the initial dose in patients with Atrial Fibrillation. Initial studies to find the optimal dose in this patient population may be required if this proof of concept trial shows activity in this indication.

6. STUDY POPULATION

6.1 Selection of Study Population and Diagnosis

Enrollment will continue until enough patients are randomized to provide at least 50 evaluable patients in the Efficacy Population. Patients must be diagnosed with AF by a medical professional and show evidence of current AF with ventricular rate ≥110 bpm at screening and prior to study drug administration.

6.2 Study Entry Criteria

6.2.1 Inclusion Criteria

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

1) Aged 18 and over
2) Has provided written informed consent
3) Patients with episodes of paroxysmal, persistent or permanent AF, presenting with AF and a ventricular rate ≥110 bpm measured over 1 minute
4) Patients should receive appropriate antithrombotic therapy as per the applicable guidelines for AF management (e.g. Canadian Cardiovascular Society (CCS) / European Society of Cardiology (ESC) guidelines)
    a. Etripamil (a calcium channel blocker) is intended for acute rate control only.[7] If rhythm control is desired (outside of the present protocol), anticoagulation as per guidelines may start after the administration of study drug.

6.2.2 Exclusion Criteria

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

1) Has evidence of atrial flutter (ECG) at presentation
2) Has a history of stroke, transient ischemic attack, or peripheral embolism within the last 3 months
3) Has received by IV route any of the following within one hour before study drug administration: flecainide, procainamide, digoxin, beta-blocker, or calcium chanel blocker

4) Has signs and symptoms of severe congestive heart failure at presentation (e.g. tachypnea, oxygen desaturation <90% unless due to known pulmonary disease, pulmonary rales, sign of peripheral hypoperfusion)
5) Hemodynamic instability, with systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg
6) Known uncorrected severe aortic or mitral stenosis
7) Hypertrophic cardiomyopathy with outflow tract obstruction
8) Has a history of second- or third-degree atrioventricular block
9) Regular rhythm suggesting a complete AV block
10) Has a history or evidence of torsades de pointes, sick sinus syndrome, or Brugada syndrome
11) Evidence of Acute Coronary Syndrome within the last 12 months except if patient was successfully revascularized
12) Positive pregnancy test result at screening, and females of childbearing potential who do not agree to use adequate method of contraception for the duration of the study
13) Has evidence of any clinically significant acute or chronic condition of the nasal cavity (e.g., rhinitis or deviated septum) which could interfere with administration of the study drug in either or both nasal cavities
14) Has a history of sensitivity to verapamil
15) Has previously participated in a clinical study for etripamil
16) Has a history of sensitivity to any components of the investigational product.
17) Signs of alcohol or drugs intoxication at the time of presentation which, in the opinion of the Investigator, would impact the validity of study results;
18) Is currently participating in another drug or device study, or has received an investigational drug or device within 30 days of Screening
19) Has evidence of clinically significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, or renal disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of study results.

6.3 Patient Completion / Discontinuation / Withdrawal

The end of study is defined as the date of the last visit of the last study participant. Last study visit of the last study participant is the date of their last follow-up contact.

All patients will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The Investigator should make every reasonable attempt to keep patients in the study; however, patients must be withdrawn from the study if they withdraw consent to participate.

Investigators must attempt to contact patients who fail to respond to the 24-hour follow-up phone/video call in order to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 9.2.

Milestone reserves the right to request the withdrawal of a patient because of protocol violations or other reasons. Any administrative or other reason for withdrawal must be documented and explained to the study participant.

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

Should a study participant decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

Study participants withdrawing from the study treatment should be followed as per protocol for the entire duration of the study unless the study participant explicitly withdraws consent for follow-up and refuses to provide further information.

If a patient is withdrawn or discontinues treatment, the reason and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF), in addition to information on any ongoing adverse event.

7. TREATMENTS

7.1 Identification of Investigational Product

The formulation of etripamil is for intranasal administration and will consist of etripamil, water, acetic acid, disodium ethylene-diamine-tetra-acetic acid (EDTA), and sulfuric acid. The dose of etripamil to be evaluated in this study is 70 mg.

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

The study drug is packaged a prefilled device, the Aptar Pharma Nasal Spray Bidose System (BDS).

7.2 Labeling and Packaging

Clinical labeling, packaging, and distribution of the study drug will be performed by PCI Pharma Services.

7.2.1 Labeling

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

language for investigative material. Proof labels, detailing actual label text, will be available in the study files.

7.2.2 Packaging

The study drug distributor will package the study drug in kits, according to current GMP and ICH GCP guidelines. Drug kits will be packaged in accordance to the randomization list provided by an unblinded biostatistician, and identified by a unique kit ID number that will maintain treatment blinding, while allowing unblinded personel to identify the treatment it contains, if necessary.

7.2.3 Distribution

The sponsor will not supply an investigator/institution with the study drug until all required approvals from the institutional review board (IRB)/ Independent Ethics Committee (IEC) and competent authority are obtained. Study drug kits will be distributed to approved sites by PCI Pharma Services.

7.3 Treatments Administered

Study drug will be administered at the clinical site by the Investigator or qualified designee. Each patient will receive a total of 200 µL of placebo or etripamil NS 70 mg (i.e., 100 µL in each nostril via the Aptar Pharma Nasal Spray Bidose System [BDS]). The devices will be prefilled and packaged. Instructions for use of the nasal spray are provided in the Appendix B. Date and time of dosing will be recorded in the eCRF.

If only one spray of the BDS is administered for any reason, it will be considered a partial dose. Missed and partial doses will be recorded in the eCRF.

7.4 Randomization and Unblinding Procedure

Each randomized patient will be assigned to receive either placebo or 70 mg etripamil NS; treatment will be randomized in a 1:1 ratio to yield at least 50 evaluable patients with AF in 2 groups of at least 25 each (placebo vs. etripamil NS). To ensure an adequate sample size, enrollment in the study will continue until each treatment group reaches the minimum of 25 evaluable patients. Throughout the study, the Milestone Medical Monitor (or designated medical reviewer) will log into the Interactive Web Randomization System (IWRS) to indicate whether or not each randomized patient meets the criteria for inclusion in the Efficacy Population (see Section 10.3).

Upon confirmation of eligibility, site personnel will log in to the IWRS to obtain a blinded treatment assignment for the patient: the IWRS will specify which drug kit is assigned to which patient, without revealing the treatment group (etripamil or placebo). The kit ID administered to each patient will also be recorded in the electronic data capture (EDC) system and in drug accountability documentation.

The randomization list will be generated by an IWRS vendor, and will only be accessible to limited unblinded personnel, e.g. drug packaging vendor, IWRS vendor. Blinding is critical for the integrity of the study. However, in the event of a medical emergency where revealing the study medication is critical to the care of the patient, the investigator may need to break the code. Before breaking the blind, the investigator should have determined that the information is necessary. It is recommended to contact the Montreal Health Innovations Coordinating Centre (MHICC) Medical

Monitor or the Sponsor Medical Director before any unblinding. The unblinding will be done through the IWRS system. If the IWRS is not accessible, the investigator will contact the Milestone Medical Monitor. This unblinding and the reason will be clearly document by the principal investigator in the study source documents.

7.5 Drug Storage and Accountability

Study drug will be stored at the clinical site at ambient room temperature (15°C to 30°C [59°F to 86°F]) and will be protected from light in a secure area with access limited to authorized personnel. For more information on study drug stability, please refer to the Investigator Brochure.

Used nasal spray devices should be maintained until study end to allow for full drug accountability to be conducted.

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

The final accountability of study drug (both used and unused kits) will be performed by the Clinical Research Associate (CRA) at the sites. The sites will be allowed to destroy used devices after CRA accountability. Unused study drug kits will be returned to PCI Pharma Services for destruction. If no study drug remains, this will be indicated in the drug accountability log.

7.6 Prior and Concomitant Therapies

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

Patients who, prior to enrollment, have received any of the following drugs by IV route may be eligible to participate at least 1 hour after these drugs were administered : flecainide, procainamide, digoxin, beta-blocker, or calcium channel blocker. Time of administration of such prior treatments must be documented in the eCRF.

After study drug administration, in case of clinical symptoms representing a safety risk for the patient, it is the investigator’s prerogative to use any additional treatment in accordance with the standard of care.

The use of any drugs of abuse (such as marijuana or prescription opioids) which, in the opinion of the Investigator, would impact the validity of the study results is prohibited.

8. STUDY PROCEDURES

Prospective study patients will be asked to sign the informed consent form before the commencement of any study-related assessments or procedures, including the cessation of prohibited concomitant therapy.

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

8.1 Study Periods, Visits, and Procedures

8.1.1 Screening Procedures

Prospective study patients will be asked to sign the informed consent form before the commencement of any study-related assessments or procedures. However, an ECG performed at presentation and in accordance to the institution's standard-of-care, but prior to ICF signature, may be used to assess the patient's eligibility to the study.

Screening ends when the patient is randomized or is deemed a Screen Failure; if an enrolled patient meets at least 1 exclusion criterion, they will be considered a screening failure. Screening and Treatment Procedures should be conducted at the same visit; however, all Screening Procedures must be completed prior to randomization.

The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Review inclusion/exclusion criteria.
    - In the event that the reference Screening ECG recording is shorter than one minute (e.g. due to the use of a standard-of-care ECG for eligibility assessment), a clinical note from qualified site personnel, documenting the monitoring of the heart rate for 1 minute, is deemed acceptable to confirm eligibility at Screening.
3. Record demographics and detailed medical history, including review of concomitant medications, and medications taken within 30 days before Screening.
4. Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems.
5. Measure height and weight.
6. Record vital signs (blood pressure, heart rate) after the patient has been in a seated position for at least 5 minutes.
7. Collect urine samples for pregnancy test (applicable only to women of childbearing potential). Alternatively, a serum pregnancy test may be performed.
8. Record any Adverse Events, as per Section 9.2.4.

8.1.2 Treatment Procedures

The Treatment Procedures will occur after Screening is completed and the patient's eligibility has been verified. The following procedures will be performed during the Treatment Period:

<u>Pre-Dose (at least 10 minutes prior to dosing)</u>

1. Confirm patient remains eligible for the study.

2. By logging in to IWRS, randomize the patient and obtain study drug kit assignment. Document the kit number in the patient's eCRF.
3. Fit the patient with a Holter monitor, and continuously record ECG from at least 10 minutes pre-dose to 6 hours after study drug administration.
4. Record blood pressure after the patient has been in a seated position for at least 5 minutes:
    1) 10 minutes prior to dosing,
    2) immediately prior to drug administration, to ensure patient eligibility prior to dosing with SBP ≥90 mmHg
5. Perform two ECGs over 10 minutes (from the Holter monitor):
    1) at 10 minutes prior to dosing to confirm the patient is in AF,
    2) immediately prior to drug administration, to confirm that Baseline HR meets ≥110 bpm threshold

    Patients must exhibit a rapid ventricular rate (≥110 bpm measured during 1 minute on the Holter report) prior to drug administration in order to receive the study drug.

Dosing

6. Administer Study Drug, and record time of drug administration. Appendix B provides detailed instructions for dosing.
    - Study drug must be administered by qualified clinical site staff.
    - 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.
    - 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.
    - Patient should not perform any strenuous physical activity for 1 hour post-dose.

Post-Dose (up to 1 hour after dosing)

7. Record blood pressure at 5, 10, 15, 30, and 60 minutes post-dose.
8. Complete the TSMQ-9 questionnaire at the end of the Treatment Period.
9. Record any adverse events, as per Section 9.2.4.
10. Record any concomitant medication taken since study drug administration
11. In case of systolic blood pressure <90 mmHg or clinical symptoms representing a safety risk for the patient, it is the investigator's prerogative to use any additional treatment within 60 minutes of study drug administration.
12. Beyond 60 minutes after study drug administration:
    - Appropriate medical care should be offered, in accordance with the standard of care.
    - The patient may be discharged from the clinic, while still wearing the Holter device as per the site staff's instructions.

8.1.3 Follow-Up Period

Following drug administration and post-dose activities, follow-up procedures will be performed. If the patient cannot be reached after 3 attempts, they will be considered lost to follow-up.

1. 24 hours post-dose (+/- 6 hours) : Safety follow-up will be performed, either via telemedicine or as an in-person visit if deemed necessary by the investigator.
    - Record any Adverse Events, as per Section 9.2.4.
    - Record any concomitant medication taken since study drug administration
    - Return of the Holter device will be arranged (e.g. by courier)
2. 1 week post-dose : Patients will be contacted by phone 7 days (+/- 1 day) post-dosing for safety follow-up.
    - Record any Adverse Events, as per Section 9.2.4.
    - Record any concomitant medication taken since study drug administration

8.2 Assessments

8.2.1 Efficacy

8.2.1.1 12-Lead ECG Recordings

A 12-lead ECG will be performed at Screening to assess eligibility (*NOTE : an ECG performed per standard-of-care on the same day but prior to ICF signature will be accepted for screening purposes*). Data from the ECG will be reviewed by qualified site personnel for potential concomitant disorders which would exclude the patient from the trial.

8.2.1.2 Holter ECG Recording

Continuous ECG recordings will be obtained during the Treatment period, from at least 10 minutes pre-dose to 6 hours post-dose via portable monitoring devices (Holter), and will provide the data for primary and secondary efficacy analyses. The files will be uploaded and stored centrally in the study database at the end of the study.

In addition, the Holter device and the associated software will be used by qualified site personnel for pre-dose Baseline HR measurements (10 minutes and immediately prior to drug administration). Following completion of patient participation, the ECGs recordings will also be reviewed by the Medical Monitor (or designee) to determine whether patients met the criteria for inclusion in the Efficacy Population.

8.2.1.3 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

After study drug administration, patients will be asked to complete the TSQM-9 (Appendix C).

The TSQM-9 is a 9 question, validated, indication agnostic patient reported outcome. It includes 3 items measuring treatment effectiveness, 3 items measuring treatment convenience, and 3 items measuring global satisfaction with treatment. The domain scores range from 0 to 100 with higher scores representing higher satisfaction with the treatment.

8.2.2 Safety

Safety assessments will include the evaluation of AEs, vital sign measurements, and ECG recordings.

8.2.2.1 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 9.

8.2.2.2 Clinical Laboratory Safety Assessments

8.2.2.2.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of assessments (Appendix A). Samples will be analyzed by the site's local laboratory:

Pregnancy Test: For women of childbearing potential only. A urine or serum test will be performed at Screening and as required to confirm any suspected pregnancy

8.2.2.3 Clinical Examinations

8.2.2.3.1 Vital Signs

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

8.2.2.3.2 Physical Examination

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

A symptom-directed physical examination will be performed after drug administration.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Events

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

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

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

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

Events that occur in patients during the Treatment Period while drug is not administered are also considered AEs.

9.1.2 Adverse Drug Reaction

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

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

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

9.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For etripamil, 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.

9.1.4 Serious Adverse Events/Drug Reaction

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, <u>does not</u> qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered a SAE.*

  ***Note: An ablation or cardioversion for treatment of atrial fibrillation will not be considered as a SAE**.*
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly.
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a patient who has received a study drug is not considered an SAE unless it is suspected that the study drug(s) interacted with a contraceptive method and led to the pregnancy.*
- Is an important medical event.
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The occurrence of malignant tumors is also to be considered serious*

9.1.5 Serious Unexpected Suspected Adverse Reaction (SUSAR)

An adverse reaction that is considered to be both serious and unexpected and of a suspected causality. Causality is defined as "reasonable suspected causal relationship to the medicinal product.

9.1.6 Treatment-Emergent Adverse Events

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

9.1.7 Adverse Events of Special Interest

Due to the mechanism of action of etripamil, patients could be at a higher risk of certain adverse events of special interest. Investigators should be on the alert for these events, or for symptoms which indicate an event may be present. Investigators should follow the standard protocol process for AE and SAE reporting for these AESI.

Below is a list of AEs which are of particular interest if they occur *within 24 hours* of study drug administration.

a) Tachyarrhythmias
   i) Supraventricular: occurrence of Atrial Tachycardia or Atrial Flutter lasting longer than 30 seconds

   ii) Ventricular:
   - Non-sustained ventricular tachycardia defined as equal or greater than 3 consecutives wide beats originating in the ventricles at a rate >100 bpm and terminating spontaneously

   - Sustained ventricular tachycardia defined as wide consecutive beats originating in the ventricles at a rate >100 bpm during >30 sec or requiring termination due to hemodynamic compromise in <30 sec

b) Bradyarrhythmia
   i) Any Sinus rate equal or less than 40 bpm lasting longer than 30 seconds

   ii) Any pause equal or greater than 3 seconds

c) Atrio-Ventricular Block
   i) New onset (not present in the ECG performed at the screening visit) of 1$^{st°}$ AV Block

   ii) Any occurrence of 2nd or 3rd degree AV Block (including AV dissociation or the presence of more than 2 consecutives non-conducted P waves)

d) Syncope and related events
   i) Syncope defined as a transient, self-limited loss of consciousness with an inability to maintain postural tone that is followed by spontaneous recovery.
   ii) Pre-syncope defined as a state consisting of light-headedness, muscular weakness, blurred vision, and feeling faint
   iii) Loss of consciousness defined as a partial or complete loss of consciousness with interruption of awareness of oneself and one's surroundings. When the loss of consciousness is temporary and there is spontaneous recovery it is referred to as syncope.
   iv) Dizziness defined as a false sense of motion or spinning, light-headedness or feeling faint, unsteadiness or a loss of balance, a feeling of floating, wooziness or heavy headedness. The episode may last seconds or days and may recur.
   v) Drop attack defined as a sudden fall without loss of consciousness
   vi) Hypotension is defined as a SBP <90 mmHg after a 5-minute rest in sitting position; when clinically severe hypotension patients experience light-headedness, nausea or vomiting.
   vii) Orthostatic hypotension defined as a physical finding defined as a systolic blood pressure decrease of at least 20 mmHg or a diastolic blood pressure decrease of at least 10 mmHg within three minutes of standing

9.2 Management of Adverse Events

Adverse events will be collected from the time of signing the ICF until 7 days post-dose, or until the patient withdraws or discontinues from the study.

9.2.1 Collection of Adverse Events

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

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

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

9.2.2 Evaluation of Adverse Events

9.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

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

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 9.1.4.

9.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 9.1.4.

9.2.2.3 Outcome at the Time of Last Observation

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

9.2.2.4 Adverse Event Relationship to the Study Drug

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

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

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

- Definitely related – An event that is clearly associated with study drug administration.

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

The following factors will also be considered:

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

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

9.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 9.2)

- AE name or term.
- When the AE first occurred (start date and time).
- When the AE stopped (stop date and time or an indication of “ongoing”).
- Severity of the AE.
- Seriousness (e.g., hospitalization or death).
- Outcome.

- Investigator opinion regarding the AE relationship to the study drug(s).

9.2.4 Follow-up of Adverse Events

Any AE / SAE (occurring up to a maximum of 7 days after single dose administration in the study) will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be included in the EDC. Patients who do not receive study drug during the study do not need AEs followed.

9.2.5 SAE Reporting

9.2.5.1 Serious Adverse Events

Initial Reports

The Investigator or designee must report all SAEs occurring from the time of signing the ICF until 7 days post-dose, or until the patient withdraws or discontinues from the study. To report the SAE, the investigator or designee must complete the SAE form electronically in the EDC system immediately and with undue delay, and under no circumstances later than 24 hours of awareness of the event. When the form is completed, MHICC Medical Monitor will be notified electronically and will retrieve the SAE form.

In case the EDC system is not available, the SAE should be reported within the same timeframe by completing the SAE paper form and send it by email to ReVeRA-SAFETY@mhicc.org. When the EDC system is once again functional, the SAE information must be entered within 24 hours of the system becoming available.

At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Patient's study number and initials
- Patient's date of birth
- Patient's gender
- Date of dosing of study drug(s)
- Adverse event term
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event (if any)
- Relevant past history information
- Relevant laboratory test findings (if any)
- Investigator's opinion of the relationship to the study drug(s). ("Is there a reasonable possibility that the study drug caused the SAE? Yes or No?").

The MHICC medical monitor will write a narrative report/CIOMS for all Suspected Serious Adverse Drug Reactions and will provide it to Milestone for immediate regulatory reporting purposes.

The MHICC medical monitor will review all SAEs that are recorded in eCRF on a regular basis.

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

Follow-up SAE Reports

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes 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 report) via e-mail to ReVeRA-SAFETY@mhicc.org. If it is not possible to access the EDC system, follow the procedures outlined above for the initial reporting of SAEs.

These documents must be thoroughly redacted to ensure that the confidentiality of the patient is maintained.

9.2.5.2 Adverse Drug Reactions

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

9.2.5.3 Nonserious Adverse Events

The MHICC medical monitor will review all nonserious AEs that are recorded in the eCRF on a regular basis.

9.3 Special Considerations

9.3.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice at least 1 form of adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected within 30 days of study drug administration.

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

Should a woman become pregnant within 30 days of receiving the study drug, the investigator must report the pregnancy as per the instructions below :

1) Investigator must report the pregnancy within 24 hours of learning of the pregnancy and record the information related to the pregnancy on the study specific "Pregnancy Form" to MHICC at ReVeRA-SAFETY@mhicc.org
2) Pregnancy in itself is not an SAE. The event of Pregnancy meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly or it is suspected that the study drug interacted with the contraceptive method and has led to pregnancy.
3) If pregnancy is associated with an SAE (e.g., if the mother is hospitalized for haemorrhage), a separate "SAE Form" must be filed in addition to "Pregnancy Form".
4) Investigator is also responsible for following the pregnancy until delivery or termination.

MHICC will be requesting follow up query with the Investigator in a "Pregnancy query form" for the status of the pregnancy (at least once in each trimester) until the outcome of the pregnancy, even if the patient has completed the study or study is closed. Also, the baby should be followed until one month post-delivery.

9.3.2 Overdose

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

Overdose that occurs during the study will be treated and documented as an AE/unexpected adverse event/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, patient identification, study drug, dose, action taken (e.g., administration of antidote [if available] or supportive measures or therapy), and any comments.

10. STATISTICS

This section describes the statistical methods to be used to analyze efficacy and safety endpoints. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications.

The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing and censoring data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses.

The SAP will take precedence over the protocol for any description of statistical analyses. The final clinical study report will discuss deviations from the SAP, if any.

10.1 Study Endpoints

10.1.1 Efficacy Endpoints

Efficacy variables will be obtained from the Holter recordings measured by a central core laboratory. In case of conversion to sinus rhythm, only heart rate measurements prior to sinus conversion will be used to derive efficacy variables.

The *primary efficacy variable* will be:

- The maximum reduction in ventricular rate, measured on Holter monitoring, within 60 minutes from drug administration.
    - Baseline ventricular rate is defined as the average heart rate over five minutes immediately prior to drug administration.
    - Nadir is defined as the lowest moving average heart rate over five minutes recorded in the primary evaluation period, i.e., 60 minutes post drug administration. The moving averages are 5 minutes' averages of different subsets of the full data set and are calculated by using the "shifting forward" method; that is, excluding the first number of the series and including the next value in the subset.
    - Maximum reduction will be calculated as the change between baseline value and nadir.

The *secondary efficacy variables* will include:

- Elapsed time from drug administration to nadir
- Percentage of patients achieving ventricular rate of <100 bpm in the 60 minutes post drug administration.
    - Elapsed time from drug administration to ventricular rate < 100 bpm
    - Duration of ventricular rate < 100 bpm in the 60 minutes post drug administration. Duration will be set to zero in patients who will not achieve ventricular rate <100 bpm and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients with 10% reduction from baseline ventricular rate in the 60 minutes post drug administration.
    - Elapsed time from drug administration to 10% reduction from baseline ventricular rate
    - Duration of 10% reduction from baseline ventricular rate in the 60 minutes post drug administration. Duration will be set to zero in patients who will not achieve 10% reduction and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients with 20% reduction from baseline ventricular rate in the 60 minutes post drug administration.
    - Elapsed time from drug administration to 20% reduction in ventricular rate
    - Duration of 20% reduction from baseline ventricular rate in the 60 minutes post drug administration. Duration will be set to zero in patients who will not achieve 20% reduction and will be calculated as the sum of the time periods during which the patient has a heart rate below the target ventricular rate.
- Percentage of patients cardioverting into sinus rhythm (for at least 30 seconds) in the 60 minutes post drug administration

- Elapsed time from drug administration to cardioversion into sinus rhythm

- Area under the curve (AUC) of heart rate over the 60 minutes and the 360 minutes post drug administration.
- Patient satisfaction with treatment, as measured by the TSQM-9.

10.1.2 Safety Endpoints

Safety variables will include clinical AEs, vital signs, and findings from electrocardiographic analysis (ventricular arrhythmia [premature ventricular contractions, non-sustained ventricular tachycardia], any AV block).

10.2 Sample Size Determination

The primary efficacy variable for this study is the maximal reduction of ventricular rate after study drug administration. Accounting for a two-sided test with a type I error rate of α=0.05, 25 patients per group will provide 93% power to detect a 20 bpm absolute difference in ventricular rate from baseline between active drug and placebo, assuming a standard deviation of 20 bpm.

10.3 Analysis Populations

The following 3 analysis populations are planned for this study:

- *Safety Population*: All randomized patients who receive the study drug. Patients will be analyzed as per actual treatment received in the Safety population.
- *Modified Intent to Treat (mITT) Population*: All randomized patients who receive the study drug and who have a Holter recording post study drug administration. Patients will be analyzed as per treatment assigned by randomization in the mITT population.
- *Efficacy Population:* All patients included in the mITT population, excluding patients who convert to sinus rhythm or with a lost ECG signal within 60 minutes post study drug administration. Patients will be analyzed as per treatment assigned by randomization in the Efficacy population.

10.4 Statistical Analyses

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

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of patients, mean, standard deviation (SD), median, minimum, Q1, Q3 and maximum. For categorical variables, these statistics will typically include the number and percentage of patients in each category.

In general, parametric analyses are planned. However, according to the distribution of the efficacy variables, non-parametric tests could be used or a logarithmic transformation could be applied on the variables before proceeding to the planned parametric analyses.

10.4.1 Efficacy Analyses

The efficacy analyses will compare placebo-treated patients versus etripamil-treated patients. Efficacy endpoint analyses will include summaries, both over time and as comparisons between

placebo and etripamil. Continuous efficacy data will be presented with n, minimum, maximum, median, mean, and standard deviation, whereas discrete efficacy data will be summarized with frequency counts and percentages.

10.4.1.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed on the Efficacy Population, and will compare the maximum reduction in ventricular rate in placebo-treated patients versus etripamil-treated patients. This comparison will be done using an analysis of covariance (ANCOVA) adjusting for the value of ventricular rate at baseline.

Sensitivity analysis for the primary efficacy endpoint will also be performed in the mITT population using an ANCOVA as described above.

10.4.1.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed on the Efficacy Population and on the mITT Population, and will compare :

- Elapsed time from drug administration to nadir. Group comparison will be done using an ANCOVA adjusting for baseline ventricular rate.
- Percentage of patients achieving ventricular rate of <100 bpm, reaching 10% and 20% reduction from baseline ventricular rate. For each of these three endpoints, group comparison will be done using a chi-square test or a Fisher exact test if more than 20% of cells have expected frequencies <5.
- Elapsed time from drug administration to ventricular rate <100 bpm, to 10% reduction from baseline ventricular rate, and to 20% reduction from baseline ventricular rate. For each of these three endpoints, group comparison will be done using the Kaplan-Meier method and a Wilcoxon test for censored data. .
- Duration of 10% and 20% ventricular rate reductions will be analyzed using an ANCOVA adjusting for baseline ventricular rate.
- Mean heart rate over time will be plotted with 95% confidence interval error bars.
- AUC of heart rate over 60 minutes. AUC will be calculated over the specific Holter recording period for each patient and indexed to a period of 60 minutes. Group comparison will be done using an ANCOVA adjusting for baseline ventricular rate.
- Patient satisfaction with treatment, as measured by the TSQM-9. Domaine scores (ranging from 0 to 100) will be analyzed using a t-test or a Mann-Whitney-Wilcoxon test, according to the distribution of the variable.
- Parameters analyzed in mITT Population only :
    - Percentage of patients cardioverting into sinus rhythm (for at least 30 seconds). Group comparison will be done using a chi-square test or a Fisher exact test if more than 20% of cells have expected frequencies <5.
    - Elapsed time from drug administration to cardioversion into sinus rhythm. Group comparison will be done using using the Kaplan-Meier method and a Wilcoxon test for censored data.

- AUC of heart rate over 360 minutes. AUC will be calculated over the specific Holter recording period for each patient and indexed to a period of 360 minutes. Group comparison will be done using an ANCOVA adjusting for baseline ventricular rate.

10.4.2 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 10.3).

Safety and tolerability will be assessed through AEs, vital signs measurements, and ECG recordings.

Safety data will be summarized with descriptive statistics. Continuous safety data will be presented with n, minimum, Q1, Q3, maximum, median, mean, and standard deviation, whereas discrete safety data will be summarized with frequency counts and percentages.

10.4.2.1 Adverse Events

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

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

Treatment Emergent Adverse Events (adverse events occur within 24 hours after study drug administration) will be coded by system organ class and analyzed for each treatment group.

10.4.3 Interim Analyses

No interim analyses are planned in this study.

11. INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

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

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 or authorized clinical research organization (CRO).

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, eCRFs and procedures for their completion, informed consent process, site and/or 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 Data Collection

Data for the study will be collected at the site and entered into the EDC for inclusion in the database. Data from the IWRS and from Holter ECG recordings will be transmitted to the sponsor or designee and integrated into the database prior to official lock. All electronic data collection systems will be designed for 21 CFR Part 11 compliance, with audit trail capability.

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

11.6 Disclosure of Data

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

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

11.7 Retention of Records

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

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

11.8 Data Protection

The Sponsor complies with applicable laws and regulations, notably the General Data Protection Regulation related to Personal Data protection arising from company-sponsored clinical trials involving EU data subjects, via a set of policies relating to data protection practice and retention of personal information, privacy notices and security measures, all supervised by the Data Protection Officer. The Sponsor and its contractors have implemented various methods to assure the security and integrity of personal information including, but not limited to: pseudonymization, logical access controls, traceability, encryption, operating systems security, data breach procedures, backup, business continuity, and disaster recovery.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information

which would make the subject identifiable will not be transferred. The subject will be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure will be explained to the subject. The subject will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor policy requires all notified breaches to be investigated, categorized, and remediation activities implemented. When the rights and freedoms of the data subject are affected then data breaches are notified to the relevant authorities and, when there is a high risk, to the data subject.

11.9 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.

11.10 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.

11.11 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.

The ReVeRA-201 Trial is sponsored and funded fully by Milestone Pharmaceuticals Inc.

12. STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

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

12.2 Protocol Authors

This study protocol was written and finalized by Milestone Pharmaceuticals employees, with external scientific advice provided by the Montreal Heart Institute.

13. FINAL CLINICAL STUDY REPORT

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

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

14. REFERENCES

1. Henrard V et al. Cardiac Remodeling With Rhythm Versus Rate Control Strategies For Atrial Fibrillation In Patients With Heart Failure: Insights From The AF-CHF Echocardiographic Sub-Study. *International Journal of Cardiology* 165 (2013) 430–436

2. Olshansky B et al. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study – Approaches to Control Rate in Atrial Fibrillation. *Journal of the American College of Cardiology* 2004;43:1201–8

3. Cain ME, Curtis AB, Rhythm Control In Atrial Fibrillation--One Setback After Another *New England Journal of Medicine* 2008; 358:2725-2727

4. Camm AJ et al. Rate Control In The Medical Management Of Atrial Fibrillation. *Heart* 2007;93:35–3

5. Fromm C et al. Diltiazem vs. Metoprolol In The management Of Atrial Fibrillation Or Flutter With Rapid Ventricular Rate In The Emergency Department. The Journal of Emergency Medicine, Vol. 49, No. 2, pp. 175–182, 2015

6. January CT et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Journal of the American College of Cardiology* (2014)

7. Andrade, JG et al., The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology 2020 Dec; 36(12): 1847-1948.

APPENDICES

A. SCHEDULE OF ASSESSMENTS

	SCREENING [a]	TREATMENT PROCEDURES [b]			FOLLOW-UP [c]	
		Pre-Dose (Baseline)	Dosing	Post-Dose	~24 hrs post-dose	~7 days post-dose
Informed Consent	X					
Eligibility Evaluation	X	X				
Demographic / Medical History	X					
Concomitant Medications	X	X		X	X	X
Physical Examination	X			X [d]		
Pregnancy test	X					
Vital Signs [e]	X	X	X	X		
Height and Weight	X					
ECG [f]	X					
Randomization [g]		X				
Holter ECG Monitoring [h]		---------- X ----------			*Return*	
Drug administration			X			
TSMQ				X		
Adverse Events [i]	X [j]	---------- X ----------			X	X

[a] Screening and Treatment procedures should be performed on the same day.

[b] Baseline / Pre-dose procedures must be performed at least 10 minutes prior to dosing.

[c] Safety follow-up will be performed approximately 24 hours post-dose; if performed via telemedicine, return of the Holter device must be arranged accordingly. An in-person visit may be performed if deemed necessary by the investigator. Patients will also be contacted by phone 7 days (+/- 1 day) post-dose for safety follow-up. If the patient cannot be reached after 3 attempts, they will be considered lost to follow-up.

[d] Post-dose physical examination can be symptom-directed.

[e] Screening vital signs include blood pressure, heart rate, weight, and height. Blood pressure must be monitored and recorded at 10 minutes pre-dose and immediately prior to dosing, to ensure patient eligibility prior to dosing with SBP $\geq$90 mmHg. Blood pressure must be recorded at 5, 10, 15, 30, and 60 minutes post-dose.

[f] Ventricular rate used to evaluate patient eligibility should be documented from the screening ECG. A standard-of-care ECG performed on the same day but prior to ICF signature may be used for eligibility assessment.

[g] Randomization procedure and study drug preparation must be completed prior to other pre-dose procedures.

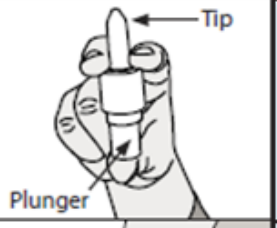
[h] Following confirmation of eligibility and randomization, patient will be fitted with a Holter monitor for continuous ECG recording throughout the treatment period (from 10 minutes pre-dose to 6 hours post-dose). Baseline ECG must be assessed 10 minutes prior to and immediately before drug administration; patients must exhibit a rapid ventricular rate ($\geq$110 bpm measured during 1 minute) prior to drug administration in order to be treated. Holter device will be returned by the following day.

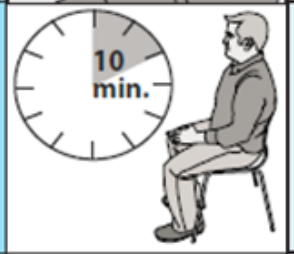
[i] Adverse events considered potentially related to treatment should be followed until resolution.

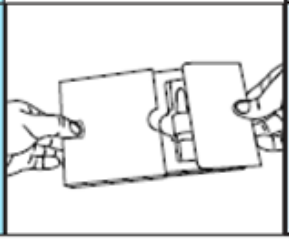
[j] Worsening of a pre-existing condition discovered during the screening period is considered an AE.

B. STUDY DRUG ADMINISTRATION INSTRUCTIONS

1	**PREPARE TO USE**		• The study drug must be administered to the patient at the clinical site, **by the investigator or a qualified designee**
			• Prior to dosing, instruct the patient to :
			  • **SIT DOWN** before receiving study drug
			  • Keep their head upright
			  • Not inhale deeply when the drug is administered

2	**HOLD THE DEVICE**		• **Hold** device between your index and middle (1st and 2nd) fingers. Place thumb on the plunger and make sure it fully covers the base. This will be important when you press it so it pushes in smoothly and does not jam. • **DO NOT PRESS THE PLUNGER YET!**
3	**SPRAY INTO FIRST NOSTRIL**		• Gently insert the tip of the spray device into the **1st** nostril and insert as far as it feels comfortable (~1/2 inch or 1 cm) • **USE YOUR THUMB TO PRESS PLUNGER FIRMLY and QUICKLY ALL THE WAY UP, then immediately let it FULLY release.** • **Patient should not inhale deeply.**
4	**SPRAY INTO SECOND NOSTRIL**		• **Immediately after Step 3**, gently insert the tip of the spray device into **2nd** nostril and insert as far as it feels comfortable (~1/2 inch or 1 cm) • **USE YOUR THUMB TO PRESS PLUNGER FIRMLY and QUICKLY ALL THE WAY UP, then immediately let it FULLY release** • **Patient should not inhale deeply**.

5	**REMAIN SEATED FOR 10 MINUTES**		• Following dosing, instruct the patient to :
			  • Resume breathing normally.
			  • Remain seated with their head upright for 10 minutes following drug administration
			  • **NOT BLOW THEIR NOSE FOR AT LEAST 10 MINUTES.** If some of the liquid drips outside their nose, they should wipe it away with a tissue

6	**RETURN USED DRUG**		• **Place used device back in carton.** • **Return the used device to the pharmacist or designee.** • **Document treatment compliance and drug accountability.**

C. TREATMENT SATISFACTION QUESTIONNIARE FOR MEDICATION (TSQM-9)

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐$_1$ Not at All Certain
☐$_2$ A Little Certain
☐$_3$ Somewhat Certain
☐$_4$ Very Certain
☐$_5$ Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

D. REGULATIONS AND GOOD CLINICAL PRACTICE GUIDELINES

1. Regulations

Refer to the following applicable regulations:

CANADA : Under the Canadian Food and Drugs Act (R.S.C., 1985, c. F-27),

- Food and Drug Regulations C.R.C c.870, Part C - Drugs, Division 5: Drugs for Clinical Trials Involving Human Subjects

  https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-134.html#h-577812

- Medical Devices Regulations SOR/98-282

  https://laws-lois.justice.gc.ca/eng/Regulations/SOR-98-282/index.html

NETHERLANDS

- Dutch Medical Research Involving Human Subjects Act (WMO)

  https://wetten.overheid.nl/BWBR0009408/2022-03-15

- EU Clinical Trial Regulation (CTR)

  https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX%3A32014R0536&from=NL

- EU Medical Device Regulation (MDR)

  https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX%3A32017R0745&from=NL

2. Good Clinical Practice Guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html