Rationale for and design of a multicenter, placebo-controlled, phase 3 study to assess efficacy and safety of intranasal etripamil for the conversion of paroxysmal supraventricular tachycardia

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Presently, acute pharmacological termination of paroxysmal supraventricular tachycardia (PSVT) unresponsive to patient-initiated vagal maneuvers requires in-hospital intervention. Etripamil, a fast-acting, nondihydropyridine, L-type calcium channel blocker, is formulated as an intranasal spray to rapidly terminate atrioventricular (AV) nodal-dependent PSVT in a medically unsupervised setting. The NODE-301 study did not meet its prespecified primary end point of PSVT conversion over 5 hours following a single dose of etripamil 70 mg. However, analysis at earlier time points demonstrated etripamil treatment effect during the first 30 minutes, consistent with its expected rapid onset and short duration of action. This led to the design of the RAPID study, which includes a new dosing regimen (up to 2 etripamil 70 mg doses separated by 10 minutes) to increase the exposure and pharmacodynamic effect of etripamil. The primary objective of RAPID (NCT03464019) is to determine if etripamil self-administered by patients is superior to placebo in terminating PSVT in an at-home setting. The secondary objective is to evaluate the safety of etripamil when self-administered by patients without medical supervision. Additional efficacy end points include the proportion of patients requiring additional medical intervention in an emergency department to terminate PSVT and patient-reported outcomes. After successfully completing a test dose to assess the safety of 2 70 mg doses of etripamil during sinus rhythm, approximately 500 patients will be randomized 1:1 to etripamil or placebo to accrue 180 positively adjudicated AV nodal-dependent PSVT events for treatment with the study drug. Etripamil may offer a new alternative to the current in-hospital treatment modality, providing for safe and effective at-home termination of PSVT. (Am Heart J 2022;253:20–29.)

Keywords: Arrhythmia termination; Atrioventricular nodal reentrant tachycardia; Atrioventricular reentrant tachycardia; Calcium channel blocker; Etripamil; Intranasal; Paroxysmal supraventricular tachycardia

Introduction

Paroxysmal supraventricular tachycardia (PSVT) is an episodic heart rhythm disorder leading to regular tachyarrhythmia (heart rate over 100 beats per minute), which is sudden in its onset and termination.[1,2] Common clinical symptoms include palpitations, chest discomfort, light-headedness, and anxiety; less common symptoms include polyuria, syncope, and serious psychological distress.[1,3] The 2 most common subtypes of PSVT are atrioventricular nodal reentrant tachycardia (AVNRT) and orthodromic atrioventricular reentrant tachycardia (AVRT), together accounting for approximately 90% of cases.[2] Because both of these types of PSVT utilize the AV node as a necessary part of the arrhythmia circuit, a pharmaceutical agent capable of transiently prolonging AV nodal re-

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Abbreviations: AC, Adjudication Committee; AE, adverse events; AESI, adverse events of special interest; ANOVA, Analysis of Variance; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; CMS, cardiac monitoring system; DBP, diastolic blood pressure; DSMC, Data Safety Monitoring Committee; ECG, electrocardiogram; ED, emergency department; GCP, Good Clinical Practice; HR, heart rate; ICH, International Conference on Harmonisation; IEC, Institutional Ethics Committee; IRB, Institutional Review Board; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia; SBP, systolic blood pressure; SR, sinus rhythm; SVT, supraventricular tachycardia; TSQM-9, Treatment Satisfaction Questionnaire for Medication©; ULN, upper limit of normal.

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fractoriness can result in termination of the arrhythmia and restoration of sinus rhythm.

Standard of care and unmet medical need for novel therapies

Intravenous (IV) calcium channel blockers (verapamil and diltiazem) and IV adenosine are effective agents for the termination of acute supraventricular tachycardia (SVT) episodes.[4,5] Verapamil and diltiazem are nondihydropyridine, L-type calcium channel blockers whose antiarrhythmic effect is due to inhibition of the calcium ion influx through the slow channel in AV node cells. Adenosine generates transient AV nodal block when injected as a rapid IV bolus via activation of AV nodal adenosine receptors with subsequent inhibition of calcium current. As both medications require IV access, they are not appropriate for self-administration in an outpatient setting. There is currently no fast-acting drug available for patient self-administration to terminate acute PSVT; however, such a drug would give patients the ability to terminate PSVT without visiting an urgent care facility or needing any other form of direct medical supervision.

Etripamil is a novel calcium channel blocker

Etripamil, a fast-acting, nondihydropyridine, L-type calcium channel blocker, is formulated for intranasal administration with a nasal spray delivery device, providing rapid onset of action (<5 minutes). Peak plasma concentrations of etripamil 70 mg occur at about 8 minutes on average and fall by approximately 60% from peak value at 25 minutes and around 80% within 50 minutes. Hence, a direct pharmacological effect of etripamil on the cardiac calcium current would be expected during the first 30-40 minutes after treatment.[6] Etripamil was designed to be rapidly inactivated by ubiquitous human blood esterase enzymes, resulting in a short duration of action and favorable safety and tolerability profile. Etripamil is being developed as a "treatment in the pocket" to be self-administered by individuals who recognize their symptoms of sustained PSVT.

Results of phase 1 and phase 2 studies of etripamil

In the first-in-human, single ascending dose phase 1 study, 72 healthy adult male participants aged 19-60 years received etripamil intranasally at doses of 3.5, 7, 14, 30, 60, 105, and 140 mg. The pharmacokinetic analysis demonstrated that etripamil was rapidly absorbed across the nasal mucosa with a time to a maximum concentration of 5 minutes in all but the lowest dosing cohort, with a dose-dependent maximum observed concentration. The prolongation of the PR interval (an ECG marker of AV conduction) was more pronounced at the 4 highest doses.[6]

Etripamil 35, 70, 105, and 140 mg were compared to placebo in 104 patients randomized in NODE-1, a phase 2 parallel design, placebo-controlled, double-blinded study conducted in electrophysiology laboratories.[7] The primary end point was the conversion of induced SVT (either AVNRT or AVRT) to sinus rhythm within 15 minutes of study drug administration. The SVT conversion rate was significantly higher at the 3 highest doses (87%, 75%, and 95% in etripamil 70, 105, and 140 mg groups, respectively, with median conversion times of about 2-3 minutes) compared with placebo (which demonstrated a conversion rate of 35%). The administration of etripamil was well tolerated; most adverse events (AEs) were associated with the nasal administration, including nasal congestion, lacrimation, nasal discomfort, rhinorrhea, throat irritation, sneezing, and cough. Cough was most likely due to postnasal drip from nasal spray administered in the supine position. Only the 2 highest doses (105 and 140 mg) transiently reduced systolic blood pressure (magnitude about 15-20 mm Hg). Based on the balance of efficacy and safety, etripamil 70 mg was selected for future studies.

Results of NODE-301

NODE-301 was a phase 3, multicenter, double-blind, placebo-controlled, randomized (2:1) event-driven study that evaluated the efficacy and safety of etripamil 70 mg administered outside the hospital setting in patients with symptomatic sustained PSVT who did not respond to an initial vagal-maneuver attempt. NODE-301 included a prespecified analysis after at least 150 positively adjudicated PSVT events had accrued. The NODE-301 study did not demonstrate significant efficacy versus placebo for PSVT conversion over 5 hours, a time period significantly longer than the drug's pharmacodynamic effects. This prolonged observation period may have enabled termination of PSVT to occur unrelated to etripamil treatment effects within the monitoring timeframe. However, an efficacy analysis at earlier time points showed a treatment effect favoring etripamil at 45 minutes (hazard ratio: 1.668, 95% confidence interval [CI]: 1.026-2.712, $P < .02$) following study drug administration, consistent with the pharmacological activity of etripamil.[8,11] The statistical analysis in NODE-301 that censored patients whose PSVT was terminated following rescue medical intervention at the time of conversion may also have confounded the results, as more patients in the placebo group than the etripamil group sought other medical interventions to terminate PSVT during the 5-hour window.[11] PSVT recurrence rates following initial conversion to sinus rhythm were quite low (<1%) during the postadministration 5-hour monitoring period.

The NODE-301 study demonstrated that etripamil 70 mg was safe and well-tolerated over 5 hours following treatment in >100 patients in PSVT. Based on the encouraging pharmacological activity and safety profile of etripamil 70 mg, we designed a follow-up study, the RAPID (ie, part 2 of the NODE-301 study) that includes a patient-selected option to self-administer a second dose of study drug (etripamil 70 mg or placebo) after the first dose if symptoms persist after 10 minutes.

Methods

General study design and conduct

RAPID is a phase 3, multicenter, randomized (1:1), double-blinded, placebo-controlled, event-driven study designed to evaluate the efficacy and safety of a new dosing regimen consisting of etripamil 70 mg administered at the time the patient experiences symptoms of PSVT and repeated with the same dose 10 minutes later if symptoms persist (see Figure 1 for study design and Supplementary Material 1 for study sites and primary investigators). The RAPID study population consists of newly enrolled patients and patients enrolled in NODE-301 who had not dosed with the study drug before the cutoff point for the part 1 analysis (January 15, 2020). All patients enrolling in RAPID (including patients enrolled in part 1 who had not dosed with the study drug or discontinued before implementation of the RAPID protocol) must pass a test dose of the RAPID dosing regimen consisting of 2 doses of etripamil 70 mg administered 10 minutes apart in sinus rhythm under medical supervision. For the test dose to be considered evaluable, both doses of the etripamil dosing regimen need to be administered. Eligible patients who pass the test dose (see Supplementary Material 2 for the eligibility criteria) are randomized to receive the etripamil dose regimen described above or an equivalent placebo regimen in a 1:1 ratio. At PSVT symptom onset, patients apply and activate a precordial cardiac monitoring system (CMS) (see the subsequent section on the postrandomization treatment period for details) that collects continuous electrocardiogram (ECG) data and perform a vagal maneuver as instructed by the investigator. If symptoms persist after the vagal maneuver, patients self-administer the study drug. If symptoms persist 10 minutes after the administration of the first dose of study medication, the patient has the option of administering a second dose of study medication. The patient records the time of administration of each dose of study medication by pushing a button on the CMS device to record the event. The CMS ECG recordings will be reviewed by an adjudication committee (AC) to confirm the episode as "true" AV nodal-dependent PSVT and determine arrhythmia termination within 30 minutes after the first dose of study drug administration with the persistence of sinus rhythm for at least 30 seconds. A data safety monitoring committee (DSMC) will provide safety oversight of the study.

Study end points and statistical analyses

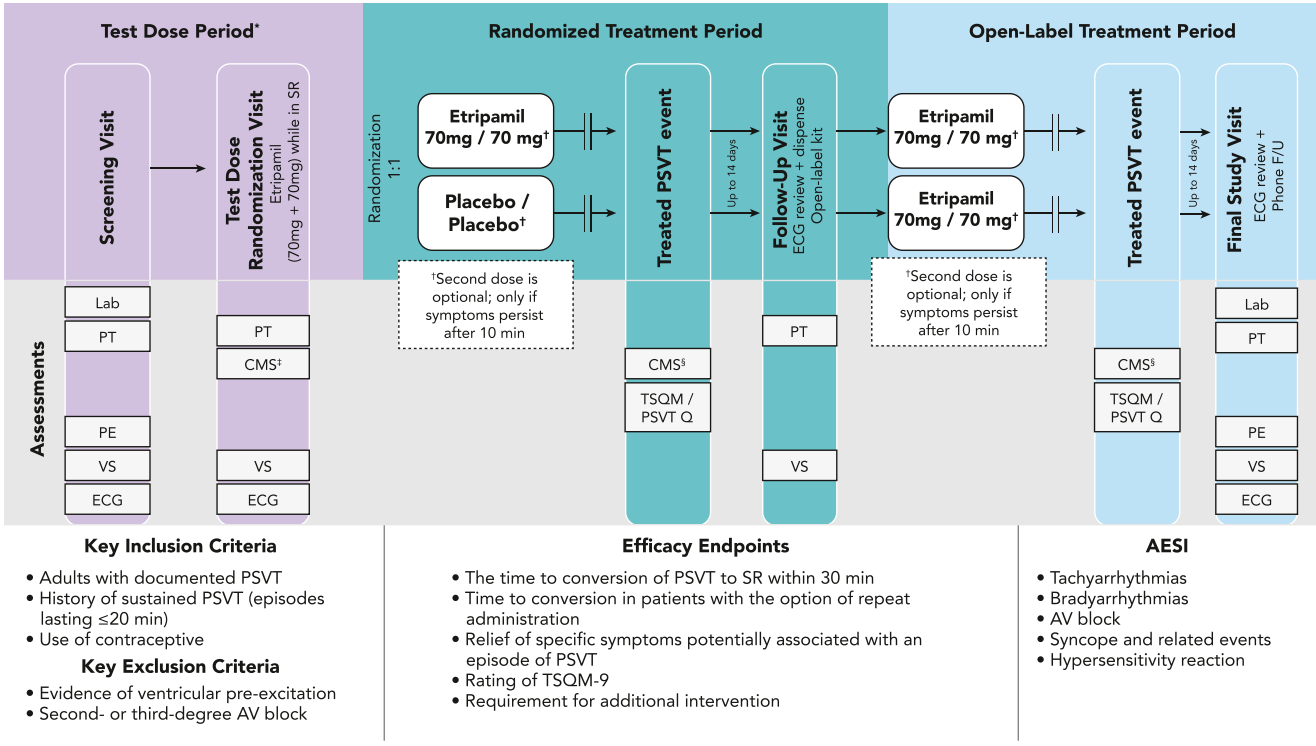
The primary objective of the study is to determine whether a dosing regimen consisting of an initial etripamil 70 mg dose and a second dose 10 minutes later if symptoms persist, is superior to a similar dosing regimen of placebo in terminating PSVT within 30 minutes of study drug administration in a medically unsupervised setting.

The treatment effect to be estimated, or the estimand[9] of the study, is the rapid conversion of PSVT to sinus rhythm (as measured by time to conversion) in a medically unsupervised setting when using a self-administered etripamil nasal spray compared to placebo. The population to be included in the estimation includes all randomized patients who use the study drug to treat a positively adjudicated episode of PSVT. The primary measure is time to adjudicated termination of a positively adjudicated PSVT event and conversion to sinus rhythm for at least 30 seconds, within 30 minutes of the first administration of study drug. Medical intervention outside the study protocol is a key intercurrent event. Thus, patients who receive additional medical intervention for perceived PSVT will be considered treatment failures and censored at the end of the observation period. Sensitivity analyses will be conducted, including a composite strategy. For the primary efficacy end point analyses, data from the single-dose regimen patients during part 1 of the study (NODE-301) who did not have an episode before the cutoff date, and were not included in the 301 analysis, will be pooled with data from the repeat dose regimen patients (RAPID) for both the etripamil and placebo arms.

The secondary efficacy end points include patient-reported relief of specific symptoms associated with PSVT and rating of the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9).[10] The TSQM-9 consists of questions (as detailed in Supplementary Material 3) designed to measure treatment effectiveness, convenience, and global satisfaction. TSQM-9 scores will be computed by adding the TSQM items in each domain (Effectiveness, Convenience, and Global Satisfaction) and then transforming the composite score into a value ranging from 0 to 100. TSQM-9 scores will be analyzed using a one-way analysis of variance (ANOVA) statistical test. The least-square means, 95% CIs, and *P*-value will be presented. The severity score for each symptom will be analyzed via an ANOVA model with treatment effects.

To control for multiplicity, the secondary end points will be analyzed in a step-down hierarchical method in which analyses of these secondary end points will only be performed if the primary efficacy end point is met. Once the superiority claim for the primary efficacy end point is met, the superiority claims for the following key

Figure 1



Graphical representation of RAPID study of intranasal etripamil in PSVT patients (*ClinicalTrials.gov: NCT03464019*). *The study population includes a number of patients who had a single (etripamil 70 mg) test dose and single dose (etripamil 70 mg or placebo) treated events between the time of the cutoff point for the phase 3 NODE-301 analysis and the introduction of the RAPID protocol. †Second dose is administered only if symptoms persist after 10 minutes. ‡45-minute recording after the first dose. §5-hour recording after the first dose. AESI, adverse events of special interest; AV, atrioventricular; CMS, cardiac monitoring system; ECG, electrocardiogram; F/U, follow-up; Lab, clinical laboratory analysis (chemistry, hematology, and urinalysis); PE, physical evaluation; PSVT, paroxysmal supraventricular tachycardia; PT, pregnancy test; SR, sinus rhythm; TSQM/PSVT Q, treatment satisfaction questionnaire for medication and paroxysmal supraventricular tachycardia symptoms questionnaire; VS, vital signs (blood pressure and heart rate).

efficacy end points will also be tested at a 2-sided significance level of 0.05.

To control for the probability of making any familywise error rates, a null hypothesis for an efficacy variable will be rejected only if all null hypotheses before it are also rejected. Other efficacy end points and sensitivity analyses will not be controlled for type I error.

Additional efficacy end points include conversion at time points earlier and later than 30 minutes, time to conversion in patients who repeated the administration of the study drug 10 minutes apart, the number of positively adjudicated PSVT events converted by performing a vagal maneuver, changes in heart rate during PSVT before conversion, the percentage of patients requiring additional medical intervention in the emergency department (ED) to terminate PSVT, and the repeat of key efficacy end points in various subgroups of interest (eg, concomitant medications). The relationship of HR reduction to symptom improvement and the need for acute medical intervention will also be assessed.

The secondary objective is to evaluate the safety of etripamil when self-administered by patients without medical supervision. Safety variables include clinical AEs, vital signs (blood pressure and heart rate), laboratory testing (see Supplementary Material 4 for a complete list of clinical laboratory analytes), arrhythmias, and conduction disorders detected on 12-lead ECG or CMS recordings.

The exploratory objectives are to evaluate the safety, hemodynamic, and cardiac conduction effects of a test dose of etripamil; the safety and efficacy of etripamil in various subgroups of interest (eg, patients receiving concomitant medications); and the safety and efficacy of a treatment regimen of etripamil, which allows a repeat dose of etripamil to terminate PSVT in a nonmedically supervised setting.

Patient disposition and baseline data will be summarized by treatment group for each analysis population. For randomized patients who discontinue the study, the primary reason for discontinuation will be summarized by treatment group. Baseline demography and disease characteristics will be summarized by descriptive statistics and by treatment group. Safety data will be summarized with descriptive statistics. Continuous safety data will be presented with n, minimum, maximum, median, mean, and standard deviation, whereas discrete safety data will be summarized with frequency counts and percentages.

Study population and setting

Patient eligibility criteria were selected to ensure recruitment of a population (aged $\geq$18 years) with electrocardiographically-documented PSVT and a history of sustained PSVT (ie, episodes typically lasting approximately 20 minutes or longer). Females with the potential for pregnancy are required to use a highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of the study drug. Male patients are required to use a highly effective form of contraception for 3 days following study drug administration. Patients are excluded from participation if they have had an allergic reaction to verapamil, a clinically significant disorder that the investigator feels will jeopardize the patient's safety, history of severe ventricular arrhythmia, evidence of ventricular preexcitation (eg, delta waves, short PR interval <100 ms, Wolff-Parkinson-White syndrome), second- or third-degree AV block, or an atrial arrhythmia that does not utilize the AV node as part of the tachycardia circuit. A complete list of inclusion and exclusion criteria is provided in the Supplementary Material 2.

Screening, recruitment, and consent

The screening and recruitment of patients, study activities, and data recording are carried out by participating sites in this Good Clinical Practice (GCP) clinical study. No study-specific procedures are conducted until after the patient has written informed consent.

Study visits and procedures

Screening visit

Inclusion/exclusion criteria are used to determine study eligibility at the screening visit. Medical history interview, physical examination, standard clinical laboratory profiles (hematology, serum chemistry, pregnancy test for females, and urinalysis), and 12-lead ECG will be performed.

Test dose randomization visit

To evaluate tolerability, patients meeting all screening criteria will self-administer a test dose of etripamil 70 mg (consisting of 2 nasal sprays with 1 spray in each nostril) at the investigational site via the Aptar Pharma Nasal Spray Bidose system, followed by a second dose of etripamil 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose. This evaluation will be conducted under medical supervision at the investigative sites with the patient in sinus rhythm and in a seated position. Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate [HR] measurements) will be obtained 10 minutes pretest dose and every 5 minutes for 45 minutes after the first test dose (as outlined in the Safety Assessments section below).

Patient education, training, and appropriate compliance with study procedures are crucial to the success of the trial. Therefore, all patients (and their caregivers, if involved with and available to help the patient with study procedures) will be given thorough instruction regarding the steps to complete when they have a perceived PSVT event outside the clinic, including identifying and reporting symptoms; use of the patient coach; setup and use of the CMS; performance of the vagal maneuver; proper

self-administration of the study drug in a seated position and recording time of study drug administration; completion of questionnaires; and reporting AEs (see Figure 2 for step-by-step instructions). During the test dose visit, the participants will perform these steps as they would if they were on their own during a PSVT event occurring outside of the clinic setting.

The CMS kit includes a wireless Preventice Solutions BodyGuardian heart monitor paired with a kit-specific smartphone. The smartphone is essential for the activation and function of the monitor and is also used to transfer ECG data to the cardiac core laboratory via cellular transmission. Patients will wear a CMS to record cardiac activity for at least 10 minutes before administration of the test dose and for at least 45 minutes after the first dose of the drug. A 12-lead ECG recording within 30 minutes pretest dose and 45 minutes after the first dose will also be required. On-screen visual ECG monitoring (at least 2 leads) will be conducted from the beginning to the end of the test dose. CMS ECG and investigator interpretation of the continuous on-screen ECG monitoring will be used to help determine eligibility for randomization. Additional blood pressure measurements and ECGs will be done in case of symptoms or rhythm abnormalities. Predefined criteria for success of the test dose are listed with the exclusion criteria in the Supplementary Material.

Patients who pass the test dose will be randomized to receive a dosing regimen consisting of either etripamil 70 mg administered upon symptomatic PSVT and repeated with the same dose of etripamil 10 minutes later if symptoms persist, or the same dosing regimen of placebo in a 1:1 double-blinded ratio, using an interactive web response system. Patients who fail the test dose but have an identifiable and modifiable cause (eg, beta-blocker therapy with the potential for discontinuation of the medication) may repeat the test dose within 14 days of stopping the medication or situation modification. Patients who do not have an identifiable and modifiable cause for failure or fail a repeat test dose will proceed to a final study visit.

Postrandomization treatment period

Patients who experience symptoms consistent with PSVT are instructed to call their sponsor-provided telephone coach to guide them through the study procedures. Patients will apply and activate the CMS on their chest and perform a vagal maneuver as previously instructed by their study physicians. If symptoms persist in a seated position, they will press the CMS event marker button (to record the time of the self-administration of the study drug) and immediately self-administer an initial dose of blinded study medication (etripamil 70 mg or placebo) as a single spray into each nostril (2 sprays total, as illustrated in Figure 2). If symptoms of PSVT do not resolve within 10 minutes after the first dose of study medication, the patient should administer a second dose of the same blinded study medication (etripamil 70 mg or placebo) by using the provided second nasal spray device. The patient will push the CMS event marker button for the second time immediately before self-administering the second dose of the study drug. The CMS will be kept on for 5 hours after study drug administration. After that time, the CMS can be removed and the recording transmitted wirelessly to the cardiac monitoring core lab.

If symptoms of PSVT do not resolve within 30 minutes after the start of study drug administration, patients are advised that they may seek appropriate additional medical care but should continue the CMS recording for the 5-hour monitoring period.

Patients are required to complete 2 questionnaires after dosing with the study drug as soon as possible after their PSVT has resolved: the PSVT symptoms questionnaire and the TSQM-9 (Supplementary Material).

Routine follow-up visits

During the study, routine follow-up visits are scheduled monthly to assess AEs and changes in concomitant medications, confirm ongoing eligibility, and retrain on PSVT procedures. These visits can be conducted at the site or via telephone. A follow-up visit (preferably at the site) is also required for patients who experience symptoms of PSVT, who apply and activate the CMS, and whose episodes terminated with a vagal maneuver.

Randomized treatment follow-up visit

An onsite follow-up visit is required within 14 days for all patients who experience symptoms of PSVT who apply and activate the CMS and self-administer study drug. Patients will need to bring the study-provided materials (specifically the nasal spray devices, BodyGuardian heart monitor and study smartphone, study identification card, and completed questionnaires) to the visit.

Open-label treatment period

An open-label treatment period follows the randomized treatment follow-up visit. It will include all randomized patients who self-administered the study drug for perceived PSVT during the randomized treatment period and did not experience any AEs associated with the study drug that would preclude their subsequent treatment with etripamil.

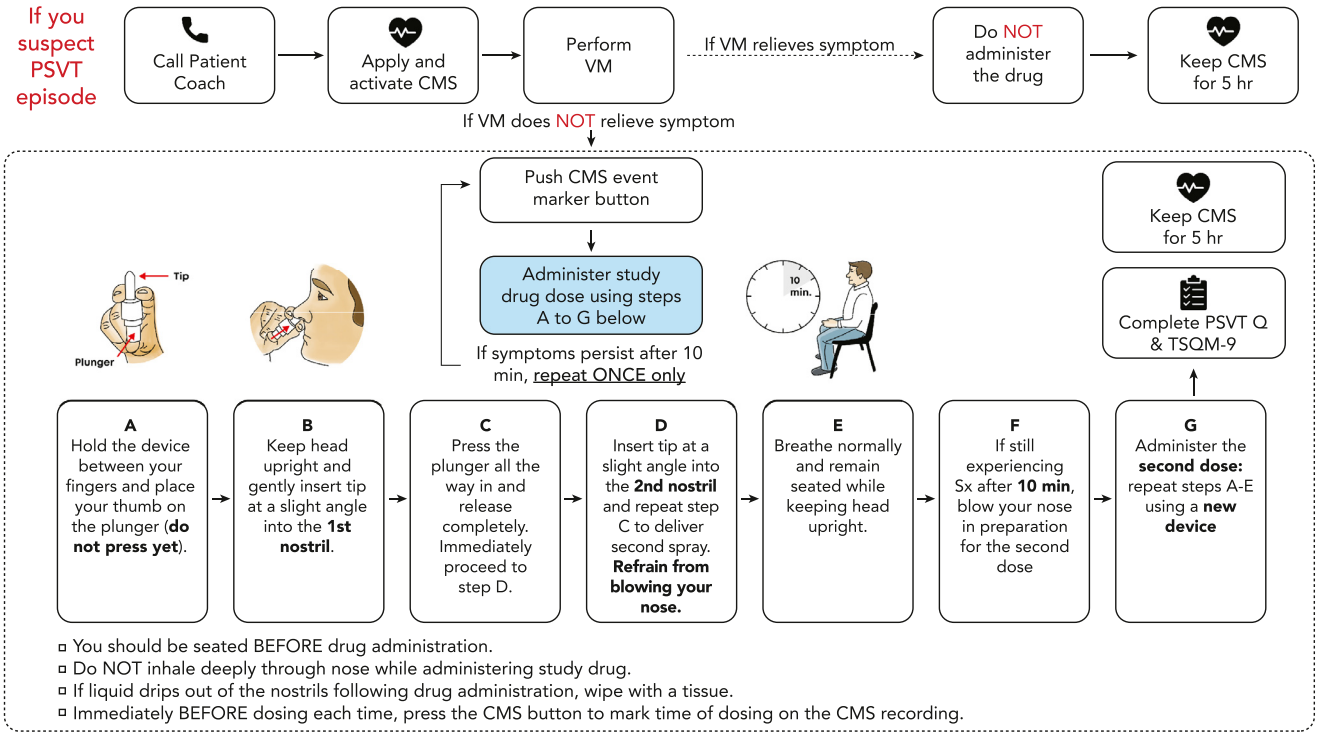
Final study visit

A final study visit will occur at the study site within 14 days after a patient self-administers study drug during the open-label treatment or under any of the following circumstances (nonexhaustive): test dose failure, self-administration of study drug, initiation of prohibited medication, withdrawal of consent, or sponsor termination of the study.

Vital signs

Vital signs (ie, SBP, DBP, and HR) will be obtained at the screening visit, the test dose randomization visit, the randomized treatment follow-up visit, and the final study visit.

Figure 2



Study procedures to guide patients when they experience a PSVT event in a nonmedically supervised setting. CMS, cardiac monitoring system; PSVT, paroxysmal supraventricular tachycardia; PSVT Q, PSVT symptoms questionnaire; Sx, symptoms; TSQM-9, 9-item *Treatment Satisfaction Questionnaire for Medication*; VM, vagal maneuver.

At the test dose randomization visit, vital signs will be obtained after at least a 5-minute rest in a seated position within 10 minutes before test dose administration. Following the etripamil administration, vital signs will be obtained every 5 minutes for 45 minutes. Additional vital signs will be obtained if the patient reports any symptoms potentially related to a drop in blood pressure.

Electrocardiograms

A 12-lead ECG will be performed at the screening visit, the test dose randomization visit, and the final study visit. During the treatment phase of the study, perceived PSVT and its termination will be evaluated by an independent AC based on the CMS recordings. The cardiac monitoring core laboratory will send the investigator summary reports of the 45-minute CMS recordings from the test dose before randomization and the 5-hour recordings from the randomized treatment and open-label treatment phases before proceeding to the open-label treatment phase or the final study visit, respectively.

Physical examinations

A physical examination will be performed at the screening visit and the final study visit. Body height and weight will be measured at the screening visit.

Safety assessments

The DSMC will regularly review accumulating safety data to detect any safety issues related to the study drug or protocol procedures involved in the patient's management of PSVT. The committee will be entitled to request a review of unblinded safety data.

Vital signs (ie, SBP, DBP, and HR), arrhythmia, conduction disorders on the ECGs, and clinical AEs will be recorded during the etripamil test dose period and reported in the overall safety population. These variables will be reported in the preidentified relevant subgroups of patients (eg, aged >70 years, aged 60-69 years receiving concomitant beta-blockers or calcium channel blockers, or aged 60-69 years with a preexisting first-degree AV block) for predefined subgroup analyses. Blood samples for safety laboratory testing (hematology, chemistry, and serum pregnancy test for females of childbearing potential) will be collected during the final study visit. A full schedule of procedures is outlined in Supplemental Table I.

Adjudication of PSVT confirmation and termination

The AC is composed of at least 5 cardiac electrophysiologists independent of the sponsor. The AC defines "true" PSVT as SVT with a rate >100 bpm that excludes sinus tachycardia, atrial fibrillation, atrial flutter, or atrial tachycardia based on their study-drug blinded review of CMS recordings. Recordings from each episode from each patient who assesses symptoms as being caused by PSVT will be reviewed by at least 2 AC members for the presence of true PSVT. The AC identifies the time(s) of study drug administration, presence of PSVT at the time of drug administration and subsequent termination (sinus rhythm for at least 30 seconds), the time between study drug administration and PSVT termination if applicable, and time of a successful medical intervention (eg, use of IV adenosine in a medical care facility), or if termination is not observed within 5 hours. The AC will also review the secondary ECG safety end points (ie, arrhythmia and conduction disorders).

The conclusions of the AC will be used in the primary and secondary analyses. Any bias will be limited by the adjudicators being fully blinded to the patient identifiers and study treatment. If the 2 adjudications by AC members are not consistent, the case will be reviewed by the AC committee, including the chairperson, and resolved by a majority vote.

Effect size and sample size

The sample size was calculated based on internal modeling of data from the NODE-301 study in which the Kaplan-Meier probability of conversion to sinus rhythm within 30 minutes was 54% in the etripamil group compared with 35% in the placebo group.[11] Patients in the etripamil group converted more rapidly (32% converted vs 14%) at 10 minutes. A total sample size of 180 patients with a positively adjudicated PSVT event treated with a randomized study drug at 1:1 (etripamil: placebo) will provide at least 90% power to detect a significant treatment difference for the primary end point at a 2-sided significance level of 0.05 using log-rank tests.

As RAPID is an event-driven study, it is anticipated that at least 500 patients may need to be randomized to accrue a sufficient number of patients experiencing an episode of PSVT for the primary analysis of the efficacy population. As of the date of manuscript submission, >500 patients have been randomized. Enrollment will continue until the required prespecified number of 180 positively adjudicated PSVT events is reached.

Analysis populations

The efficacy population includes all randomized patients who use the study drug at the time of a positively adjudicated AV nodal-dependent PSVT event. This population does not include patients who take the study drug for negatively adjudicated PSVT. The patients will be included in the treatment arm in which they are randomized.

The modified intent-to-treat population includes all randomized patients who take the randomized study drug for perceived PSVT. The patients will be included in the treatment arm in which they were randomized.

The test-dose-only population includes all patients who receive the test dose of etripamil as 2 × 70 mg doses 10 minutes apart but do not self-administer the randomized drug.

The safety population includes all randomized patients who take the randomized study drug for perceived PSVT.

The overall safety population includes all patients who receive the drug, ie, the safety population and the test-dose-only population combined.

Ethics

This clinical study complies with the Declaration of Helsinki, International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and applicable local regulatory requirements. The institutional review board or institutional ethics committee (IRB and IEC, respectively) will review all relevant study documentation to safeguard patients' rights, safety, and well-being. The study will be conducted only at sites where IRB/IEC approval has been obtained. All patients will undergo an informed consent process, including signing the study's extensive informed consent form, before having any study-specific procedures. This study is registered at www.ClinicalTrials.gov with unique identifier NCT03464019.

Results

The results of this pivotal trial will be communicated at scientific/medical conferences and in peer-reviewed publications and used in drug applications made to regulatory agencies, including the US Food and Drug Administration, for commercial approval of etripamil as a patient-administered option for PSVT termination outside of the health care setting.

Discussion

Etripamil is a fast-acting, nondihydropyridine, L-type calcium channel blocker developed to fill this unmet medical need for safe and reliable medically unsupervised therapy. Its intranasal route of delivery provides rapid onset of action. The RAPID study allows patients an option to enhance exposure to etripamil by self-administering a second etripamil 70 mg dose 10 minutes after the first one if symptoms of PSVT persist. It is hypothesized that this new repeated-dose drug regimen will significantly improve the pharmacodynamic activity of etripamil for acute PSVT termination without a decline in blood pressure observed in some cases in the phase 2 trial when a single higher dose was administered.

An approved, safe, fast-acting drug that can be self-administered on-demand without medical supervision to rapidly terminate acute PSVT is currently lacking. Such a drug could shorten the time to arrhythmia termination, reduce patient symptoms and anxiety, and decrease health care costs. This therapy would allow patients to self-manage their PSVT, giving them control of their health and potentially avoiding urgent reliance on the health care system. It would also give patients and their health care providers an additional treatment option for managing PSVT that is currently limited to no treatment, chronic oral medical therapy, or invasive catheter ablation for PSVT.

Limitations

The lack of a prespecified time after PSVT initiation when study drug must be taken could influence the conversion rate and the time to conversion in each group, although patients are encouraged to self-administer early. Due to some of the more involved aspects of the study, such as the requirement to complete a supervised test dose and the use of a CMS paired to a smartphone application, the study population may not be fully representative of the general population with AVNRT or orthodromic AVRT lasting 20 minutes or longer. Additionally, the contraception requirement may further select the study population. The outcomes of this study rest on effective patient education and adherence to the study protocols, which may be challenging for some patients. The availability of telephone coach guidance proved helpful to patients in the prior NODE-301 study.

Conclusions

The RAPID study investigates whether patients can self-administer etripamil in a medically unsupervised setting to convert PSVT to sinus rhythm with superiority versus placebo and with an acceptable safety profile. A successful RAPID pivotal study outcome carries the promise for etripamil nasal spray to change the treatment paradigm for the outpatient treatment of PSVT.

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Conflict of interest

Silvia Shardonofsky, Douglas Wight, and Francis Plat are salaried employees of Milestone Pharmaceuticals. A. John Camm and Philip T. Sager have received honoraria as consultants for Milestone Pharmaceuticals. Philip T. Sager also holds equity in Milestone Pharmaceuticals. Bruce S. Stambler and Michael Chen received compensation as investigators and or/consultants from Milestone Pharmaceuticals.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.06.005.

CRediT authorship contribution statement

Bruce S. Stambler: Conceptualization, Methodology, Supervision, Writing – review & editing. **Francis Plat:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Philip T. Sager:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Veronica Lubkov:** Visualization, Writing – review & editing. **Silvia Shardonofsky:** Supervision, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Douglas Wight:** Data curation, Resources, Writing – review & editing. **Michael Chen:** Methodology, Software, Writing – review & editing. **A. John Camm:** Conceptualization, Methodology, Supervision, Writing – review & editing.

References

1. Delacrétaz E. Clinical practice. Supraventricular tachycardia. N Engl J Med 2006;354(10):1039–51.
2. Issa ZF, Miller JM, Zipes DP. Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2012.
3. Saksena S, Bharati S, Chen S, et al. Chapter 14. Paroxysmal supraventricular tachycardias and the preexcitation syndromes. Cardiac rhythms and arrhythmias. Electrophysiological disorders of the heart. London, UK: Churchill Livingstone; 2005. p. 249–81.
4. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients with Supraventricular Tachycardia: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in Circulation. 2016;134(11):e234-5]. Circulation 2016;133:e506–74.
5. Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. Circulation 2003;107:1096–9.
6. Ip JE, Wight D, Seng Yue C, et al. Pharmacokinetics and pharmacodynamics of etripamil, an intranasally administered, fast-acting, non-dihydropyridine calcium channel blocker. Manuscript in preparation.
7. Stambler BS, Dorian P, Sager PT, et al. Etripamil nasal spray for rapid conversion of supraventricular tachycardia to sinus rhythm. J Am Coll Cardiol 2018;72:489–97.
8. Stambler BS, Plat F, Sager PT, et al. Etripamil nasal spray for acute termination of spontaneous episodes of paroxysmal supraventricular tachycardia. NODE-301 trial. Heart Rhythm 2020;17:1200 Abstract D-LBCT01-01.
9. E9(R1) Statistical principles for clinical trials: Addendum: Estimands and sensitivity analysis in clinical trials. 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical. Accessed May 26, 2022.
10. Bharmal M, Payne K, Atkinson MJ, et al. Validation of an abbreviated treatment satisfaction questionnaire for medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009;7:36.
11. Stambler BS, Plat F, Sager PT, et al. The first randomized, multicenter, placebo-controlled study of self-administered 2 intranasal etripamil for acute conversion of spontaneous paroxysmal supraventricular 3 tachycardia (NODE-301), *Circulation: Arrhythmia and Electrophysiology*, Submitted for publication.