Rationale and design of the NODE-303 study: evaluating the safety of symptom-prompted, self-administered etripamil for paroxysmal supraventricular tachycardia episodes in real-world settings

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Background Paroxysmal supraventricular tachycardia (PSVT) is a common episodic arrhythmia characterized by unpredictable onset and burdensome symptoms including palpitations, dizziness, chest pain, distress, and shortness of breath. Treatment of acute episodes of PSVT in the clinical setting consists of intravenous adenosine, beta-blockers, and calcium channel blockers (CCBs). Etripamil is an intranasally self-administered L-type CCB in development for acute treatment of AV-nodal dependent PSVT in a nonmedical supervised setting.

Methods This paper summarizes the rationale and study design of NODE-303 that will assess the efficacy and safety of etripamil. In the randomized, double-blinded, placebo-controlled, Phase 3 RAPID trial, etripamil was superior to placebo in the conversion of single PSVT episodes by 30 minutes post initial dose when administered in the nonhealthcare setting; this study required a mandatory and observed test dosing prior to randomization. The primary objective of NODE-303 is to evaluate the safety of symptom-prompted, self-administered etripamil for multiple PSVT episodes in real-world settings, without the need for test dosing prior to first use during PSVT. Secondary endpoints include efficacy and disease burden. Upon perceiving a PSVT episode, the patient applies an electrocardiographic monitor, performs a vagal maneuver, and, if the vagal maneuver is unsuccessful, self-administers etripamil 70 mg, with an optional repeat dose if symptoms do not resolve within 10 minutes after the first dose. A patient may treat up to four PSVT episodes during the study. Adverse events are recorded as treatment-emergent if they occur within 24 hours after the administration of etripamil.

Results Efficacy endpoints include time to conversion to sinus rhythm within 30 and 60 minutes after etripamil administration, and the proportion of patients who convert at 3, 5, 10, 20, 30, and 60 minutes. Patient-reported outcomes are captured by the Brief Illness Perception Questionnaire, the Cardiac Anxiety Questionnaire, the Short Form Health Survey 36, the Treatment Satisfaction Questionnaire for Medication and a PSVT survey.

Conclusions Overall, these data will support the development of a potentially paradigm-changing long-term management strategy for recurrent PSVT. (Am Heart J 2024;270:55–61.)

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Background

Paroxysmal supraventricular tachycardia (PSVT) is an arrhythmia characterized by recurrent episodes of regular, rapid heartbeats[1] that start and stop abruptly.[2,3] Symptoms can be severe and distressing, including palpitations, weakness or fatigue, shortness of breath, dizziness, syncope, anxiety, and chest pain.[3-5] PSVT is cate-

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gorized mechanistically into atrioventricular (AV) nodal reentry tachycardia (AVNRT), AV reentrant tachycardia (AVRT), and atrial tachycardia. Self-treatment of acute episodes of PSVT outside of the clinical setting consists of vagal maneuvers,[3,4] but success rates are low.[6,7] Pharmacological treatments available in the clinical setting such as the emergency department include intravenous (IV) adenosine, calcium channel blockers (CCBs), and beta-blockers.[3] Oral formulations of CCBs and beta-blockers may be useful, but evidence is limited regarding their efficacy and safety for acute episodes of PSVT.[8,9] Consequently, a substantial unmet need exists for effective and rapidly acting treatment options for acute episodes of PSVT outside of the clinical setting.

Etripamil is a fast-acting intranasal L-type CCB currently under investigation for self-treatment of acute AV-nodal dependent PSVT episodes outside the clinical setting.[7,10,11] It is rapidly absorbed by the nasal mucosa, with a time to maximum plasma concentration of approximately 7 minutes after a 70 mg dose.[10] NODE-301 Part 1 study evaluated a single-dose regimen of etripamil 70 mg for the treatment of PSVT outside of the hospital setting, and although the results confirmed the safety of etripamil, the primary efficacy endpoint of conversion of PSVT at 5 hours was not met.[11] The RAPID study, also known as NODE-301 Part 2, evaluated a repeat dose regimen of etripamil 70 mg, with the second dose administered 10 minutes after the first dose if symptoms persisted, and the primary efficacy endpoint was conversion of PSVT to SR at 30 minutes.[12] The results of the RAPID study demonstrated that etripamil was superior to placebo, and the drug was observed to be well-tolerated with only mild to moderate, transient, localized treatment-emergent adverse events.[7]

Although prior clinical studies have established the efficacy and safety of etripamil administered during a single episode of PSVT, further data are needed to evaluate the potential safety and efficacy of etripamil for the treatment of *multiple* episodes of PSVT in real-world settings. Here, we report the study design of the NODE-303 study, which was intended to evaluate the safety of etripamil in a real-world type setting, with broader inclusion criteria, and to further assess the safety and efficacy of the optional, repeat-dose regimen (NCT04072835).

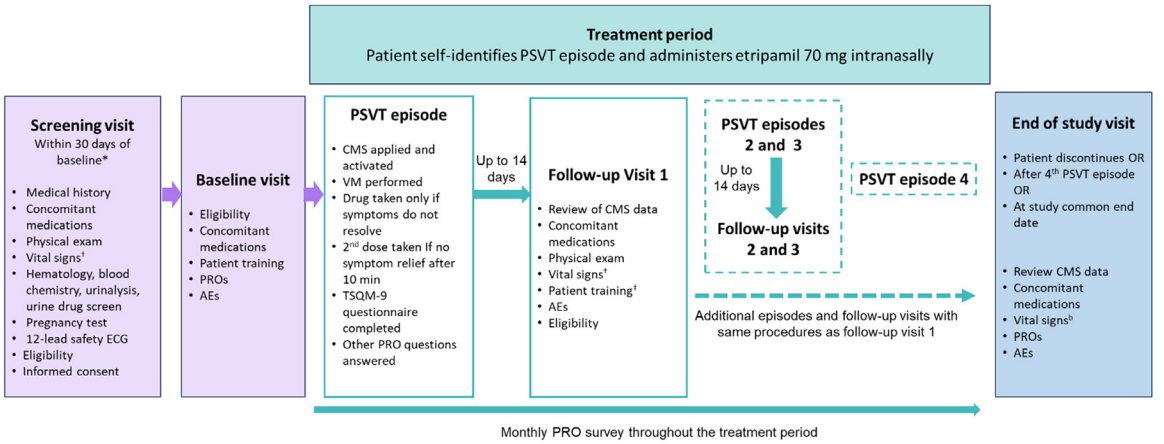
Materials and methods

General study design and conduct

NODE-303 is an event-driven, multicenter, multinational, open-label, single-arm phase 3 study, conducted at 148 sites in the USA, Canada, Argentina, Brazil, and Colombia, with a study start date of September 23, 2019. The study design and visit schedule are summarized in Figure 1 and Supplementary Table 1.

Patients are provided with a precordial ambulatory cardiac monitoring system (CMS) that collects continuous electrocardiographic (ECG) data during symptomatic episodes perceived as PSVT by the patient. At PSVT symptom onset, a patient applies and activates their ECG CMS recording, performs a vagal maneuver they were previously trained in, and, if the vagal maneuver is ineffective, the patient self-administers a 70 mg dose of

Figure 1



Overview of NODE-303 study design. *A protocol amendment in February 2021 permits the screening visit and the baseline visit to occur on the same day in order to reduce the number of site visits during the COVID-19 pandemic. †Vital signs include blood pressure, heart rate, and weight at the screening visit only. ‡At follow-up visits, sites retrain patients on study procedures or devices. *AE*, adverse event; *CMS*, cardiac monitoring system; *ECG*, electrocardiogram; *exam*, examination; *PRO*, patient-reported outcome; *PSVT*, paroxysmal supraventricular tachycardia; *TSQM-9*, Treatment Satisfaction Questionnaire for Medication 9; *VM*, vagal maneuver.

etripamil from a preloaded nasal spray device, using one spray in each nostril (100 μL per spray). No specific VM technique was recommended at the baseline visit and left to the physician-investigator's discretion. Approximately 2 years after the start of the study, a protocol amendment allowed an optional, repeat dose of etripamil 70 mg if symptoms persisted for 10 minutes after the first dose. Time of etripamil administration is recorded on the CMS. If symptoms persist up to 30 minutes after the first dose of etripamil, the patient may seek medical attention. The CMS device acquires ECG data for at least one hour after etripamil administration.

Up to 14 days after each episode of patient-perceived, etripamil-treated PSVT, there is a follow-up visit for the investigator to evaluate the results of etripamil treatment and check the patient's eligibility to continue in the study according to the criteria of the most current protocol; participants are slated to complete the latest version of the informed consent. Follow-up procedures include reviewing the CMS data for quality and adherence to the protocol, and for the determination of AEs and other safety assessments. The investigator collects any AE data during the treatment period, records concomitant medications and evaluates any additional medical interventions (including vagal maneuvers) the patient has received for PSVT episodes during the treatment period. Patient-reported outcome (PRO) questionnaires are reviewed for quality and adherence. Vital signs and weight are measured at each follow-up visit. Patients are given any additional training needed on study procedures or devices. Two study-drug kits are provided at the baseline visit and follow-up visits if the patient remains eligible for continuation in the study.

Patients can self-treat with etripamil for up to four perceived PSVT episodes in the treatment period. After a fourth perceived PSVT episode, the patient attends a final study visit. A final study visit is also required for patients who discontinue or withdraw from the study, and for patients who complete the overall study once the common study end date is announced, which depends upon the accrual rate of unique patients with PSVT episodes. Final study visits procedures are similar to those of follow-up visits, with the exclusion of patient training and eligibility checking.

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Central review of CMS recordings

CMS ECG recordings were reviewed centrally by a team of cardiologists, electrophysiologists, and cardiac nurse practitioners. Unclear cases were sent to external electrophysiologists for their review; this was done to confirm the episode was a "true" AV-nodal dependent PSVT (AVNRT or AVRT) event or a non-PSVT rhythm (Supplementary Materials). Options for the diagnosis before administration of study drug are SR, AV-nodal dependent PSVT, atrial fibrillation, atrial flutter, and atrial tachycardia. The central review determines whether there is conversion to SR maintained for >30 seconds within 1 hour of the initial drug dose. Safety endpoints for identification within the 1-hour timeframe are tachyarrhythmias lasting for >30 seconds, AV block, and bradyarrhythmias (Supplementary Materials).

Ethical conduct

The NODE-303 protocol complies with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and applicable local regulatory requirements. All study sites are required to have the approval of the Institutional Review Board/Ethics Committee. Written informed consent from patients is required before enrollment.

Eligibility

There are broader inclusion criteria than prior etripamil phase 2/3 studies and they include: a diagnosis of PSVT by a medical professional and a patient report of at least one previous episode of symptomatic PSVT, suspected to be AV-nodal dependent; age $\geq$ 18 years; women of childbearing potential must be willing to use at least one form of effective contraception method during the study; and patients must agree to participate in the study for at least 1 episode of PSVT. ECG documentation of prior PSVT was not required for study enrollment. NODE 303 allowed for patients with a history of atrial fibrillation (AF) or atrial flutter in addition to PSVT. Patients might treat up to 4 perceived PSVT episodes during their participation in the study. Full eligibility criteria are provided in the Supplementary Materials.

Exclusion criteria include a history of only atrial arrhythmias not involving the AV node as part of the tachycardia circuit, a history of syncope with an arrhythmic etiology at any time, unexplained syncope in the previous 5 years, acute coronary syndrome, or stroke within 6 months of screening, and a history of allergic reaction to verapamil. History or evidence of ventricular preexcitation on 12-lead ECG, second- or third-degree AV block, or severe ventricular arrhythmia are also exclusion criteria. Patients cannot have symptoms of heart failure (New York Heart Associations Class II to IV), systolic blood pressure < 90 mmHg at any visit, severe symptoms of hypotension during PSVT episodes, or evidence of renal dysfunction determined by an estimated glomerular filtration rate at screening. Patients are excluded if they are currently taking digoxin, or any Class I or III antiarrhythmic drug, have previously taken etripamil in a clinical trial, have participated in a clinical

trial of other investigative products in the last 30 days, or are pregnant or breastfeeding. Patients were permitted to take a concomitant beta blocker or CCB during the trial.

Study endpoints

As an open-label study, the primary endpoint of NODE-303 is to evaluate the safety of self-administered etripamil for PSVT episodes outside the clinical setting. The safety variables include clinical adverse events, adverse events of special interest (such as hypotension or syncope), and any arrhythmias detected within 1-hour ECG CMS recordings (eg, AV block, conversion pauses > 3 seconds).

Secondary efficacy endpoints include time to conversion of PSVT to SR for ≥ 30 seconds after etripamil administration to assess speed of response, and the proportion of patients who convert 3, 5, 10, 20, 30, and 60 minutes after etripamil administration to inform successful rate of conversion at specific time intervals; frequency of additional medical interventions to treat PSVT, such as emergency department visits, hospital visits and admissions; vagal maneuver outcome, concomitant medication use, and ablations. Changes in the use of oral beta-blockers and CCBs are analyzed over the duration of the study.

Secondary endpoints relating to patients' quality of life and symptoms are captured by the Brief Illness Perception Questionnaire (BIPQ), the Cardiac Anxiety Questionnaire (CAQ) and the Short Form Health Survey 36 (SF-36) questionnaire, which are completed at baseline and every 6 months thereafter, and a PSVT survey completed at baseline and then monthly. Soon after each PSVT episode has resolved, patients complete a per-episode PSVT survey (Supplementary Materials) and, if they have taken etripamil, the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

Exploratory endpoints include the frequency of patient-reported PSVT episodes and their characteristics, and use of etripamil, captured by questions in the monthly and per-episode PSVT surveys. Additionally, number and frequency of perceived and verified PSVT episodes, either treated or resolved by vagal maneuvers, are analyzed from the data recorded in the CMS and at site visits.

Safety monitoring is conducted throughout the study from the time of informed consent. New AEs are recorded at every visit and followed for up to 30 days after the patient's last dose of etripamil in the study. An AE is defined as treatment emergent (TEAE) if the first onset or worsening occurs after study drug administration, the AE is considered related to the study drug, and the AE has a start date/time up to 24 hours after study drug administration. A serious AE (SAE) is defined as an AE that results in death, is considered life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability; is a congenital anomaly, or is considered to be an important medical event. Serious adverse events are followed until satisfactory resolution, even after database lock. Adverse events of special interest if occurring within 24 hours after administration of etripamil, are tachyarrhythmias, bradyarrhythmias, AV block, hypotension and/or syncope. Adverse events are coded according to MedRA v 22.0 and classified by clinical severity (mild, moderate, or severe) and seriousness (SAE or nonserious AE). The relationship of an AE to the study drug (not, unlikely, possibly, probably, or definitely related) is a clinical decision based on the information available when the event is reported. Other safety variables are vital signs measured at the screening visit, follow-up visits and the final study visit, and arrhythmias and conduction disorders detected on surface ECG CMS recordings.

Technology: electrocardiographic cardiac monitoring system device and software application for patient-reported outcomes

The ECG CMS device is a wireless Preventice Body Guardian Mini (Preventice Solutions, Boston Scientific, Boston, USA) for ambulatory ECG CMS recording. This device replaced the original BioTel ePatch (BioTelemetry Inc., Johanneshov, Sweden) after a protocol amendment. The patient is required to apply and activate the device to their chest in the event of acute symptoms of a PSVT episode. At the follow-up visit, study personnel upload ECG data from the CMS device to the CMS service provider's online site for an automated analysis subsequently reviewed by the study's expert medical team.

All patient-reported outcomes are administered by a single application on a smartphone or tablet in the "home setting,'' except for baseline surveys conducted at the study site. Internet connectivity is not required during completion of the questionnaires; the responses are automatically uploaded when the phone or tablet next has an online connection. The PRO application includes a walk-through of procedures for the patient to follow, designed for use during a PSVT episode.

Full training in using the CMS and the PRO device is given at the baseline visit and follow-up visits if necessary.

Protocol amendments

The study was initiated in September 2019. In March 2021, a protocol amendment implemented the optional repeat dose regimen of etripamil if symptoms persisted 10 minutes after the first dose. This followed demonstration of the safety of this optional repeat dose regimen in blinded examination of RAPID study data and phase 1 clinical data.

The change in CMS device from a BioTel ePatch to a Preventice Body Guardian Mini was formalized by a

protocol amendment in February 2021 due to the relatively high proportion of episodes with no data, uninterpretable data, artifacts, or duplicate data with the former device. However, this version of the protocol was not implemented at any site and the subsequent version of the protocol was implemented in March 2021.

Sample-size determination and statistical analyses

NODE-303 is designed to complete once the safety database for the etripamil clinical development program has sufficient documented self-administrations of etripamil to meet regulatory requirements (1000 to 1500 patients across all studies), estimated to entail enrollment of up to 3000 patients to achieve this goal within 24 months.

All patients enrolled will be included in the overall population for analysis. Patients who self-administer study drug for at least one episode of perceived PSVT will be included in the safety population. The efficacy population includes patients who self-administer study drug for an event confirmed as PSVT of apparent AV-nodal dependent mechanism and not another rhythm (eg, SR, sinus tachycardia, AF/atrial tachycardia/atrial flutter).

Efficacy analyses will be performed on the efficacy population. Comparative analyses may be conducted on data available from patients in the safety population. Efficacy endpoint analyses will include summaries, both over time and as comparisons between the efficacy population and the safety populations for the endpoints: medical interventions, patient quality of life, treatment satisfaction, and PSVT episode characteristics.

Summary descriptive statistics will be generated for demographic and baseline clinical characteristics, exposure to etripamil, efficacy endpoints, and safety findings. Categorical variables summary statistics will include the number and percentage of patients in each category. Continuous variables will be given as mean, standard deviation, median, minimum, and maximum. Two-sided 95% confidence intervals of means and/or percentages will also be calculated for the number of medical interventions to terminate episodes of PSVT, the number of hospital visits, and changes in concomitant PSVT medications and PRO scores, and TSQM-9 scores. Time to conversion to SR will be estimated by Kaplan-Meier analysis. The analyses will include only observed data with no imputation for missing data. There will be no formal hypothesis testing.

Results

NODE-303 commenced on September 23, 2019, and completed on February 24, 2023 (database lock 26 February 2023, with an overall population of 1,116 patients) with 148 study sites having screened at least 1 patient. The results of the trial will be communicated at scientific conferences and in peer-reviewed publications.

Discussion

NODE-303 investigates the efficacy and safety of self-administered intranasal etripamil in a medically unsupervised setting, over multiple episodes and without the need for a test dose prior to randomization. In previous studies, patients received a single dose of etripamil 70 mg during sinus rhythm as a test dose before they were randomized to a treatment arm. In NODE-301 part 1,10/431 (2.3%) patients did not tolerate the test dose.[11] Further, in RAPID only 9/706 (1.3%) patients did not tolerate etripamil.[7] As such, the NODE-303 study design removes the test dose of etripamil during sinus rhythm at the time of enrollment, which may reflect the future potential real-world use of this medication.

Efficacy of conversion of PSVT to SR will be assessed, along with the optional repeat dose regimen if PSVT symptoms persist 10 minutes after the first dose. NODE-303 will provide essential additional data to the safety database of etripamil in support of the full investigation of self-administered use of etripamil for multiple PSVT episodes outside the healthcare setting. The event-driven design of NODE-303 should ensure the capture of sufficient data for on-demand acute treatment of episodic events of unpredictable frequency. Secondary efficacy endpoints will contribute to the evaluation of benefit-risk profile of etripamil using a symptom-prompted, optional repeat dose regimen.

Additional contributions from the NODE-303 study design include the use of a panel of validated PROs and survey questions drafted specifically for the study. The unpredictable nature of PSVT and alarming symptoms can have a significant negative effect on patients' quality of life. Patients with symptomatic cardiac arrhythmias report impacts on daily activities, work, and family life, often generating fear and anxiety.[13] The validated PROs in NODE-303 encompass a wide range of concepts. The BIPQ assesses cognitive and emotional representations of illness,[14,15] the CAQ measures anxiety related to cardiac functioning in the domains of fear, avoidance and heart-focused attention,[16,17] and SF-36 is one of the most widely used tools assessing quality of life in multiple domains of physical and mental health.[18] The PSVT survey questions will also monitor symptom control with etripamil and help understand the impact of patients' active engagement in their own care on symptom control.

A potential limitation of NODE-303 is the dependence of study outcomes on effective patient education and adherence to study protocols, which may be challenging for some patients. For example, gaining familiarity with the ECG CMS device and PRO application may be more difficult for older patients. These risks will be mitigated by training that will take place prior to enrollment followed by retraining if needed (both protocol-specified). The role of patient anxiety and symptom sensitivity may result in potential non-PSVT events being

identified incorrectly by the patient. The study procedures account for this potential occurrence by including both metrics of anxiety and device confirmations and physician review postevent. In summary, NODE-303 will provide data on the efficacy and safety of etripamil in an interventional trial designed to approximate a real-world setting. As part of the body of evidence from the etripamil clinical study program, these data have the potential to help transform the treatment paradigm for outpatient treatment of PSVT, empowering patients to treat their episodes outside of a healthcare setting, and potentially reduce the need for additional medical interventions and emergency department visits.

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Conflicts of interest

Sarah Omodele, Silvia Shardonofsky and David B. Bharucha are employees of Milestone Pharmaceuticals. Bruce S. Stambler received compensation as a consultant for Milestone Pharmaceuticals. Peter Noseworthy declares no conflict of interest. Hanh Bui declares no conflict of interest. A John Camm received compensation as a consultant for Milestone Pharmaceuticals; grants and personal fees from Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, and Daiichi Sankyo; personal fees from Medtronic, Boston Scientific, Menarini, and Biotronik; and support from Anthos, Sanofi, Abbott, GlaxoSmithKline, and Johnson & Johnson. Benoit Coutu declares no conflict of interest. Maria Leonor Parody declares no conflict of interest. Samuel F Sears received compensation from Medtronic and Abbott as a consultant; he also received speaker compensation from Medtronic, Zoll, and Biotronik; serves as a quality-of-life consultant for Thyve, Tenaya, and Milestone Pharmaceutical. Narendra Singh declares no conflict of interest. Juan Agudelo Uribe declares no conflict of interest. John Vyselaar declares no conflict of interest.

CRediT authorship contribution statement

James E Ip: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Hanh Bui:** Investigation, Writing – review & editing, Resources, Conceptualization. **A John Camm:** Conceptualization, Writing – review & editing. **Benoit Coutu:** Writing – review & editing, Conceptualization, Investigation, Resources. **Maria Leonor Parody:** Investigation, Resources, Writing – review & editing. **Samuel F Sears:** Conceptualization, Methodology, Writing – review & editing. **Narendra Singh:** Investigation, Resources, Writing – review & editing, Conceptualization. **Juan Agudelo Uribe:** Investigation, Resources, Writing – review & editing, Conceptualization. **John Vyselaar:** Investigation, Resources, Writing – review & editing, Conceptualization. **Sarah Omodele:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Silvia Shardonofsky:** Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **David B. Bharucha:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Project administration, Visualization. **Bruce Stambler:** Investigation, Resources, Writing – original draft, Writing – review & editing.

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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.2024.01.007.

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