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Etripamil Nasal Spray for Recurrent Paroxysmal Supraventricular Tachycardia Conversion: Results From the NODE-303 Open-Label Study

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ABSTRACT

Introduction: Etripamil is a fast-acting intranasally self-administered calcium-channel blocker developed for termination of paroxysmal supraventricular tachycardia (PSVT). Prior studies have demonstrated safety and efficacy of etripamil for PSVT termination following an initial medically supervised test dose during sinus rhythm. NODE-303 is an open-label, single-arm study that evaluated etripamil for multiple, at-home PSVT episodes, without test dose before first use.

Methods: Patients applied an ECG monitor at symptom onset and self-administered etripamil (70 mg) if a vagal maneuver was unsuccessful. ECG monitoring occurred for ≥ 1 h following study drug administration. A repeat 70-mg dose was introduced during the study for symptoms persisting 10 min after the first dose. Safety measures included treatment-emergent adverse events (TEAEs) and ECG arrhythmia-surveillance. Efficacy measures were captured for PSVT termination during treatment of each of the multiple episodes.

Results: 1054 perceived PSVT episodes were etripamil-treated in 503 of 1116 patients enrolled. TEAEs within 24 h were mostly mild or moderate and localized: 30.2% of patients experienced nasal discomfort, nasal congestion (13.9%), rhinorrhea (13.1%), epistaxis (7.4%). TEAE frequencies decreased across multiple PSVT episodes and were similar for single versus repeat doses. For first PSVT episodes, 70.5% of patients converted to sinus rhythm by 60 min post etripamil (median time to conversion = 18.3 min [14.2–25.6]). Conversion in earlier episodes was consistently predictive of conversion in subsequent episodes.

Conclusions: Etripamil nasal spray self-administered in a real-world setting was well tolerated, effective, and had a consistent safety profile as a single- or repeat-dose regimen across multiple PSVT episodes.

Trial Registration: ClinicalTrials.gov NCT04072835

Abbreviations: AESI, adverse event of special interest; AV, atrioventricular; CCB, calcium channel blocker; CMS, cardiac monitoring system; ECG, electrocardiogram; NS, nasal spray; PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm; TEAE, treatment emergent adverse event; TTC, time to conversion.

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1 | Introduction

Paroxysmal supraventricular tachycardia (PSVT) often results in significant symptoms and can have a negative impact on physical, social, and psychological aspects of health-related quality of life [3]. In addition, PSVT is associated with significant healthcare resource utilization, including urgent care and emergency-department visits [4]. Prevalence of symptomatic PSVT in the United States is ~333 per 100,000 persons, with higher rates in female patients [5].

Vagal maneuvers are not consistently successful in terminating PSVT, and despite modified techniques, their effectiveness can remain low [1, 6–9]. When vagal maneuvers are ineffective, sustained PSVT episodes require treatment with intravenous (IV) medications such as adenosine, beta-blockers or calcium channel blockers (CCB) to restore sinus rhythm [1, 2]. Although effective, these therapies must be administered by medical personnel. Orally administered CCBs, ß-blockers. and other antiarrhythmic drugs may be administered as a pill-in-pocket approach but have delayed onset of action, low success rates, and can be associated with serious adverse effects [10, 11]. Chronic use of oral medications for PSVT prophylaxis has inconsistent success and may be associated with adverse effects [12–15].

Etripamil is a non-dihydropyridine, L-type CCB in development for the treatment of atrioventricular (AV)-nodal-dependent PSVT and atrial fibrillation with a rapid ventricular rate (AF-RVR) [8, 17–21]. The nasal spray results in a short time to maximum plasma concentration (≤ 7 min), and a terminal half-life of ~2.5 h [17]. NODE-301 Part 1 (NCT03464019) was a randomized, double-blind study that evaluated a 70 mg dose of etripamil nasal spray, self-administered outside the healthcare setting, in patients with symptomatic PSVT. Analyses showed significant rates of conversion of PSVT to SR for etripamil treatment versus placebo (54% vs. 35%, respectively, by 30 min) [18]. The RAPID study (NODE-301 Part 2), evaluated a symptom-prompted, repeat-dose 70-mg regimen and demonstrated superior efficacy of etripamil vs placebo (64% vs. 31%; HR 2.62; 95% CI: 1.66–4.15; $p < 0.0001$) with a median time to conversion of 17.2 min vs. 53.5 min, respectively [8]. Etripamil was safe and well tolerated in NODE-301 studies; most adverse events (AEs) were localized to the administration site, mild or moderate, and transient, resolving without intervention [8, 19, 20]. Patients in NODE-301 studies had to pass a medically-supervised test dose of etripamil during sinus rhythm before randomization. In NODE-301 Part 1, 2.3% of patients, and in RAPID, 1.3%, did not proceed to randomization after the test dose [8, 19].

NODE-303 study was an open-label, Phase 3 safety study with the objectives of evaluating the safety and efficacy of etripamil, self-administered for up to 4 episodes of AV-nodal-dependent PSVT outside of the healthcare setting, and without the requirement of a prior test dose. Secondary objectives were to evaluate the safety and efficacy of etripamil when used for multiple PSVT episodes, and the impact of the drug on burdens of this arrhythmia such as patients seeking emergency care [21, 22].

2 | Methods

NODE-303 (NCT04072835) has previously been described [21, 22] and is summarized here.

2.1 | Overall Study Design and Patient Population

NODE-303 was an event-driven, multi-center, open-label, single-arm Phase 3 study, conducted at 148 clinical study sites in the United States, Canada, Argentina, Brazil, and Colombia. The trial was conducted between June 21, 2019, through February 24, 2023. Its end date was declared once the program's safety database had accrued more than 1000 patients with self-administration of etripamil.

NODE-303 assessed etripamil in a "real-world setting" -- there was no prior test dose requirement; compared to prior trials, inclusion criteria were broadened to include patients with comorbid atrial fibrillation (AF) or flutter; and assessments were performed over multiple episodes of PSVT (up to four). Self-administration of drug was prompted only by symptoms. During the treatment period, patients self-identified episodes of PSVT, applied an ECG cardiac monitoring system (CMS), performed a pre-trained vagal maneuver, and self-administered a single dose of etripamil 70 mg if the vagal maneuver was unsuccessful. The ECG CMS device was initially a wireless BioTel ePatch (BioTelemetry Inc., Johanneshov, Sweden) which, for technical improvement reasons was replaced by a Preventice Body Guardian Mini (Preventice Solutions, Boston Scientific, Boston, USA); and reflected in a protocol amendment. Approximately 21 months after the study started, the protocol was amended to allow a repeat 70-mg dose to be self-administered if symptoms persisted 10 min following the first dose (the 10-min interval was supported by Phase 1 and Phase 3 data [8, 17]). The CMS documented the time of etripamil administration and continuous ECG data for ≥ 1 h after administration. A questionnaire was completed by patients as soon as possible after perceived PSVT episodes.

To obtain sufficient data to assess safety across multiple episodes, a patient could self-administer etripamil for up to four perceived PSVT episodes. Patients attended a follow-up visit within 14 days after each drug-treated episode to record safety data and download ECG CMS and questionnaire data. Final study visits occurred upon completion or withdrawal from the study, including for a reason of treatment with ablation or reaching the maximum of four treated episodes; and could occur after < 4 episodes treated. The final visit included patients with 1, 2, 3 or 4 treated perceived PSVT episodes.

Eligibility criteria (see Supporting Information) included diagnosis of PSVT by a healthcare professional (HCP), which was determined to be SVT that included the AV node as a critical part of reentrant circuit. Appropriate documentation to support enrollment could include suspected AV-nodal-dependent SVT based on ECG, Holter study, ambulatory monitoring, or electrophysiology study; confirmed arrhythmia conversion or symptom resolution after vagal maneuver, adenosine, beta-blocker or CCB administration, or HCP documentation of

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prior PSVT. All treated episodes were evaluated via central ECG review to determine if they met protocol specified criteria and definitions. Patients were ≥ 18 years old and had ≥ 1 prior episode of sustained PSVT. Patients with histories of both PSVT and AF or atrial flutter were eligible. Women of child-bearing potential agreed to use contraception and discontinued if they planned to or became pregnant during the study. Key exclusion criteria included history of second- or third-degree AV block or severe ventricular arrhythmia, or evidence of ventricular pre-excitation, symptoms of heart failure Class II-IV, systolic blood pressure < 90 mmHg at any study visit, or symptoms of marked hypotension or syncope associated with a PSVT episode. Digoxin or a Class I or III antiarrhythmic drug had to be stopped at least 5 half-lives before etripamil administration, except oral amiodarone, which had to be discontinued 30 days before enrollment.

2.2 | Ethical Conduct

The study complied with the Declaration of Helsinki, the protocol was approved by the ethics committee of each site, and all patients provided informed written consent.

2.3 | Outcomes

Safety measures included AEs, vital signs, arrhythmias and conduction disorders detected on ECG or CMS recordings. A treatment-emergent adverse event (TEAE) was defined as an AE with an onset after administration of the study drug and recorded until the end of study participation. For conservatism, the definition of TEAE was expanded after database lock to include AEs that may have been patient-reported to occur as early as 12 h before drug administration to avoid under-reporting of adverse events. Additionally, a TEAE24h was defined as a TEAE starting or worsening ≤ 24 h after study drug receipt. A TEAE was classified as mild, moderate, or severe and drug-related if the investigator considered it possibly, probably, or definitely related to etripamil administration. Adverse events of special interest (AESI) were tachyarrhythmias, bradyarrhythmias, AV block, hypotension, and/or syncope (Supporting Information).

Efficacy measures were collected for secondary or exploratory endpoints, including time to conversion to SR after etripamil administration, proportions of patients converting to SR (maintained for ≥ 30 s) 30 min and 60 min after administration of etripamil, and emergency department visits to terminate episodes of PSVT (patient-reported). No formal, statistical hypothesis was tested. Changes to concomitant AV-nodal acting medications during the study were assessed. Patient-reported outcomes relating to symptoms, quality of life, and treatment satisfaction will be reported separately.

2.4 | Protocol Amendments

Protocol revisions were implemented ~21 months after NODE-303 commenced, including the option of a repeat 70-mg dose of etripamil 10 min after the first dose if PSVT symptoms persisted [21], and replacement of the BioTel CMS device with the Preventice device.

2.5 | Statistical Analysis

Summary descriptive statistics were compiled for data in the safety population, which comprised patients who received study drug. TEAEs were presented by MedDRA version 22 system organ class (SOC) and preferred term (PT).

The efficacy population was prospectively comprised of patients who received study drug for a confirmed episode of AV-nodal dependent PSVT. ECG CMS recordings were reviewed centrally by a team of cardiologists, electrophysiologists, and cardiovascular nurse practitioners to confirm AV-nodal dependent PSVT for each episode; to determine whether a patient had converted to SR within 1 h of etripamil administration and, if so, the elapsed time after drug administration was calculated and whether after 1 or 2 doses of etripamil were used was determined. Efficacy data are presented as summary descriptive statistics with 95% confidence intervals (CI). Time to conversion was estimated via Kaplan-Meier methods and conversion rates by 30 and 60 min after etripamil administration were estimated by SAS PROC LIFETEST. To determine the consistency and predictiveness of conversion to SR across multiple episodes, x^2-square tests were used.

3 | Results

3.1 | Study Populations

After screening 1342 patients, there were 1,116 patients enrolled, of whom 503 (45.1%) treated ≥ 1 perceived PSVT episode (Figure 1). Baseline patient characteristics in the safety and efficacy populations were similar: female 68.4% and 67.3%, respectively; white 82.9% and 85.9%, respectively; use of concomitant AV-nodal acting (ß-blocker or CCB), 70.6% and 66.7%, respectively; and using a non-dihydropyridine CCB, 18.3% and 21.5%, respectively (Table 1). There were small differences in the number of patient-reported PSVT episodes in the past year, and in visits to an arrhythmia clinic or hospital for PSVT since diagnosis, in the safety and efficacy populations.

In the safety population, 360 patients had consented to the single-dose regimen, and 216 to the optional repeat-dose regimen including those who re-consented after prior enrollment with the single-dose regimen. There were 503 patients in the safety population and 312 patients in the efficacy population (Figure 1). A patient not being included in the efficacy population was due to inadequate ECG CMS data or a recorded arrhythmia not being an AV-nodal-dependent PSVT (Table 2).

3.2 | PSVT Episodes

A total of 408 of 503 patients (81.1%) had ECG CMS recordings of ≥ 1 h duration. The study captured 1,054 etripamil-treated

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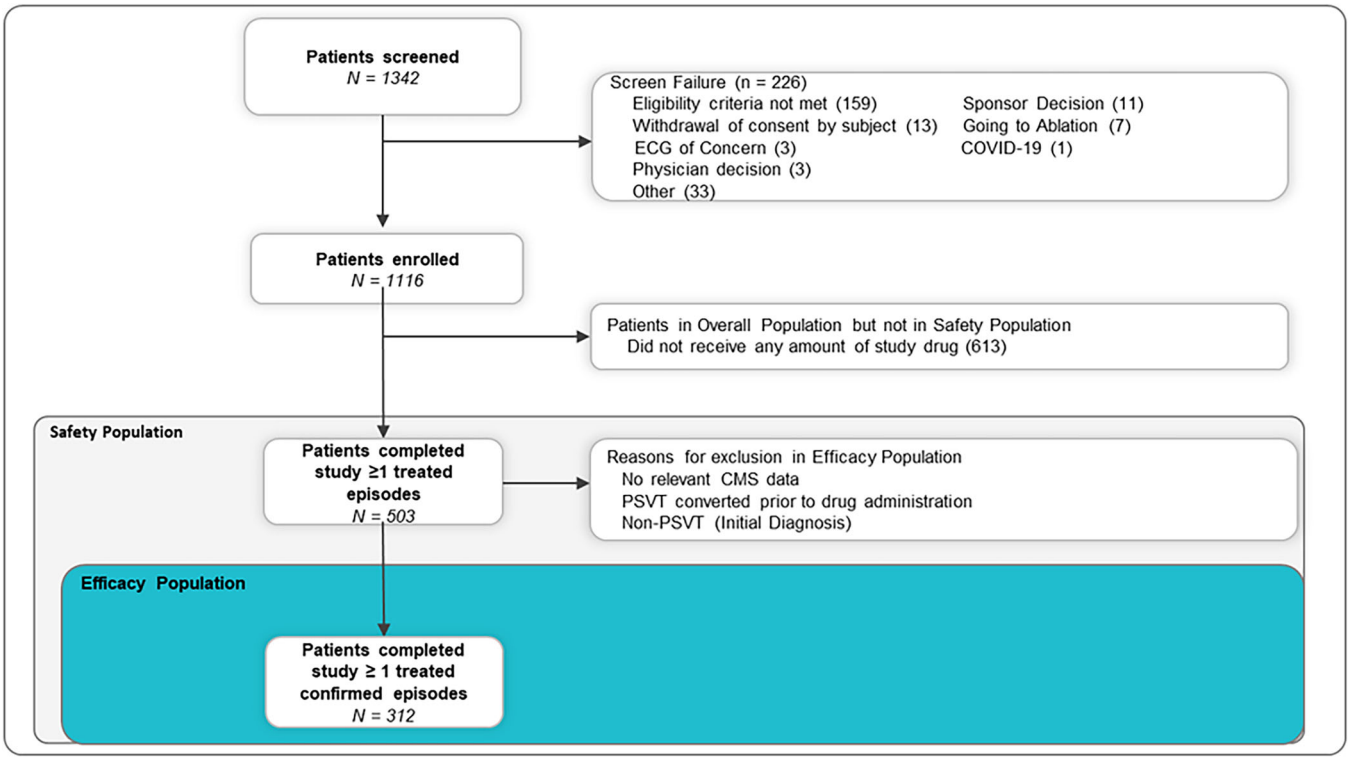

FIGURE 1 | Subject disposition and analyses populations. Of 1342 patients, 1116 patients were enrolled in the study. Primary reasons for screen failure included eligibility criteria not met, withdrawal of consent by subject, and sponsor decision. 503 patients who took study drug for at least 1 episode of perceived PSVT were included in the safety population; 312 patients treated a confirmed AV-nodal dependent PSVT episode and were included in the efficacy population. Reasons for exclusion from efficacy population are listed in Table 1. AV, atrioventricular; CMS, cardiac monitoring system; ECG, electrocardiogram; PSVT, paroxysmal supraventricular tachycardia.

perceived PSVT episodes, of which 727 had fully interpretable ECG CMS data and, of these, 552 (75.9%) were confirmed as AV-nodal-dependent PSVT. Non AV-nodal-dependent rhythms included sinus rhythm (12.7%), AF (2.4%), atrial flutter (0.4%), and atrial tachycardia (0.4%) (Table 2; Figure 2).

3.3 | Study Drug Exposure and Treatment Compliance

A total of 220, 118, 62, and 103 patients completed the study with 1, 2, 3, and 4 etripamil-treated perceived episodes of PSVT, respectively. In the safety population, 428 (85.1%) patients administered a single dose of etripamil (70 mg) for an episode and 75 (14.9%) patients administered two doses (70 mg x 2). Of 1054 etripamil-treated perceived PSVT episodes, 503 were first, 283 were second, 165 were third, and 103 were fourth episodes (Supporting Table 1). Study drug discontinuation occurred in 26 (5.2%) patients (Supporting Table 2), 12 (2.4%) considered related to treatment, 7 of whom for nasal discomfort (Table 3). The most common protocol deviations were related to patients' electronic Clinical Outcome Assessment for baseline surveys and CMS noncompliance.

3.4 | Adverse Events

There were 997 TEAEs in the safety population with 59.8% of patients experiencing ≥ 1 TEAE; 43 events were judged as severe, occurring in 6.2% of patients (Table 4). None of the 33 serious TEAEs in 26 patients (5.2%) were considered related to study drug by the investigator (Supporting Table 3). The proportions of patients with any TEAE, TEAE24h, serious TEAE, serious TEAE24h, drug-related TEAE, drug-related TEAE24h, and clinical AESI were similar between those self-administering 1 versus 2 doses of etripamil. The rates of TEAEs and TEAEs 24 h leading to study drug discontinuation were lower in the repeat-dose group than in the single-dose group. TEAEs by SOC and PT are presented in Supporting Table 4.

A total of 776 TEAEs 24 h in 269 (53.5%) patients were reported, of which 22 events in 16 (3.2%) patients were considered severe (Table 4). Most TEAEs 24 h in the safety population were mild or moderate, transient, and localized to the drug-administration site, including nasal discomfort (30.2%), nasal congestion (13.9%), rhinorrhea (13.1%), and epistaxis (7.4%) (Supporting Table 5); headache was also commonly reported (5.2%). There were 5 serious TEAEs 24 h, reported in 5 (1.0%) patients, none of which were considered related to etripamil, including acute coronary syndrome, acute myocardial infarction, AF, stress cardiomyopathy, and appendicitis.

A total of 706 TEAEs 24 h, in 249 (49.5%) patients, were judged by investigators to be related to etripamil (Table 4). Of these, 19 TEAEs 24 h, in 14 (2.8%) patients, were severe; none were serious; and 24 led to study drug discontinuation in 12 (2.4%) patients. There were no TEAEs 24 h leading to death.

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TABLE 1 | Demographics and baseline characteristics of the safety and efficacy populations.

	Safety population $N = 503$		Efficacy population $N = 312$	
	Mean (SD) or patients, *n* (%) for categorical variables	Median (range)	Mean (SD) or patients, *n* (%) for categorical variables	Median (range)
Age, y	54.9 (13.6)	56.0 (19.0–88.0)	55.1 (12.8)	57.0 (19.0–84.0)
Sex, *n* (%)				
Female	344 (68.4)	NA	210 (67.3)	NA
Male	159 (31.6)	NA	102 (32.7)	NA
Race, *n* (%)				
American Indian or Alaska Native	2 (0.4)	NA	1 (0.3)	NA
Asian	14 (2.8)	NA	6 (1.9)	NA
Black or African American	31 (6.2)	NA	9 (2.9)	NA
Native Hawaiian or other Pacific Islander	2 (0.4)	NA	1 (0.3)	NA
White	417 (82.9)	NA	268 (85.9)	NA
Other	38 (7.6)	NA	28 (9.0)	NA
Not reported	3 (0.6)	NA	2 (0.6)	NA
Age at first PSVT diagnosis, y	47.7 (16.8)	49.9 (1.0–83.2)	47.1 (16.3)	49.8 (1.0–79.0)
Time since first PSVT diagnosis, y	7.0 (9.2)	3.0 (−0.6–46.5)[d]	7.5 (9.3)	3.4 (0.0–46.5)
PSVT episodes in past year, *n*	9.8 (17.6)	4.0 (0.0–40.0)	6.9 (12.0)	4 (0–100)
Patient-reported emergency department visits for PSVT since diagnosis, *n*	3.9 (5.7)	2.0 (0.0–40.0)	4.3 (6.4)	2 (0–40)
Weight at screening, kg	84.0 (22.5)	81.6 (30.0–212.7)	83.7 (23.1)	81.0 (30.0–212.7)
Patients with concomitant medications of interest, *n* (%)[a]				
ß blocker or calcium-channel blocker	355 (70.6)	NA	208 (66.7)	NA
ß blocker only[b]	238 (47.3)	NA	129 (41.3)	NA
Calcium channel blocker only[c]	68 (13.5)	NA	49 (15.7)	NA
ß blocker and calcium-channel blocker	49 (9.7)	NA	30 (9.6)	NA
NDHP calcium channel blocker (verapamil or diltiazem)	92 (18.3)	NA	67 (21.5)	NA

Abbreviations: NA, not applicable; NDHP, non-dihydropyridine; PSVT, paroxysmal supraventricular tachycardia; SD, standard deviation; y, years.
[a]Drugs acting on the atrioventricular node that were started at any time and were taken at any time after the date of informed consent until the end of the follow-up period.
[b]Beta blocker only category does not include calcium channel blockers.
[c]Calcium channel blockers only category does not include beta blockers.
[d]The negative value (−0.6) resulted from a patient whose diagnosis was confirmed after the informed consent date.

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TABLE 2 | Summary of reasons patients were excluded from efficacy population, overall and by study visit.

Patients in overall population, *N*	**1116**				
	613 (54.9%)				
Patients that did not receive study drug, *n* (%)	**Overall episodes, *n* (%)**	**Follow-up study visit 1, *n* (%)**	**Follow-up study visit 2, *n* (%)**	**Follow-up study visit 3, *n* (%)**	**Final study visit, *n* (%)**
Safety population, *n*	1054	451	262	155	186
Efficacy population, *n*	552	231	138	90	93
Patients in safety population but not in efficacy population, *n*[a]		220	124	65	93
Insufficient ECG CMS Data	327 (31.0)	138 (13.1)	83 (7.9)	39 (3.7)	67 (6.4)
PSVT converted before drug administration	7 (0.7)	4 (0.4)	2 (0.2)	0	1 (0.1)
Non PSVT (Initial Diagnosis)	168 (15.9)	78 (7.4)	39 (3.7)	26 (2.5)	25 (2.4)
Sinus Rhythm/Sinus tachycardia	134 (12.7)	65 (6.2)	31 (2.9)	21 (2.0)	17 (1.6)
Atrial Fibrillation	25 (2.4)	10 (0.9)	8 (0.8)	4 (0.4)	3 (0.3)
Atrial Flutter	4 (0.4)	1 (0.1)	0	1 (0.1)	2 (0.2)
Atrial Tachycardia	4 (0.4)	2 (0.2)	0	0	2 (0.2)
Indeterminate Arrhythmia	1 (0.1)	0 (0)	0	0	1 (0.1)

Note: Safety population includes patients who self-administered study drug for at least one episode of perceived PSVT. Efficacy population includes patients who received study drug for an event confirmed as PSVT by medical review of the ECG CMS data.
Abbreviations: CMS, cardiac monitoring system; ECG, electrocardiogram; PSVT, paroxysmal supraventricular tachycardia.
[a]Percentage is calculated using number of total episodes in the safety population for corresponding visit as denominator.

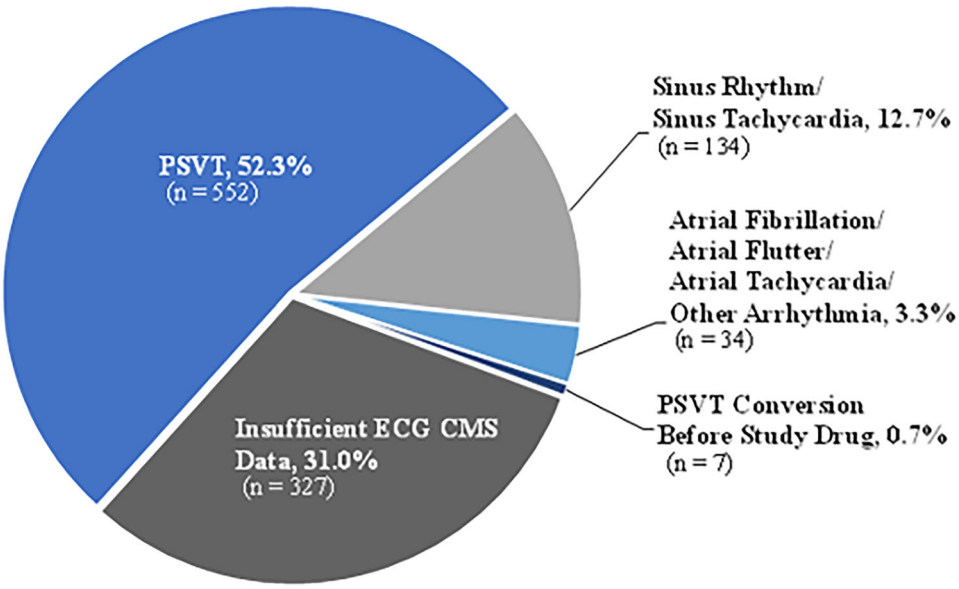

FIGURE 2 | Types of rhythm captured on ECG CMS during perceived PSVT. A total of 1054 perceived episodes occurred in the safety population. 552 episodes were confirmed PSVT episodes and were included in the efficacy population. 3.3% of episodes were non-AV-nodal dependent atrial rhythms (atrial fibrillation, atrial flutter, atrial tachycardia), and 12.7% were sinus rhythm/sinus tachycardia. There was no relevant ECG CMS data for 31% of episodes and 0.7% converted to PSVT before administering study drug. CMS, cardiac monitoring system; ECG, electrocardiogram; PSVT, paroxysmal supraventricular tachycardia.

Etripamil-related TEAEs 24 h leading to study discontinuation in > 1 patient included nasal discomfort (7 patients [1.4%]), nasal congestion (3 patients [0.6%]), epistaxis (3 patients [0.6%]), rhinalgia (2 patients [0.4%]) and single events in individual patients including mild facial pain and mild hypoesthesia, mild oral discomfort, cough, rhinorrhea, sneezing and throat irritation (Table 3). Etripamil-related TEAEs 24 h leading to discontinuation were generally associated with the

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TABLE 3 | Summary of drug related TEAEs leading to study drug discontinuation.

System organ class preferred term	Drug-Related TEAEs overall $N = 503$	
	No. of events	*n* (%)
Any TEAE	24	12 (2.4)
Gastrointestinal disorders	1	1 (0.2)
Oral discomfort	1	1 (0.2)
General disorders and administration site conditions	1	1 (0.2)
Facial pain	1	1 (0.2)
Nervous system disorders	2	2 (0.4)
Syncope[a]	1	1 (0.2)
Hypoaesthesia	1	1 (0.2)
Respiratory, thoracic and mediastinal disorders	19	9 (1.8)
Nasal discomfort	7	7 (1.4)
Epistaxis	3	3 (0.6)
Nasal congestion	3	3 (0.6)
Rhinalgia	2	2 (0.4)
Cough	1	1 (0.2)
Rhinorrhoea	1	1 (0.2)
Sneezing	1	1 (0.2)
Throat irritation	1	1 (0.2)
Vascular disorders	1	1 (0.2)
Hypotension[b]	1	1 (0.2)

Note: TEAEs defined as AEs with a start date occurring after administration of study drug.
Abbreviations: AE, adverse event; ER, emergency room; NSR, normal sinus rhythm; PSVT, paroxysmal supraventricular tachycardia; TEAEs, treatment emergent adverse events.
[a]One patient with reported syncope 5 min after etripamil administration, however, investigation showed no reported loss of consciousness, judged as no syncope by study sponsor.
[b]One patient experienced an event of hypotension 1 h and 6 min after etripamil administration while in PSVT in the ER (BP 72/27 mmHg). Patient restored to NSR after cardioversion. The investigator considered the event of hypotension as severe in intensity and probably related to etripamil. The study sponsor considered the event of hypotension as unlikely related to etripamil due to elapsed time between event and drug administration based on the half-life of etripamil.

patient's first treated PSVT episode except for 2 events in 1 patient that occurred after the third treated episode.

The types of TEAEs 24 h were similar across episodes and were consistent with the results for the total safety population (Table 5). There were similar rates of TEAE24h whether a single dose or a repeat dose regimen was used (Table 6). There was a downward trend in the percentage of patients with any TEAE24h with successively treated PSVT episodes (46.9%, 40.3%, 37.8%, and 32.0% for episodes 1, 2, 3, and 4, respectively) (Table 5).

Overall, 23 AESIs were identified in 18 (3.6%) patients in the safety population, most mild or moderate (Table 7). Two severe AESIs reported were considered not related to etripamil after review; one patient was initially reported to have syncope occurring 5 min after a single dose of etripamil, however, investigation indicated no loss of consciousness; and one episode of severe hypotension was reported but with onset > 1 h after a dose of etripamil in a patient who required electrical cardioversion.

The most frequent bradyarrhythmia detected by central review of ECG CMS data was first-degree AV block > 30 s (11 patients [2.7%] in 14 PSVT episodes [1.9%]). The most frequent tachyarrhythmia was non-sustained ventricular tachycardia (NSVT) (≥ 3 wide consecutive beats, average 5 beats duration, asymptomatic) occurring in 22 patients (5.4%) in 24 (3.3%) PSVT episodes. The central ECG CMS review reported recurrent episodes of PSVT after initial conversion to SR in 11 patients (2.7%), in 16 (2.2%) episodes, and after an average of 11.5 min.

The profile of TEAEs 24 h was similar in patients taking any concomitant medication for any cardiovascular indication compared with the total safety population, including those aged ≥ 60 to < 70 years and those aged ≥ 70 years (Supporting Table 6).

3.5 | Efficacy Outcomes

For the first etripamil-treated episode experienced after enrollment, conversion of PSVT to SR for ≥ 30 s occurred in 59.9% of patients by 30 min and 70.5% of patients by 60 min post drug-administration (Kaplan-Meier analysis). The median time to conversion after etripamil administration was 18.3 min (95% CI: 14.2, 25.6) for episode 1. Conversion rates by 30 min after etripamil administration were 61.6%, 54.9%, and 66.7% for episodes 2, 3, and 4, respectively (Supporting Table 7). Conversion rates by 60 min after etripamil administration were 73.5%, 57.7%, and 77.8% for episodes 2, 3, and 4, respectively (Supporting Table 7). The median times to conversion were 14.0 to 19.1 min across episodes 1 to 4. In all PSVT episodes, the rate of conversion was 69.9% (386/552) by 60 min post drug, and the median time to conversion was 17.0 min (95% CI: 13.9, 22.3) (Figure 3; Supporting Table 7).

For 77.5% (706/911) of perceived PSVT episodes, patients reported performing a vagal maneuver pretreatment; there was successful resolution of PSVT within 1 min in < 1% of these cases. Visits to the emergency department and hospital visits and admissions were reported for 11.9% (54/455) and 3.7% (17/455) of etripamil-treated PSVT episodes, respectively, corresponding to 14.4% (45/312) and 4.8% (15/312) of patients, respectively (Central illustration 1).

A total of 9.9% (31/312) of patients in the efficacy population had received ablation before the study, 2.6% (8/312) received ablation during the study, and 10.6% (33/312) patients discontinued the study to receive ablation before treating four episodes of PSVT. Treatment with an oral ß-blocker or CCB was initiated by 18.6% (95% CI: 14.4, 23.4 [$n = 58/312$]) of patients and discontinued by 16.3% (95% CI: 12.4, 20.9 [$n = 51/312$]) of patients during the study.

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TABLE 4 | Overview of treatment-emergent adverse events in the safety population.

	Single dose (70 mg) $N = 428$		Optional repeat dose (2×70 mg) $N = 75$		Total safety population $N = 503$	
TEAE category	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**
Any TEAE	838	253 (59.1)	159	48 (64.0)	997	301 (59.8)
Severe	33	24 (5.6)	10	7 (9.3)	43	31 (6.2)
Any TEAE24h	652	228 (53.3)	124	41 (54.7)	776	269 (53.5)
Severe	16	12 (2.8)	6	4 (5.3)	22	16 (3.2)
Serious TEAE	28	22 (5.1)	5	4 (5.3)	33	26 (5.2)
Drug-related	0	0	0	0	0	0
Leading to death[a]	4	4 (0.9)	0	0	4	4 (0.8)
Serious TEAE24h	5	5 (1.2)	0	0	5	5 (1.0)
Drug-related	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0
Drug-related TEAE	604	211 (49.3)	115	39 (52.0)	719	250 (49.7)
Severe	13	10 (2.3)	6	4 (5.3)	19	14 (2.8)
Drug-related TEAE24h	591	210 (49.1)	115	39 (52.0)	706	249 (49.5)
Severe	13	10 (2.3)	6	4 (5.3)	19	14 (2.8)
TEAE leading to study drug discontinuation	38	25 (5.8)	2	1 (1.3)	40	26 (5.2)
Drug-related	22	11 (2.6)	2	1 (1.3)	24	12 (2.4)
TEAE24h leading to study drug discontinuation	29	17 (4.0)	2	1 (1.3)	31	18 (3.6)
Drug-related	22	11 (2.6)	2	1 (1.3)	24	12 (2.4)
Any clinical AESI 24h	19	14 (3.3)	3	3 (4.0)	22[b]	17 (3.4)[b,c]

Note: Patients are grouped by their maximum exposure to etripamil in any perceived PSVT episode. Percentage is calculated using the number of patients (N) in the corresponding subgroup as the denominator. Patients with > 1 occurrence of a TEAE in a category are counted once. The severity of TEAEs is considered to be its maximum severity. TEAEs with missing severity are considered severe. Drug-related TEAEs include those classified as possibly, probably or definitively related to study drug. TEAE24h defined as TEAEs starting or worsening within 24 h after study drug administration, or AEs started within 12 h before study drug administration.
Abbreviations: AE, adverse event; AESI, adverse-event of special interest; CMS, cardiac monitoring system; ECG, electrocardiogram; PSVT, paroxysmal supraventricular tachycardia; TEAE, treatment-emergent adverse event.
[a]TEAEs leading to death were not related to etripamil and include acute myocardial infarction, cardio-respiratory arrest, septic shock and high-grade B cell lymphoma.
[b]AESIs were identified by the Investigator and do not include those identified from the ECG CMS data.
[c]An additional AESI (mild hypotension) was identified in one additional patient post-database lock.

Rates of conversion of confirmed PSVT episodes to SR by 60 min and time to conversion in subgroups of special interest are presented in (Supporting Table 8).

Conversion to SR was measured across 1–3 successive patient episodes and, for each, the conversion to SR on the next episode was recorded. Among patients treating at least two confirmed PSVT episodes ($N = 151$), 108 (71.5%) successfully converted to SR with etripamil by 60 min in the first episode and, of these, 87 (80.6%) converted PSVT with etripamil during their second episode ($p = 0.0019$) (Table 8). A consistent pattern was observed between later episodes as conversion on the second episode was associated with 71.7% (38/53) conversion during the next episode ($p < 0.0001$). Similarly, conversion on the third episode was associated with 72.7% (8/11) conversion during the subsequent episode ($p = 0.5182$). Among 43 patients who did not successfully convert to SR during their first episode, over half of them (55.8%, 24/43) still successfully converted PSVT to SR on the second episode with etripamil. Of patients who treated a fourth episode, 94.4% (17/18) had converted to SR within 60 min on at least one of their prior three episodes.

4 | Discussion

NODE-303 was the first study to evaluate the treatment of multiple perceived episodes of PSVT with single- and optional repeat-dose etripamil, self-administered outside of the health-care setting and without requiring a medically supervised test dose before first use. This new, real-world use study design contrasts with those that solely followed symptom resolution and the previously completed NODE-301 studies which required patients to pass a medically supervised test dose of etripamil during sinus rhythm before randomization. In NODE-301 Part 1, 2.3% of patients, and in RAPID, 1.3%, did not proceed to randomization after the test dose [8, 19]. In addition, NODE-303 did not exclude patients with a history AF or atrial flutter, broadening the study's potential applicability. Overall,

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TABLE 5 | Summary of TEAEs in safety population by episode.

TEAEs System organ class preferred term	Episode 1 ($N = 503$) Etripamil 70 mg $N = 463$ Etripamil 2 × 70 mg $N = 40$		Episode 2 ($N = 283$) Etripamil 70 mg $N = 256$ Etripamil 2 × 70 mg $N = 27$		Episode 3 ($N = 165$) Etripamil 70 mg $N = 147$ Etripamil 2 × 70 mg $N = 18$		Episode 4 ($N = 103$) Etripamil 70 mg $N = 89$ Etripamil 2 × 70 mg $N = 14$	
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Any TEAE	564	264 (52.5)	260	127 (44.9)	127	68 (41.2)	46	33 (32.0)
Severe	26	19 (3.8)	13	9 (3.2)	1	1 (0.6)	3	3 (2.9)
Any TEAE24h	418	235 (46.7)	206	114 (40.3)	107	62 (37.6)	45	33 (32.0)
Respiratory, thoracic and mediastinal disorders	314	205 (40.8)	154	103 (36.4)	77	52 (31.5)	34	30 (29.1)
Nasal discomfort	126	125 (24.9)	56	55 (19.4)	31	30 (18.2)	17	17 (16.5)
Nasal congestion	55	54 (10.7)	26	26 (9.2)	7	7 (4.2)	5	5 (4.9)
Rhinorrhea	50	50 (9.9)	25	25 (8.8)	17	17 (10.3)	2	2 (1.9)
Drug-related TEAE	397	222 (44.1)	185	105 (37.1)	96	57 (34.5)	41	31 (30.1)
Serious TEAE	14	11 (2.2)	13	10 (3.5)	4	4(2.4)	2	2 (1.9)
Drug-related	0	0	0	0	0	0	0	0
TEAE leading to study drug discontinuation	30	18 (3.6)	7	6 (2.1)	3	2 (1.2)	0	0

Note: Data are presented for TEAEs 24 h that occurred in ≥ 5% of patients (by preferred term) in the total safety population. Within each system organ class and within each preferred term, patients with more than one event are counted once only. A TEAE24h was defined as an AE starting or worsening within 24 h after study drug administration, or an AE that started within 12 h before study drug administration.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

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TABLE 6 | Treatment-related, treatment-emergent adverse events 24 h (TEAE24h) in the safety population.

System organ class preferred term TEAE	Single dose (70 mg) $N = 428$		Repeat dose (70 mg × 2) $N = 75$		Total safety population $N = 503$	
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Any TEAE24h	591	210 (49.1)	115	39 (52.0)	706	249 (49.5)
Respiratory, thoracic and mediastinal disorders	477	196 (45.8)	96	39 (52.0)	573	235 (46.7)
Nasal discomfort	187	124 (29.0)	42	26 (34.7)	229	150 (29.8)
Rhinorrhea	76	54 (12.6)	18	12 (16.0)	94	66 (13.1)
Nasal congestion	80	59 (13.8)	13	11 (14.7)	93	70 (13.9)
Epistaxis	38	33 (7.7)	6	4 (5.3)	44	37 (7.4)

Note: Patients are grouped by their maximum exposure to etripamil in any perceived PSVT episode. Data are presented for TEAEs 24h that occurred in ≥ 5% of patients (by preferred term) in the total safety population. Within each system organ class and within each preferred term, patients with more than one event are counted once only. A TEAE was defined as an AE starting or worsening after study drug administration, an AE that started within 12 h before study drug administration, or an AE classified as related to the study drug. No epistaxis was severe or led to medical intervention.
Abbreviations: AEs, adverse event; TEAE, treatment-emergent adverse event.

TABLE 7 | Treatment-emergent adverse event of special interest (AESI) in safety population.

System organ class preferred term	Single dose (70 mg) $N = 428$		Repeat dose (2 × 70 mg) $N = 75$		Total safety population $N = 503$	
	Events, *n*	Patients, *n* (%)	No. of Events	*n* (%)	No. of Events	*n* (%)
Any AESI	20	15 (3.5)	3	3 (4.0)	23	18 (3.6)
Cardiac disorders	6	3 (0.7)	3	3 (4.0)	9	6 (1.2)
Sinus arrest (≥ 3 s)	2	1 (0.2)	1	1 (1.3)	3	2 (0.4)
AV block first degree	1	1 (0.2)	1	1 (1.3)	2	2 (0.4)
AV block second degree[a]	2	1 (0.2)	0	0	2	1 (0.2)
AV block, third degree	0	0 (0.0)	0	0	0	0 (0.0)
Atrial flutter	0	0	1[b]	1 (1.3)	1	1 (0.2)
Atrial fibrillation	1[c]	1 (0.2)	0	0	1	1 (0.2)
Nervous system disorders	12	10 (2.3)	0	0	12	10 (2.0)
Dizziness[d]	11	9 (2.1)	0	0	11	9 (1.8)
Syncope[e]	1	1 (0.2)	0	0	1	1 (0.2)
Vascular disorders	2	2 (0.5)	0	0	2	2 (0.4)
Hypotension[f]	2	2 (0.5)	0	0	2	2 (0.4)

Note: Patients are grouped by their maximum exposure to etripamil in any perceived PSVT episode. AESIs were identified by the Investigator and do not include those identified from the ECG CMS data. By definition, AESI occurred within 24 h of etripamil administration. All events were of mild severity and classified as treatment-related unless otherwise noted.
Abbreviations: AESI, adverse event of special interest; AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia.
[a]All AV block second degree were accessed as Mobitz type I.
[b]Moderate severity.
[c]Not related to study drug.
[d]Two events of dizziness were of moderate severity.
[e]One event of syncope was severe.
[f]One event of hypotension was mild and one event of hypotension was severe.

the results show that etripamil, used as intended, in an unsupervised setting for multiple PSVT episodes, has similar safety and effectiveness to that demonstrated in the RAPID Phase 3 randomized, controlled trial [8]. Adverse events were similar to those in prior studies [8, 19, 20], mostly related to nasal irritation. There was a downward trend of TEAE frequencies with subsequently treated episodes, suggesting patients acclimating to local, administration-site side effects and improved tolerance with repeat use. Finally, successful PSVT conversion with etripamil in earlier episodes was consistently predictive of conversion in subsequent episodes, suggesting reproducible success with recurrent episodes.

Key and innovative features of the NODE-303 study design were the use of ECG data from monitoring devices to demonstrate restoration of sinus rhythm, not requiring a test dose in sinus rhythm before first use of etripamil, not excluding patients with a history of atrial fibrillation or atrial flutter

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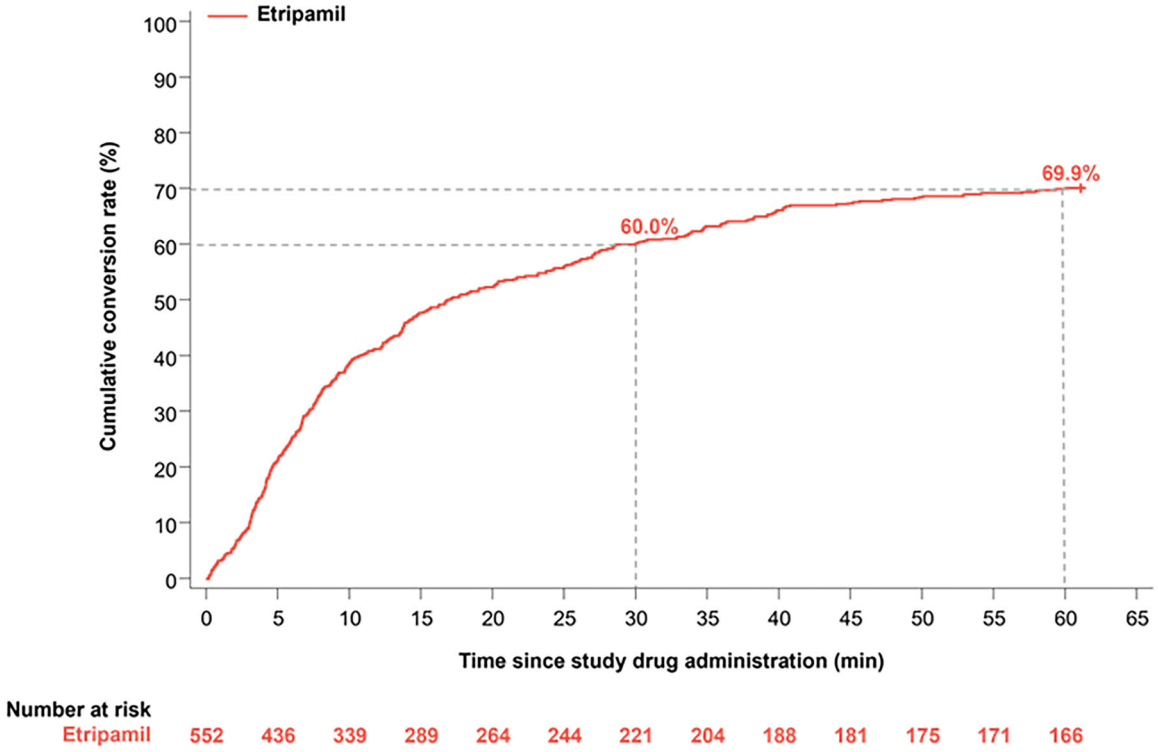
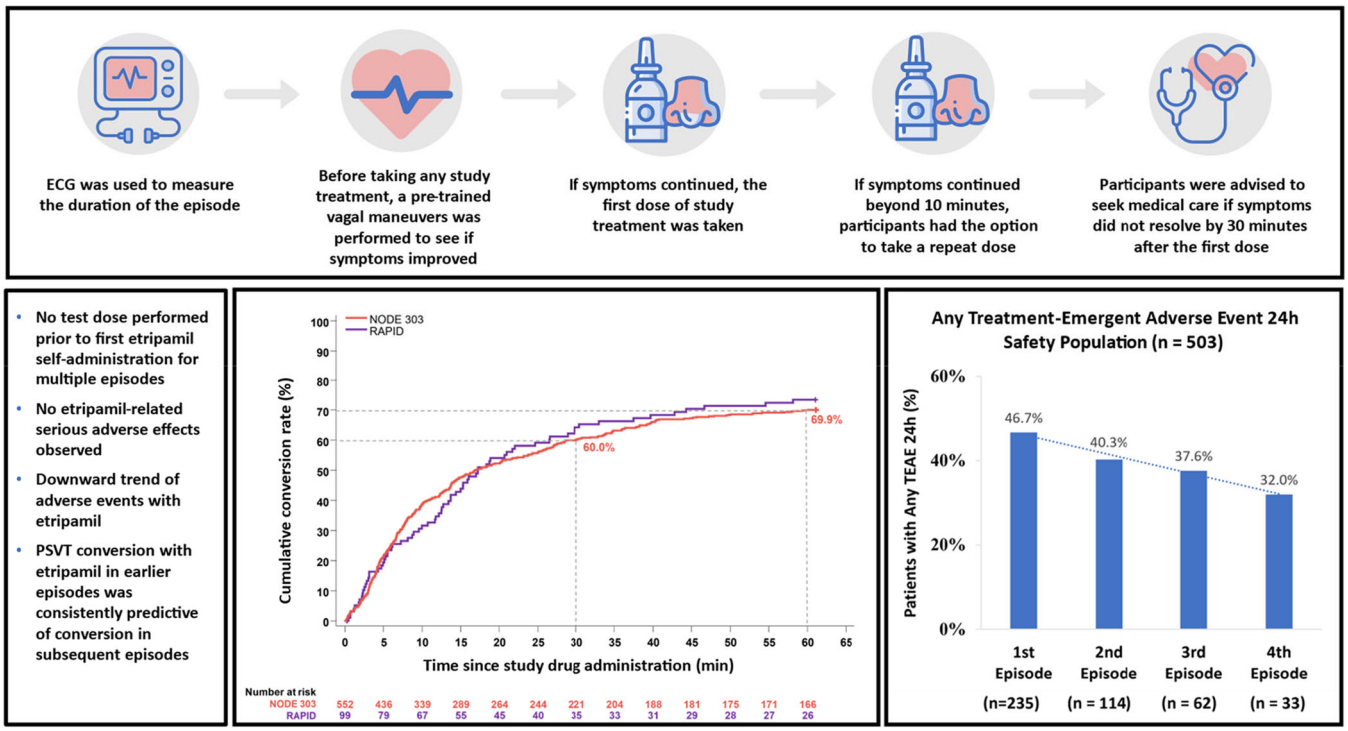


FIGURE 3 | Kaplan-Meier probability of PSVT conversion to SR: all episodes combined. Kaplan-Meier estimate of conversion of all confirmed PSVT episodes in the efficacy population ($n = 552$) at 30 min was 60.0% and at 60 min was 69.9% with median time to conversion of 17.0 min (95% CI, 13.9–22.3). PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm.



CENTRAL_ILLUSTRATION 1 | Etripamil nasal spray self-administered in a real-world setting was well tolerated, effective, and had a consistent safety profile as a single- or repeat-dose regimen across multiple PSVT episodes.

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TABLE 8 | Predictiveness of conversion of PSVT at 60 min between episodes[a].

	Conversion on next episode[b]	No conversion on next episode
Conversion on 1st episode	87/108 (80.6%)	21/108 (19.4%)
No conversion on 1st episode	24/43 (55.8%)	19/43 (44.2%)
Chi-square = 9.6681, p value = 0.0019		
Conversion on 2nd episode	38/53 (71.7%)	15/53 (28.3%)
No conversion on 2nd episode	3/18 (16.7%)	15/18 (83.3%)
Chi-square = 16.6772, p value < 0.0001		
Conversion on 3rd episode	8/11 (72.7%)	3/11 (27.3%)
No conversion on 3rd episode	6/7 (85.7%)	1/7 (14.3%)
Chi-square = 0.4174, p value = 0.5182		

[a]Patients treating ≥ 1 episode (Efficacy Population), $N = 312$.
[b]Conversion by 60 min was assessed by adjudication of ECG data.

(compared to previous etripamil trials), and treatment of multiple episodes of PSVT. These centrally reviewed data demonstrated no significant concerns of brady- or tachy-arrhythmias following etripamil use. The safety profile of etripamil in NODE-303 was consistent with that observed in Phase 2 and Phase 3 randomized, placebo-controlled trials of the drug [8, 19, 20]. Consistent with the use of a nasal spray device, the most common TEAEs were localized to the nasal administration site and were mild and transient. In the RAPID study, the most frequent TEAEs reported were nasal discomfort (23% etripamil vs. 5% placebo), nasal congestion (13% vs. 1%), rhinorrhea (9% vs. 3%), and epistaxis (6% vs. 2%). No cases of the latter required medical attention [8]. Despite use of concomitant cardiac medications in 71% of patients and not requiring a pre-enrollment test dose of drug, there were no serious adverse events related to unsupervised etripamil use such as atrioventricular block, hypotension, or syncope. Further, there was observed consistency for patients receiving single or repeat doses of etripamil in a given episode. These findings are of importance to the symptom-prompted use of etripamil 'on-demand' by patients who may experience multiple sporadic episodes over time. In future evaluations of self-administered etripamil, wearable ECG devices which can confirm PSVT, or even AVN-dependent PSVT, could be used to prompt therapy in addition to experiencing symptoms.

The lack of symptomatic hypotension, pre-syncope or syncope from etripamil treatment is notable and reassuring. This contrasts with other agents used for the acute termination of PSVT, including IV adenosine, verapamil, diltiazem, and beta blockers, that can be associated with bradycardia, AV block, hypotension, and, in the case of adenosine, transient asystole and dyspnea. Additionally, orthostatic dizziness and hypotension occurred in 4 of 15 (27%) patients treated with a single oral dose of diltiazem and propranolol after an induced PSVT episode in a randomized cross-over placebo-control trial [11]. In a trial of oral diltiazem and propranolol or oral flecainide for the acute, pill-in-pocket treatment of PSVT, hypotension was reported in 1 of 33 and 2 of 33 episodes, respectively [10]. Of note, 1 patient in this trial had syncope with trauma 15 min after ingestion of diltiazem and propranolol. Therefore, prescribing a pill-in-pocket management strategy for PSVT should be considered with caution, and using such an approach has been either removed or downgraded to a class IIB recommendation in the most recent clinical guidelines [1, 2].

Etripamil treatment resulted in conversion of PSVT to SR for ≥ 30 s at rates similar to those observed in prior placebo-controlled studies, with similar median times to conversion and equivalently low rates of PSVT recurrence [8, 19]. Median time to conversion of PSVT to SR in NODE-303 was within the range of median values of other etripamil studies (13.7–25.0 min) [8, 19, 20]. The estimated 59.9% rate of conversion by 30 min (episode 1) in NODE-303 was similar to the rates in NODE-301 (53.7%) [19], NODE-302 (60.2%) [20] and the RAPID study (64.3%) [8].

Furthermore, these demonstrations of efficacy in NODE-303 were shown across multiple episodes of PSVT and with no attenuation of treatment effect. Conversion of PSVT to SR with etripamil occurred in the majority of patients over multiple episodes, and that conversion in earlier episodes was consistently predictive of conversion in subsequent episodes. However, an unsuccessful conversion to SR with etripamil during an earlier episode was not predictive of subsequent lack of conversion with a repeat episode. A possible explanation for successful PSVT conversion in later episodes despite initial non-conversion may be the increasing familiarity with etripamil self-administration because this NODE-303 cohort did not undergo test dosing of etripamil before first use.

These NODE-303 data are also consistent with findings from NODE-302, in which the estimated rate of conversion within 60 min of etripamil administration across multiple episodes was 75.1% [20]. The proportion of patients with emergency department visits after etripamil-treated PSVT episodes (14.4%) was equivalent to that in etripamil-treated patients in RAPID (14%), rates that are lower than those observed for placebo-treated patients in Phase 3 trials (21%–25%) [8, 19].

In this study, 3.1% of patients had AT/AF as their adjudicated rhythm during perceived episode rather than AV-nodal-dependent PSVT. This may partly be explained by not excluding patients who had a history of AT/AF. In the ReVeRA-201 trial, patients treated with etripamil during AF with rapid ventricular rates experienced significantly greater ventricular rate reductions and improved symptom relief compared to

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placebo [16]. Therefore, etripamil appears to show effectiveness and tolerability in the acute treatment of supraventricular tachyarrhythmias.

A fast-acting drug, self-administered outside the healthcare setting, to terminate PSVT episodes may alleviate the burden of PSVT for both patients and clinicians, especially when vagal maneuvers are ineffective. Etripamil nasal spray treatment improved symptoms and reduced tachycardia rate during PSVT, compared with placebo [23]. An effective acute treatment for PSVT episodes that can be self-administered without medical supervision could potentially reduce the burden on emergency departments and provide patients with a safe option for self-management. Although catheter ablation can provide durable treatment for PSVT and may be considered a first-line therapy for symptomatic PSVT, some patients do not undergo ablation due to inaccessibility or hesitancy because of potential procedural risks and infrequent episodes [24]. Interestingly, 10% of patients in the efficacy population had undergone ablation before enrolling in the study, and 11% withdrew during the study to undergo ablation, suggesting the potential role of etripamil for refractory or high-risk ablation cases or as a bridge to ablation.

4.1 | Study Limitations

Limitations of this study include those inherent to an open-label single-arm design as there is no comparison to placebo and efficacy endpoints were not tested statistically formally. Despite review by an expert electrophysiologist adjudication team, limitations of the recording device (e.g., two-lead configuration, recording quality) introduced the possibility of misclassifying some PSVT episodes as AVN-dependent when they were not. However, this potential misclassification favors the underestimation of efficacy because non AVN-dependent PSVT would not be expected to respond to etripamil. There were quality issues identified regarding the completeness of ECG data from the first CMS device requiring a switch an alternate CMS; this may have contributed to the proportion of patients with insufficient ECG CMS data (Figure 2). As pre-specified and described herein, the efficacy population was a subset of the safety population, and efficacy findings should be interpreted with this consideration. The application of an ECG CMS device could have introduced bias as patients needed to take time (~5 min) to apply and may have already selected for refractory episodes (e.g., vagal maneuver resistant PSVT cases). The introduction of the repeat-dose regimen during the study limited the number of patients given the opportunity for this option. The present analysis did not investigate patients who took etripamil and did not have confirmed AV nodal-dependent PSVT, however etripamil has shown a consistent safety and efficacy profile when administered in sinus rhythm and non-PSVT atrial arrhythmias, including atrial fibrillation, across multiple previous studies of etripamil [8, 16, 19]. In a post-hoc analysis of the NODE-303 study, patients with atrial fibrillation who received etripamil demonstrated significant heart rate reduction, with an average maximum reduction in VR ± SEM of 27.4 bpm ± 6.1 at 22 min, and the treatment was well tolerated with no serious adverse events reported within this subgroup [25]. Based on the previous safety profile of etripamil demonstrated in various settings, there is low concern of administering etripamil during a non AV nodal-dependent PSVT rhythm. While not a limitation, the definition of TEAE was expanded, post database lock, to allow for a more conservative approach and to broadly capture any potential TEAEs. NODE-303 had 12 patients (2.4%) with drug-related study discontinuation, similar to rates in prior Phase 3 studies [8, 19], suggesting discontinuations were not a limitation in this study.

5 | Conclusion

NODE-303, a study that mimicked a real-world setting without a prior test dose, demonstrated symptom-prompted self-administered etripamil nasal spray to have a favorable benefit-risk profile, with rapid and sustained benefit in conversion rates and reduction in TEAE frequency, and across multiple episodes of PSVT. The safety profile was similar for single and repeat 70 mg doses of etripamil, characterized by predominantly mild adverse events localized to the drug's administration site. The results of the NODE-303 study are consistent with previous clinical studies and support the potential benefit of self-administration of etripamil in treating PSVT in a medically unsupervised setting.

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Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Table 1: Summary of perceived PSVT episodes treated in the safety population. **Supplementary Table 2:** Summary of TEAEs leading to study drug discontinuation. **Supplementary Table 3:** Summary of treatment-emergent serious adverse events (TESAEs); none related to study drug. **Supplementary Table 4:** Most common (≥ 5%) treatment-emergent adverse events in the safety population. **Supplementary Table 5:** Most common (≥ 5%) treatment-emergent adverse events 24h (TEAE24h) in the safety population. **Supplementary Table 6:** Treatment-emergent adverse events commencing etripamil administration in patients taking cardiovascular medications by age. **Supplementary Table 7:** Kaplan-Meier analyses of confirmed PSVT to SR conversion at 60 min by episode in the efficacy population. **Supplementary Table 8:** Conversion of PSVT episodes to SR by 60 min after administration of etripamil, by prespecified subgroups of interest (all visits).

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