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ORIGINAL RESEARCH

Etripamil Nasal Spray for Conversion of Repeated Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia During Long-Term Follow-Up: Results From the NODE-302 Study

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BACKGROUND: Self-administration of investigational intranasal L-type calcium channel blocker etripamil during paroxysmal supraventricular tachycardia (PSVT) appeared safe and well-tolerated in the phase 3 NODE-301 (Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia) trial of adults with sustained atrioventricular nodal-dependent PSVT. The NODE-302 open-label extension further characterized etripamil safety and efficacy.

METHODS AND RESULTS: Eligible patients were monitored via self-applied cardiac monitoring system for 5 hours after etripamil self-administration. The primary end point was time-to-conversion of positively adjudicated PSVT to sinus rhythm after etripamil treatment. Probability of conversion to sinus rhythm was reported via Kaplan-Meier plot. Adverse events were based on self-reported symptoms and clinical evaluations. Among 169 patients enrolled, 105 self-administered etripamil ≥1 time for perceived PSVT (median [range], 232 [8–584] days' follow-up). Probability of conversion within 30 minutes of etripamil was 60.2% (median time to conversion, 15.5 minutes) among 188 PSVT episodes (92 patients) positively adjudicated as atrioventricular nodal dependent by independent ECG analysis. Among 40 patients who self-treated 2 episodes, 75% had a significantly consistent response by 30 minutes; 9 did not convert on either episode, and 21 converted on both episodes (χ^2=8.09; P=0.0045). Forty-five of 105 patients (42.9%) had ≥1 treatment-emergent adverse event, generally transient and mild-to-moderate, including nasal congestion (14.3%), nasal discomfort (14.3%), or rhinorrhea (12.4%). No serious cardiac safety events were observed within 24 hours of etripamil.

CONCLUSIONS: In this extension study, investigational etripamil nasal spray was well tolerated for self-treating recurrent episodes of PSVT without medical supervision.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03635996.

Key Words: etripamil ■ NODE-302 ■ paroxysmal supraventricular tachycardia ■ self-administered

No medications are currently approved for the acute termination of paroxysmal supraventricular tachycardia (PSVT) without direct medical supervision. Calcium channel blockers (CCBs), β-blockers (BBs), and adenosine are effective treatments for acute PSVT, but these medications require intravenous administration

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CLINICAL PERSPECTIVE

What Is New?

- Self-administration of investigational intranasal L-type calcium channel blocker etripamil during paroxysmal supraventricular tachycardia (PSVT) appeared effective in the NODE-302 (Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia) open-label extension study.
- Etripamil was well-tolerated, and most adverse events were mild to moderate, local, and transient; no patients experienced any serious adverse events related to the study drug for up to 11 repeated doses.
- Similar to the NODE-301 study, etripamil was associated with 60% conversion of PSVT to sinus rhythm within 30 minutes (75% within 60 minutes), with a median of 15.5 minutes to conversion.

What Are the Clinical Implications?

- Etripamil may be a potential therapeutic option for patients to self-treat recurrent episodes of PSVT without medical supervision.
- This intranasal medication with rapid onset of action could be an alternative to pill-in-the-pocket strategies for PSVT.
- Use of etripamil could potentially reduce emergency medical service use for treating vagal maneuver-resistant PSVT episodes.

Nonstandard Abbreviations and Acronyms

AE	adverse event
BB	β-blocker
CMS	cardiac monitoring system
PIP	pill-in-the-pocket
SR	sinus rhythm
SVT	supraventricular tachycardia
TEAE	treatment-emergent adverse event
VM	vagal maneuver

for rapid termination, because their oral formulations have a delayed onset of action due to their inconsistent and prolonged rates of absorption and first-pass metabolism.[1–3] Although some patients may acutely self-administer oral BBs or CCBs to manage their recurrent PSVT episodes, limited evidence supports the efficacy and safety of this pill-in-the-pocket (PIP) approach for symptomatic, sustained PSVT.[1,4–6]

Etripamil is a nondihydropyridine, L-type CCB developed to enable patients to rapidly self-terminate their atrioventricular nodal-dependent PSVT episodes via nasal spray. In the first-in-human, single-ascending dose, phase 1 study, 72 healthy adults received etripamil at doses of 3.5, 7, 14, 30, 60, 105, and 140 mg. In the phase 2, a randomized, double-blind NODE-1 (Multi-Center, Placebo-Controlled, Dose-Ranging Phase 2 Electrophysiological Study of Intranasal Administration of MSP-2017 for the Conversion of Induced Paroxysmal Supraventricular Tachycardia to Sinus Rhythm) study (NCT02296190), 104 patients were randomly chosen to receive placebo or etripamil (with doses ranging from 35 to 140 mg) during PSVT episodes induced in an electrophysiology laboratory.[7] Findings from the phase 1 and phase 2 studies suggested that etripamil nasal spray was rapidly absorbed across the nasal mucosa with a dose-dependent, time-to-maximum concentration of 5 to 8.5 minutes at doses ≥14 mg. Treatment with etripamil appeared to be well-tolerated, and most adverse events (AEs) were associated with the nasal route of administration (eg, nasal congestion, lacrimation, nasal discomfort, and rhinorrhea). Based on results from the phase 1 and 2 studies, the etripamil 70-mg nasal spray dose was chosen for further evaluation in the phase 3 study.

The randomized, double-blind, placebo-controlled, phase 3, multicenter NODE-301 (Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia) study (NCT03464019) evaluated the efficacy and safety of etripamil 70-mg nasal spray, self-administered by patients for the termination of a single episode of spontaneous, symptomatic PSVT in a medically unsupervised setting.[8] The NODE-302 (Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia) study (NCT038635996) described here was an open-label extension of NODE-301. The primary objective for NODE-302 was to evaluate the safety of etripamil 70-mg nasal spray for the treatment of multiple, spontaneous episodes of PSVT over long-term follow-up. Efficacy outcomes included the probability of conversion of PSVT to sinus rhythm (SR) within 30 minutes after etripamil nasal spray administration and the median time to conversion of PSVT episodes over 5 hours of ECG-recorded observation.

METHODS

Data Availability Statement

Data sharing requests for studies with products/uses approved may be submitted 12 months after marketing authorization in all planned regions. Qualified researchers from an appropriate institution may request access to individual participant data that underlie the results reported in this article, after deidentification. Upon

approval of a data sharing request, information necessary to address the research question will be provided under the terms of a signed data sharing agreement. Requests should be submitted to: datasharing@milestonepharma.com.

Study Design

NODE-302 was an open-label extension of the phase 3, multicenter, double-blind, placebo-controlled NODE-301 Part 1 study, which evaluated the efficacy and safety of etripamil 70-mg nasal spray administered outside the medically supervised setting in patients with symptomatic, sustained PSVT.[8] Details of the NODE-301 Part 1 study design and patient population have been reported previously.[8] Patients who were randomly assigned and completed a single treatment of spontaneous perceived PSVT in NODE-301 with etripamil or placebo, either negatively or positively adjudicated, could transition to the NODE-302 safety extension study if they continued to meet the inclusion criteria and lacked exclusion criteria (the full inclusion and exclusion criteria are in Data S1). The study was conducted at 65 centers in the United States and Canada (the list of participating centers and investigators is shown in Table S1). After each treated episode of PSVT, patients who did not meet any of the withdrawal criteria had the option to continue in the NODE-302 study and self-treat subsequent episodes of perceived PSVT with etripamil 70-mg nasal spray, for up to 11 episodes. The schedule of procedures is presented in Table S2.

Patients included in the study received training on steps to follow during suspected spontaneous PSVT (eg, how to apply the cardiac monitoring system [CMS; BodyGuardian Heart; Preventice], perform a vagal maneuver [VM], and self-administer the study drug while marking the time that the drug was taken using the patient-event marker of the CMS). Patients received a study kit that included the study drug, a patient diary, and a CMS paired with a smartphone for data transfer to an independent adjudication committee. The adjudication committee consisted of at least 5 cardiac electrophysiologists who adjudicated the presence of an atrioventricular nodal-dependent PSVT as well as termination due to VM if PSVT was present. They were also responsible for confirming the conversion of positively adjudicated episodes of supraventricular tachycardia to SR for at least 30 seconds after etripamil administration and observing any pauses, nonsustained ventricular tachycardia, atrioventricular block, or bradycardia. Non-PSVT episodes, including but not limited to SR, sinus tachycardia, atrial tachycardia, atrial fibrillation, and atrial flutter, were considered negatively adjudicated and were not included in the efficacy analysis, nor were episodes without ECG recordings because of technical problems (Figure 1). Patients who received medical intervention or in whom PSVT did not convert within the 5-hour observation period were censored at the end of the observation period, and patients in whom PSVT converted before study drug administration were censored at the beginning time point (ie, 0 minutes).

Outcomes

The primary end point for this study was safety. Safety variables were based on patient self-reports and clinician assessments after each dose of etripamil and included frequencies of AEs, serious AEs, treatment-emergent AEs (TEAEs; defined as AEs occurring within 24 hours of a study dose), and etripamil-related TEAEs. Other safety variables included vital signs (blood pressure and heart rate), results of laboratory tests (hematology, blood chemistry, and urinalysis), arrhythmias, and conduction disorders detected on surface ECGs or CMS recordings. Efficacy was also assessed. The primary efficacy end point for NODE-302 was defined as conversion of a positively adjudicated episode of atrioventricular nodal-dependent PSVT to SR for at least 30 seconds.

Statistical Analysis

The primary efficacy variable was calculated for patients in the efficacy population (all patients who used etripamil to treat a positively adjudicated episode of PSVT). Kaplan-Meier estimates of time to conversion were also calculated. All safety analyses were performed on the safety population (all patients who took etripamil for at least a single dose), and data were summarized with descriptive statistics. Continuous safety data were presented with the number of patients, minimum, maximum, median, mean, and SD; discrete safety data were summarized with frequency counts and percentages. Summary statistics were reported for demographic characteristics (eg, age, sex, race, and ethnicity) and for baseline disease variables (eg, age at enrollment, demonstrated history of sustained PSVT, number of PSVT episodes in the past year, number of previous lifetime visits to the emergency department, and atrioventricular nodal-blocking medications).

Ethics

The NODE-302 study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice guideline, and applicable local regulatory requirements. Institutional review board approval was obtained at each participating center, and all patients underwent an informed consent process that included signing an informed consent form before the conduct of any study-specific procedures.

RESULTS

Patient Characteristics

In total, 169 patients transitioned into the NODE-302 extension study (Figure 1). Among those who transitioned to NODE-302, 105 patients (62.1%) used etripamil 70-mg nasal spray for 1 or more perceived episodes of PSVT (median of 232 days of follow-up) and were therefore included in the safety population. Patients in the safety population had a mean±SD age of 58.0±13.75 years (range, 21–90 years) (Table 1). Most patients were women (65 [61.9%]) and White (87 [82.9%]), and most reported an ethnicity of non-Hispanic or non-Latino (100 [95.2%]). The mean±SD age at PSVT diagnosis was 57.2±13.79 years, and the mean±SD duration since diagnosis was 1.3±1.73 years. The mean number of PSVT episodes per patient in the year before enrollment in the NODE-301 study was 9.7, and patients had a mean of 2.7 lifetime emergency department visits for PSVT.

Disposition and Treated Episode Characteristics

There were 235 episodes treated with etripamil in the extension study overall; 97% were treated with 2 sprays (100 µL in each nostril, 70 mg total), and 3% were treated with 1 spray (35 mg total), most likely because of user error. In total, 188 episodes were adjudicated as positive episodes, 33 were adjudicated as negative episodes, and 14 were unable to be adjudicated because of missing ECG data. Most negatively adjudicated episodes (20 [60.6%]) were SR, and 6, 3, 3, and 1 episode were negatively adjudicated as sinus tachycardia, atrial fibrillation, atrial tachycardia, and junctional rhythm, respectively. Furthermore, 29 of 188 positively adjudicated PSVT episodes were censored; 7 of 188 (3.7%) were censored at the beginning period because PSVT converted to SR before etripamil administration, 6 of 188 (3.2%) were censored at the end of the 5-hour observation period because PSVT did not convert to SR, and 16 of 188 (8.5%) required additional

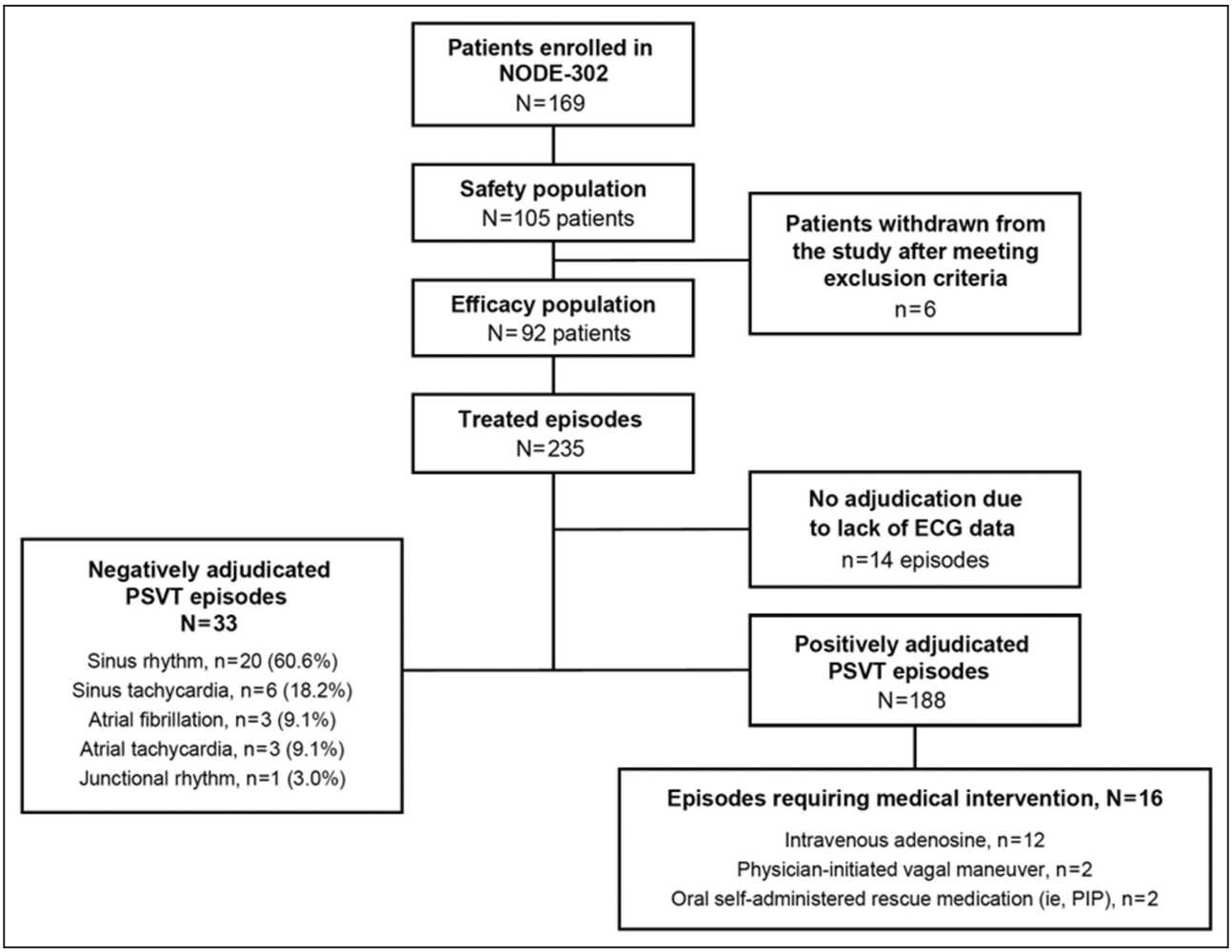

Figure 1. Patient disposition.
PIP indicates pill-in-the-pocket; and PSVT, paroxysmal supraventricular tachycardia. NODE-302: Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia.

Table 1. Demographics and Patient Characteristics

Category	Safety population (N=105)	Efficacy population (N=92)
Age at informed consent, mean (SD), y	58.0 (13.75)	58.4 (13.12)
Median (range)	61.0 (21–90)	61.0 (21–90)
Female sex, n (%)	65 (61.9)	53 (57.6)
Race, n (%)		
White	87 (82.9)	75 (81.5)
Black	8 (7.6)	8 (8.7)
Asian	3 (2.9)	3 (3.3)
Native Hawaiian or Pacific Islander	2 (1.9)	1 (1.1)
Other	5 (4.8)	5 (5.4)
Ethnicity, n (%)		
Hispanic or Latino	1 (1.0)	1 (1.1)
Non-Hispanic or non-Latino	100 (95.2)	87 (94.6)
Not reported	3 (2.9)	3 (3.3)
Unknown	1 (1.0)	1 (1.1)
Age at confirmation of PSVT, mean (SD), y	57.2 (13.79)	57.6 (13.04)
Median (range)	60.0 (21–87)	60.2 (21–87)
PSVT confirmation duration, mean (SD), y	1.3 (1.73)	1.3 (1.71)
Median (range)	0.6 (0–12)	0.6 (0–12)
PSVT episodes in the year before NODE-301, mean (SD)	9.7 (11.79)	9.4 (12.06)
Median (range)	6.0 (1–60)	6.0 (1–60)
Emergency department visits for PSVT in a lifetime	N=103	N=90
Mean (SD)	2.7 (2.74)	2.6 (2.77)
Median (range)	2.0 (0–13)	2.0 (0–13)
Selective BB, n (%)	37 (35.2)	
Nonselective BB, n (%)	4 (3.8)	
DHP CCB, n (%)	9 (8.6)	
Non-DHP CCB, n (%)	22 (20.9)	

BB indicates β-blocker; CCB, calcium channel blocker; DHP, dihydropyridine; and PSVT, paroxysmal supraventricular tachycardia.

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

Table 2. PSVT Episodes, Etripamil Nasal Spray Exposure, Duration of Study

Category	Safety population (N=105)
Calculated no. of treated episodes per year, mean (SD), events/y*	6.0 (7.84)
Median (range)	3.7 (1–46)
Calculated number of positive PSVT episodes per year, mean (SD), events/y*	4.4 (6.11)
Median (range)	2.6 (0–41)
Enrollment to first etripamil-treated positively adjudicated PSVT episode, d†	N=92
Mean (SD)	89.8 (112.79)
Median (range)	46.5 (3–518)
Enrollment to second etripamil-treated positively adjudicated PSVT episode, d†	N=40
Mean (SD)	119.5 (88.69)
Median (range)	93.5 (18–290)
Enrollment to third etripamil-treated positively adjudicated PSVT episode, d†	N=25
Mean (SD)	156.1 (107.97)
Median (range)	121 (28–402)
Patients with ≥1 perceived PSVT episodes treated with etripamil, n (%)	N=105
1	52 (49.5)
2	24 (22.9)
3	12 (11.4)
4	8 (7.6)
5	2 (1.9)
≥6	7 (6.7)
Patients with ≥1 adjudicated PSVT episodes treated with etripamil, n (%)	N=92
1	52 (56.5)
2	15 (16.3)
3	14 (15.2)
4	4 (4.3)
5	1 (1.1)
≥6	6 (6.5)

PSVT indicates paroxysmal supraventricular tachycardia.

*Events per y=([number of events]÷[days in study])×365.

†Excluding patients with 0 episodes.

medical intervention within the observation period. Of the 16 positively adjudicated PSVT events in 12 of 92 (13%) patients who required additional intervention, 12 (6.4%) episodes were treated with intravenous adenosine, 2 (1.1%) were treated with physician-assisted VM, and 2 (1.1%) were treated with oral self-administered rescue medication or PIP (Table S3; Figure S1).

Among 105 patients who self-administered etripamil for a perceived PSVT event, 92 (87.6%) had a positively adjudicated PSVT episode (efficacy population). Most patients (76 [72.4%]) had 1 (52 [49.5%]) or 2 (24 [22.9%]) perceived PSVT episodes treated with etripamil; however, 29 (27.6%) patients had ≥3 episodes, including 2 patients who self-administered etripamil for a total of 11 perceived episodes (Table 2).

Two of 169 patients (1.2%) reached study completion, defined as meeting the maximum of 11 episodes of perceived PSVT self-treated with etripamil 70-mg nasal spray and completing treatment. Among the remaining patients, 6 (3.6%) experienced an AE that met an exclusion criterion, 20 (12%) withdrew voluntarily, and 94 (56.3%) continued in the trial until the sponsor terminated the study in October 2020. No patients withdrew from the study because of etripamil-related AEs.

A total of 188 positively adjudicated PSVT episodes occurred in 92 patients. The median (range)

time in the study was 223 days (1–584 days). The median (range) duration from patient enrollment to the second positively adjudicated PSVT episode treated with etripamil was 93.5 days (18–290 days), with a median (range) duration of 121 days (28–402 days) until the third positively adjudicated PSVT episode treated with etripamil. The calculated median (range) number of treated episodes per year and positively adjudicated PSVT episodes per year were 3.7 (1–46) and 2.6 (0–41), respectively.

Safety Outcomes

In the safety population, 67 of 105 patients (63.8%) reported ≥1 AE and 45 (42.9%) reported ≥1 TEAE (defined as an AE occurring within 24 hours of a study dose; Table 3). The most common TEAEs (by preferred term) were nasal discomfort (15 patients [14.3%]), nasal congestion (15 [14.3%]), and rhinorrhea (13 [12.4%]) and were generally mild (36 [34.3%]) or moderate (7 [6.7%]). TEAEs localized to the drug administration site, including nasal discomfort, throat irritation, and lacrimation, significantly decreased in frequency with repeated administrations over the time from the NODE-301 feeder study to the same patients' administrations in this NODE-302 extension study (Figure S1). Severe TEAEs were reported in only 2 patients (1.9%) (epistaxis [n=1] and rhinorrhea and epistaxis [n=1]). However, only 34 patients (32.4%) had a TEAE that the investigator considered to be related to the study drug.

Overall, 8 patients (7.6%) experienced at least 1 serious AE, none of which appeared to be etripamil-related or treatment emergent (ie, none occurred within 24 hours of etripamil administration). The most frequently reported serious AE was supraventricular tachycardia (3 patients [2.9%]); all other serious AEs were reported by 1 patient (1.0%) each: bradycardia (occurring 112 days after etripamil administration), syncope (50 days after etripamil administration), ataxia (53 days after etripamil administration), pancreatitis (7 days after etripamil administration), and troponin elevation (1 day after etripamil administration). Six patients (5.7%) experienced an AE that met an exclusion criterion and thus led to study withdrawal; 3 patients (2.9%) experienced atrial fibrillation, and 1 patient each (1.0%) experienced syncope, bradycardia, and ataxia. A complete summary of TEAEs is presented in Table S4. There were no clinically significant changes in laboratory blood test results during the study. There were no reported cases of syncope or symptoms of hypotension following etripamil administration during PSVT. Moreover, there were no episodes of atrioventricular block, bradycardia, or pauses after PSVT conversion with etripamil recorded by the CMS.

Table 3. Summary of AEs and TEAEs*

Category	Safety population (N=105)
Patients with any AE, n (%)	67 (63.8)
Patients with any SAE, n (%)†	8 (7.6)
Patients with any AE leading to death, n (%)	0 (0.0)
Patients with any TEAE, n (%)	45 (42.9)
Mild	36 (34.3)
Moderate	7 (6.7)
Severe‡§	2 (1.9)
Patients with any TEAE related to etripamil, n (%)	34 (32.4)
Nasal discomfort	15 (14.3)
Nasal congestion	15 (14.3)
Rhinorrhea	13 (12.4)
Epistaxis	5 (4.8)
Sneezing	4 (3.8)
Cough	2 (1.9)
Throat pain	2 (1.9)
Headache	2 (1.9)
Lacrimation increased	2 (1.9)
TEAE severity, n (%)	34 (32.4)
Mild	28 (26.7)
Moderate	4 (3.8)
Severe‡ (epistaxis [2 episodes], runny nose)	2 (1.9)
Patients with any TEAE after patient's first episode of etripamil, n (%)	38 (36.2)
Patients with any TEAE after patient's second episode of etripamil, n (%)§	15 (28.3)

AE indicates adverse event; SAE, serious adverse event; and TEAE, treatment-emergent adverse event.

*Defined as an AE occurring within 24 hours of etripamil administration.

†None of the SAEs were considered by an investigator to be etripamil related.

‡Local irritation included epistaxis and rhinorrhea (n=1) and epistaxis (n=1).

§N=53 was used as the denominator for second episodes.

Efficacy Outcomes

In the efficacy population (188 positively adjudicated PSVT episodes in 92 patients), among all, first, and second positively adjudicated PSVT episodes, 7, 4, and 2 episodes, respectively, were censored at the beginning time point (0 minutes) owing to PSVT conversion recorded before drug administration. Overall, 109 of 181 (60.2%) converted to SR by 30 minutes (Figure 2A), and the median time to conversion was 15.5 minutes (Table 4). During the patients' first positively adjudicated PSVT episodes, PSVT converted to SR by 30 minutes in 47 of 88 patients (53.4%) (Figure 2B), with a median time to conversion of 21.1 minutes. In patients with a second positively adjudicated PSVT episode, PSVT converted to SR within 30 minutes in 24 of 38 (63.2%) (Figure 2C), with a median time to conversion of 13.7 minutes.

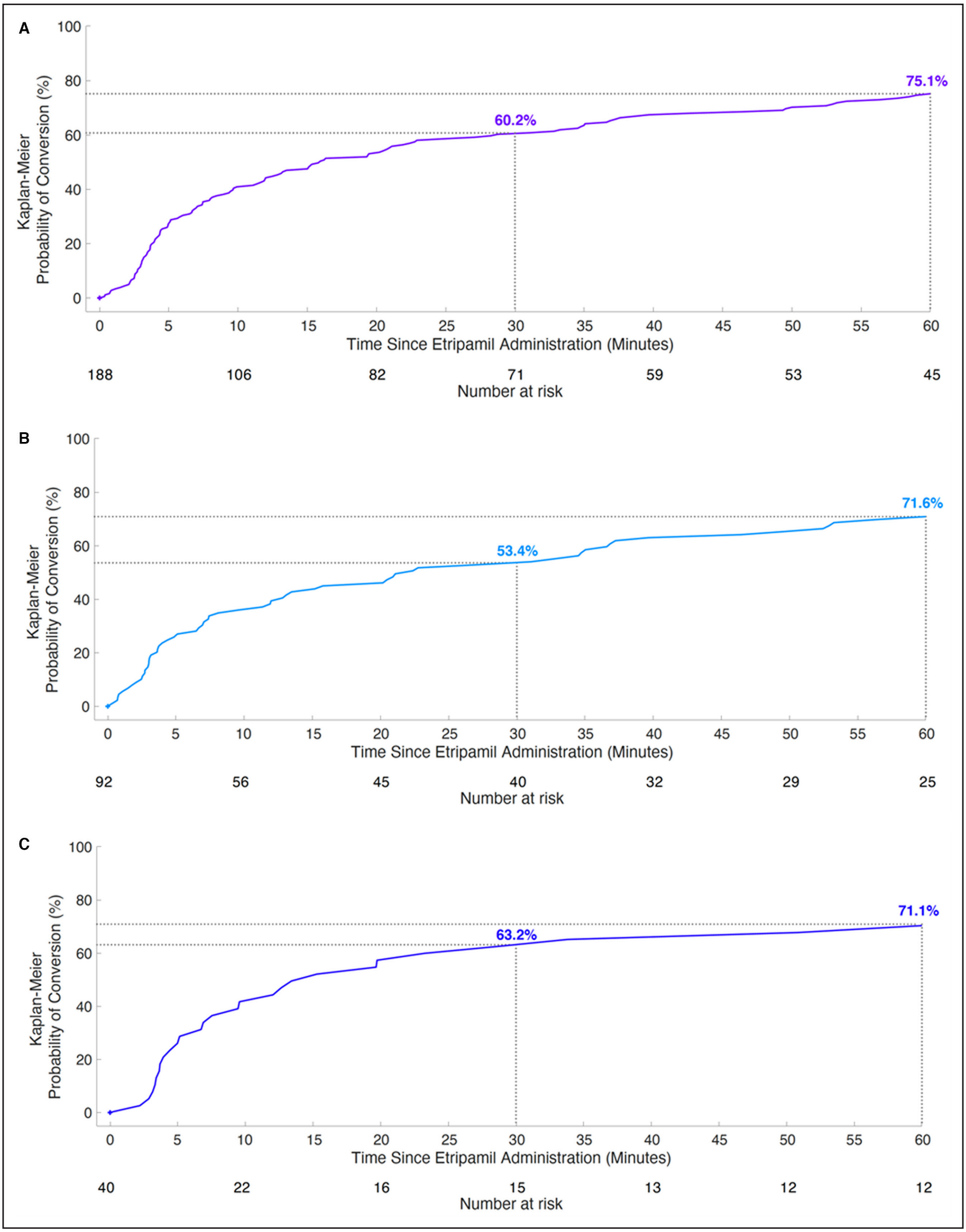

Figure 2. Kaplan-Meier plot of conversion up to 60 minutes in all (A), first (B), and second (C) positively adjudicated PSVT episodes in the efficacy population.

Among all, first, and second positively adjudicated PSVT episodes, 7, 4, and 2 episodes, respectively, were censored at the beginning time point (0 minutes) owing to PSVT conversion to SR before etripamil administration. PSVT indicates paroxysmal supraventricular tachycardia; and SR, sinus rhythm.

Table 4. Summary of Adjudicated PSVT to SR Conversions: All Events, First Episodes, Second Episodes, and Third Episodes

Characteristic	Efficacy population (N=92)
All events	
No. of episodes	188*
Episodes converted to SR by 30 min, n (%)	109 (60.2)
Kaplan-Meier estimate, median (95% CI), min	15.5 (11.3–22.1)
First episode	
No. of patients	92*
Episodes converted to SR by 30 min, n (%)	47 (53.4)
Kaplan-Meier estimate, median (95% CI), min	21.1 (11.6–35.5)
Second episode	
No. of patients	40*
Episodes converted to SR by 30 min, n (%)	24 (63.2)
Kaplan-Meier estimate, median (95% CI), min	13.7 (6.6–32.3)
Third episode	
No. of patients	25
Episodes converted to SR by 30 min, n (%)	19 (76.0)
Kaplan-Meier estimate, median (95% CI), min	8.2 (5.5–15.8)

PSVT indicates paroxysmal supraventricular tachycardia; and SR, sinus rhythm.

*Among all, first, and second positively adjudicated PSVT episodes, 7, 4, and 2 episodes, respectively, were censored at the beginning time point (0 min) owing to PSVT conversion to SR before etripamil administration.

Patient responses on their first PSVT episode appeared to be predictive of responses on their second episode (Table 5). Seventy-five percent of patients (30 of 40) had a consistent response (ie, responded for both episodes or did not respond for either episode). Among patients in whom PSVT was successfully terminated with etripamil during their first episode, 21 of 26 (81%) also had successful termination of PSVT with etripamil during their second episode. A logistic regression model suggested a statistically significant relationship between a patient's first and second episodes for conversion to SR at 30 minutes (χ^2=8.09; P=0.0045). This relationship was even stronger when the response was defined as conversion to SR at 15 minutes (χ^2=15.1; P=0.0001).

Table 5. Consistency of Conversion at 30 Minutes Between the First and Second Adjudicated PSVT Episodes (N=40)*

Variable	No response on first episode	Response on first episode
No response on second episode, n (%)	9 (22.5%)	5 (12.5%)
Response on second episode, n (%)	5 (12.5%)	21 (52.5%)

*PSVT indicates paroxysmal supraventricular tachycardia. χ^2 test of the comparison indicates a statistically significant relationship between responses during a patient's first and second episodes (χ^2=8.09; P=0.0045).

DISCUSSION

This is the first long-term follow-up study evaluating the safety and efficacy of self-administered etripamil 70-mg nasal spray for repeated symptomatic PSVT episodes that are unresponsive to VMs. Over clinically separate episodes, the safety and tolerability of repeat self-administration of etripamil, without medical supervision, appeared to be maintained during this study, with no reported cases of syncope, hypotension, or ECG recordings of atrioventricular block, bradycardia, or conversion pauses after etripamil administration. Moreover, the data suggest that etripamil was well-tolerated, and most AEs were mild to moderate, local, and transient, likely because of the intranasal delivery and acidic solution of the study drug. No patients experienced any serious AEs related to the study drug. One patient experienced atrial fibrillation before study drug administration. These findings further indicate that self-administered etripamil has the potential to be safe and effective for treatment of atrioventricular nodal-dependent supraventricular tachycardia in a medically unsupervised setting over long-term follow-up.

Etripamil was associated with conversion of positively adjudicated PSVT to SR within 30 minutes of self-administration in most episodes (109 of 181 [60.2%]), with a median of 15.5 minutes to conversion. It is noteworthy that the median time to conversion is consistent with the pharmacological profile of etripamil, and the PSVT termination rates are consistent with results from the NODE-301 trial, which reported a 54% conversion rate at 30 minutes, compared with 35% for placebo.[8] Responses to etripamil appeared to be consistent across repeated episodes of PSVT, with responses to the first PSVT episode being predictive of responses during a second episode; 21 of 26 patients (81%) who had a first PSVT episode terminated with etripamil had a second PSVT episode terminated with etripamil. Interestingly, in 5 of 14 patients (35.7%) in whom PSVT did not terminate in response to etripamil during the first episode, PSVT still converted during the second episode. These findings suggest that etripamil maintains persistent efficacy for conversion of PSVT over subsequent episodes and should still be tried for subsequent episodes even when ineffective for an initial episode.

Atrioventricular nodal-dependent PSVT can recur without warning, sometimes with increasing frequency or high burden. It is estimated that in the United States, there are >140 000 emergency department visits for PSVT annually, with a prevalence of >1.3 million patients.[9] Among patients who had an ECG-adjudicated PSVT event in NODE-301, and subsequently transitioned into the NODE-302 described here, patients

had a median of 6.0 PSVT episodes in the year before enrollment in the trial. Furthermore, over a median of 232 days after NODE-302 enrollment, >60% of patients developed recurrent, symptomatic PSVT episodes, which the patient deemed to require self-treatment with etripamil after VMs were ineffective. Notably, patients in NODE-302 had a calculated median (range) of 3.7 (1–46) treated PSVT episodes per year. This high arrhythmia burden occurred although 63 patients were prescribed chronic concomitant oral therapy for PSVT, including BBs or CCBs.

Current recommendations for outpatient treatments to manage recurrent PSVT episodes that are refractory to VMs include oral BBs or CCBs, which are prescribed as daily therapy or as needed during PSVT episodes. However, there is limited clinical evidence to support the efficacy and safety of this latter PIP strategy. In a small (N=33) clinical trial of crushed flecainide versus crushed diltiazem+propranolol for induced PSVT, conversion to SR occurred within 2 hours in 52%, 61%, and 94% of patients following treatment with placebo, flecainide, and diltiazem+propranolol, respectively (P<0.001). The mean±SD time to conversion was 32±22 minutes with diltiazem+propranolol, 74±37 minutes with flecainide, and 77±42 minutes with placebo (P<0.001).[5] In comparison, the rates of conversion 30 and 60 minutes after self-administration of investigational etripamil in our study were 60.2% and 75.1%, respectively.

Furthermore, our data suggest the continued safety of etripamil for both single and recurrent supraventricular tachycardia episodes. By contrast, 4 of 33 patients (12%) developed hypotension requiring electrical termination of PSVT after receiving placebo (1 patient), flecainide (2 patients), or diltiazem+propranolol (1 patient) in the small aforementioned trial; during that study's 17±12 months (range, 4–48 months) of follow-up, AEs during supraventricular tachycardia episodes were reported in 11 of 31 patients (35%) and included asthenia (6 patients), nausea (1 patient), vomiting (2 patients), cephalea (1 patient), and syncope with trauma (1 patient).[5]

In previous studies, outpatient follow-up of PIP treatments for PSVT involved self-reported efficacy without any ECG verification of PSVT or termination. In contrast, in the NODE-302 study described here, PSVT episodes and terminations were independently adjudicated using ECG monitoring, and no treatment-related atrioventricular block, pauses, or bradycardia were observed after conversion.

Because of the limited evidence for PIP strategies, the most recent (2019) European supraventricular tachycardia guidelines omitted their use, despite their inclusion in the prior 2003 guidelines.[1] Self-administered oral BB, diltiazem, and verapamil carry a class IIB indication in the latest US guidelines for the ongoing management of patients with infrequent, well-tolerated episodes of atrioventricular nodal-reentrant tachycardia.[10] The latter guidelines highlight overall safety concerns with PIP BBs/CCBs for PSVT treatment because of the potential risks of syncope, hypotension during supraventricular tachycardia, and bradycardia following conversion observed in previous studies using this approach.

STUDY LIMITATIONS AND FUTURE DIRECTIONS

The open-label design of NODE-302 has inherent limitations. All patients in this study received etripamil, and as such, efficacy measurements cannot be compared with placebo, as in the preceding NODE-301 study. It is also possible that patients who had a negative experience (either safety or efficacy related) with the study drug in NODE-301 would be less likely to enroll in the open-label NODE-302 study. Nevertheless, results from this study demonstrate the consistent safety of etripamil 70-mg nasal spray, self-administered for symptomatic PSVT treatment without medical supervision. No patients withdrew from this trial because of etripamil-related AEs.

Another important limitation of the NODE-302 study was that patients were permitted to use, and were provided with, only a single dose of etripamil 70-mg for each PSVT episode. Similar to the use of intravenous adenosine for termination of atrioventricular nodal-dependent PSVT, the response to etripamil is likely dose dependent. Therefore, optimal dosing of etripamil for improved efficacy and persistent safety continues to be actively investigated. The ongoing phase 3, randomized, placebo-controlled RAPID (Multi-Centre, Ranomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia) trial (NODE-301 Part 2) includes an option for patients to self-administer a second dose of the study drug 10 minutes after the first dose if symptoms persist during spontaneous PSVT. Following their first treated PSVT event in the RAPID trial, an open-label treatment phase and subsequent enrollment in the NODE-X study will allow patients to treat subsequent PSVT episodes with etripamil, using up to two 70-mg doses, over continued long-term follow-up. These studies will provide valuable insight on the efficacy and safety of the new dose regimen for the long-term management of recurrent symptomatic PSVT episodes. The study design, which did not specify a time when etripamil must be taken after PSVT initiation, and unobserved patient behaviors (to verify proper drug administration), could have influenced the conversion rate and the time to PSVT conversion. However, the NODE-302 study

was designed to reflect the anticipated real-world use of etripamil. Although patients were instructed on how to use etripamil beforehand, were observed using a test dose during the NODE-301 study, and were provided access to written instructions and a telephone coach, the NODE-302 study described here did not involve direct observation of etripamil use during a PSVT event. Study personnel verified that returned spray devices were used after each event, and 3% of episodes were treated with only half of the dispensed dose. Finally, some PSVT episodes (n=14, 6%) could not be adjudicated because of missing ECG data and were not included in the efficacy analysis.

The results from the NODE-302 study suggest that investigational etripamil is a safe and effective self-administered treatment for treating spontaneous, VM-refractory PSVT without medical supervision. There were no signals of new safety concerns or AEs during this long-term follow-up of repeat drug administration for up to 11 episodes. This therapeutic approach could potentially reduce emergency medical service use for treating VM-resistant PSVT episodes. Pending studies of a second dose of intranasal etripamil during ongoing PSVT without medical supervision will provide additional safety and efficacy data to assess its potential therapeutic application.

ARTICLE INFORMATION

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J.E.I. serves on the steering committee for Milestone Pharmaceuticals. B.S.S, P.S., M.C., and A.J.C. are consultants for Milestone Pharmaceuticals. P.S. has equity in Milestone Pharmaceuticals. S.S. and F.P. are employees of Milestone Pharmaceuticals. A.J.C. has received 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. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Table S1–S4
Figure S1

REFERENCES

1. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, Calkins H, Corrado D, Deftereos SG, Diller GP, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:655–720. doi: 10.1093/eurheartj/ehz467
2. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA III, Field ME, Goldberger ZD, Hammill SC, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2016;13:e92–e135. doi: 10.1016/j.hrthm.2015.09.018
3. Krikler DM, Spurrell RA. Verapamil in the treatment of paroxysmal supraventricular tachycardia. *Postgrad Med J*. 1974;50:447–453. doi: 10.1136/pgmj.50.585.447
4. Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. *Circulation*. 2003;107:1096–1099. doi: 10.1161/01.cir.0000059743.36226.e8
5. Alboni P, Tomasi C, Menozzi C, Bottoni N, Paparella N, Fuca G, Brignole M, Cappato R. Efficacy and safety of out-of-hospital self-administered single-dose oral drug treatment in the management of infrequent, well-tolerated paroxysmal supraventricular tachycardia. *J Am Coll Cardiol*. 2001;37:548–553. doi: 10.1016/s0735-1097(00)01128-1
6. Yeh SJ, Lin FC, Chou YY, Hung JS, Wu D. Termination of paroxysmal supraventricular tachycardia with a single oral dose of diltiazem and propranolol. *Circulation*. 1985;71:104–109. doi: 10.1161/01.cir.71.1.104
7. Stambler BS, Dorian P, Sager PT, Wight D, Douville P, Potvin D, Shamszad P, Haberman RJ, Kuk RS, Lakkireddy DR, et al. Etripamil nasal spray for rapid conversion of supraventricular tachycardia to sinus rhythm. *J Am Coll Cardiol*. 2018;72:489–497. doi: 10.1016/j.jacc.2018.04.082
8. Stambler BS, Plat F, Sager PT, Shardonofsky S, Wight D, Potvin D, Pandey AS, Ip JE, Coutu B, Mondésert B, et al. First randomized, multicenter, placebo-controlled study of self-administered intranasal etripamil for acute conversion of spontaneous paroxysmal supraventricular tachycardia (NODE-301). *Circ Arrhythm Electrophysiol*. 2022;15:e010915. doi: 10.1161/circep.122.010915
9. Sacks NC, Cyr PL, Preib MT, Everson K, Wood DR, Raza S, Pokorney SD. Healthcare resource use and expenditures in patients newly diagnosed with paroxysmal supraventricular tachycardia. *Am J Cardiol*. 2020;125:215–221. doi: 10.1016/j.amjcard.2019.10.015
10. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA III, Field ME, Goldberger ZD, Hammill SC, 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. *Heart Rhythm*. 2016;13:e136–e221. doi: 10.1016/j.hrthm.2015.09.019