SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Full List of Inclusion/exclusion Criteria .

Patients who met all of the following criteria were eligible to participate in the study:

1. Male or female patients at least 18 years of age.
2. Signed the NODE-302 written informed consent.
3. Previously randomized in Part 1 of the NODE-301 study:
    - Completed test dose of etripamil 70 mg (during sinus rhythm) without meeting any exclusion criteria.
    - Completed randomized study dose to treat perceived PSVT during NODE-301 study.
    - Received etripamil to treat symptoms that the patient believed were consistent with an episode of PSVT during Part 1 of the NODE-301 study, irrespective of the study drug efficacy.
4. Willing and able to comply with all aspects of the study.
5. Females of childbearing potential who were sexually active must have agreed to use an approved, highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of etripamil. Females of childbearing potential should have had a negative urine pregnancy test result at the qualification visit and at the follow-up visit(s) and must have used an approved form of contraception between the two visits. Approved forms of contraception included hormonal intrauterine devices and hormonal contraceptives (oral birth control pills, Depo-Provera®, patch, or other injectables) together with supplementary double-barrier methods, such as condoms or diaphragms with spermicidal gel or foam.
6. The following categories define females who were NOT considered to be of childbearing potential:
    - Premenopausal females with 1 of the following:
        i. Documented hysterectomy,
        ii. Documented bilateral salpingectomy, or
        iii. Documented bilateral oophorectomy, or
    - Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause.
7. Male patients, except those who are surgically sterile, must have used an approved, highly effective form of contraception during the three days after etripamil administration.

Patients who met any of the following criteria were excluded from participation in the study:

8. Evidence of new severe arrhythmia discovered since Part 1 of the NODE-301 test dose randomization visit, including those reported on the CMS report of the outpatient PSVT event treated with etripamil in Part 1 of the NODE-301 study, including but not limited to the following:

a. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm;

b. Significant symptomatic sinus bradycardia heart rate ≤40 bpm or sinus pauses (≥3 seconds);

c. Any significant ventricular arrhythmia (premature ventricular beats and couplets [>6 premature ventricular contractions per 45 seconds ECG] are considered significant); and

d. Atrial fibrillation (event lasting longer than 30 seconds) or atrial flutter.

9. Any drug-related or procedure-related SAE during Part 1 of the NODE-301 study.
10. Any severe AE in Part 1 of the NODE-301 study that was severe enough to preclude the administration of etripamil NS 70 mg in the NODE-302 study.
11. Any new drug prescribed after the end of the patient's participation in Part 1 of the NODE-301 study that may have lowered blood pressure or decreased AV node conduction.
12. Systolic blood pressure <90 mm Hg after a 5-minute rest in the sitting position at the NODE-302 qualification visit.
13. Any symptoms consistent with clinically severe hypotension, such as presyncope, medically significant lightheadedness, syncope, nausea, or vomiting.
14. New therapy with digoxin, amiodarone, or any class I or III antiarrhythmic drug added after the end of the patient's participation in Part 1 of the NODE-301 study.
15. New evidence of ventricular pre-excitation (eg, delta waves, short PR interval, and Wolff-Parkinson-White syndrome) on the ECG since randomization in Part 1 of the NODE-301 study.
16. New symptoms of congestive heart failure defined by the New York Heart Association class II to IV since randomization in Part 1 of the NODE-301 study.
17. New stroke since randomization in Part 1 of the NODE-301 study.
18. New evidence of a significant physical or psychiatric condition, including drug abuse, which, in the opinion of the investigator, could jeopardize the safety of the patient or impede the patient's capacity to follow the study procedures since randomization in Part 1 of the NODE-301 study.
19. New syncope following randomization in Part 1 of the NODE-301 study, especially if observed during the monitoring of the event treated in Part 1 of the NODE-301 study.
20. New evidence of hepatic dysfunction, defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin >2 × ULN, unless due to Gilbert syndrome, observed at the NODE-302 qualification visit.
21. New evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the NODE-302 qualification visit as follows:

    a. <60 mL/min/1.73 m^2 for patients <60 years of age;
    a. <40 mL/min/1.73 m^2 for patients ≥60 and <70 years of age; and
    b. <35 mL/min/1.73 m^2 for patients ≥70 years of age.

22. Participation in any investigational drug or device study or the use of any investigational drug or device since the final study visit in Part 1 of the NODE-301 study.

Table S1. Study Investigators and Sites.

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Table S2. Schedule of Procedures.

Assessment	Qualification visit[*]	Treatment period(s)[†]	Follow-up visit(s)[‡]	Final study visit[§]	Early termination visit[¶]
Informed consent	X				
Eligibility	X[#]		X		
Review postdose AEs from NODE-301 Part 1	X				
Contact the telephone coach		X[**]			
Recent medical status	X[††]		X	X	
Concomitant medications	X		X	X	
Physical examination[‡‡]	X			X	
Vital signs (blood pressure and heart rate)	X		X	X	
Hematology, chemistry, and urinalysis	X[§§]		X[¶¶]	X[##]	
Pregnancy test[***]	X		X	X	
12-lead ECG	X				
AEs		X	X	X	
Dispensed study kit[†††]	X		X[‡‡‡]		
Reviewed CMS safety report[§§§]	X		X	X	
Administered etripamil NS 70 mg and recorded time of dosing		X[¶¶¶]			
Reviewed/patient completed patient diary entries on scoring scales		X	X	X	
Identified PSVT episode		X			
Applied and started CMS		X[###]			
Performed VM		X			
Evaluated medical intervention during the treatment period(s)	X[****]		X	X	
Collected study kit			X[††††]	X[‡‡‡‡]	X[‡‡‡‡]
Identified reason(s) for study completion or withdrawal				X	X
Closed case with IRT				X	X
Obtained signed withdrawal form					X

AE indicates adverse event; CMS, Cardiac Monitoring System; CMS safety report, analysis of the ECG tracing by a core laboratory for cardiac safety; ECG, electrocardiogram; IRT, interactive response technology; NS, nasal spray; PSVT, paroxysmal supraventricular tachycardia; TSQM, Treatment Satisfaction Questionnaire for Medication; and VM, vagal maneuver.

Note: Patients were asked to sign the NODE-302 informed consent form before commencement of any study-related assessments or procedures, and the signed informed consent form was applicable for the initial and all subsequent episodes of PSVT.

[*]The qualification visit of this study may have coincided with the NODE-301 Part 1 final study visit, or it may have been conducted at a future time.

[†]The treatment period began immediately following the qualification visit. Eligible patients performed a sequence of steps, including etripamil NS 70 mg self-administration, when patients identified symptoms of PSVT.

[‡]All patients who experienced an episode of PSVT and self-administered etripamil NS 70 mg were instructed to return to the site within 7 days after each episode. Patients may have continued to use etripamil NS 70 mg up to a maximum of 11 doses in the NODE-302 study. If the patient used the CMS for an episode of PSVT that subsequently was terminated by a successful VM (ie, the patient did not use etripamil NS 70 mg), the patient was instructed to return to the site within 7 days after the episode to ensure that all data had been downloaded from the CMS.

[§]A final study visit occurred under prespecified circumstances. A complete assessment was performed by the investigator.

[¶]The investigator made every attempt to complete an early termination visit for patients that withdrew or were discontinued from the study.

[#]Confirmation of eligibility at the qualification visit included confirmation of PSVT diagnosis.

[**]If possible, the telephone coach guided the patient through the study procedures. If the patient was unable to reach the telephone coach, the patient might have proceeded with the procedures using the printed and electronic guides.

[††]Recent medical status since the completion of NODE-301 Part 1.

[‡‡]Including height and weight.

[§§]Hematology, chemistry, and urine safety tests were performed for all patients in the NODE-301 Part 1 final study visit, and these safety results may have been used as a baseline for the NODE-302 study if the NODE-302 qualification visit occurred within 48 hours of the NODE-301 Part 1 final study visit. However, if the qualification visit occurred after 48 hours of the NODE-301 Part 1 final study visit, the hematology, chemistry, and urine tests were repeated.

[¶¶]Hematology, chemistry, and urine samples were collected only at the first follow-up visit, for which the patient took etripamil NS 70 mg.

[##]Hematology, chemistry, and urine safety tests were performed only if the patient took etripamil NS 70 mg.

[***]For females of childbearing potential, a urine pregnancy test was required at the qualification visit and at the follow-up visit(s).

[†††]The study kit included etripamil NS, a CMS, a study identification card, the patient's study instructions, and other study-related material.

[‡‡‡]After the initial study kit was dispensed, patients who decided to continue in the study received a new study kit (up to a maximum of 11 doses of etripamil NS 70 mg) after each episode of PSVT. Patients may have retained the study identification card (if unused, but otherwise, it was replaced). The patient was provided with a new diary (TSQM and relief of symptoms numeric scoring scales). The CMS safety report for the treated episode of PSVT must have been reviewed before an additional drug kit was dispensed.

[§§§]The interpretation of the CMS ECG was provided to the site by the cardiac monitoring core laboratory. These reports were sent to the site and the medical monitor. The presence of an episode of PSVT and termination was evaluated by an independent adjudication committee. The adjudication committee's evaluations were done using the complete CMS ECG recorded during the patient's PSVT episode.

[¶¶¶]During the treatment period(s), etripamil NS 70 mg should have only been administered if the VM did not resolve the patient's symptoms. The patient pushed the CMS event marker button to record the time of dosing immediately prior to self-administering etripamil NS 70 mg intranasally as instructed. If symptoms of an episode of PSVT did not resolve within 20 minutes after etripamil NS 70 mg administration, patients might have sought appropriate medical care.

[###]The CMS recording during an episode of PSVT should have continued for at least 5 hours regardless of treatment outcome.

[****]For the treatment period in Part 1 of the NODE-301 study.

[††††]Including used etripamil and CMS. The CMS was checked to ensure that all data were downloaded and transmitted to the core laboratory prior to being given back to the patient.

[‡‡‡‡]Including used or unused etripamil and CMS and study identification card.

Table S3. Summary of Additional Medical Interventions for Positively Adjudicated PSVT Events.

Category, n (%)	**Efficacy population (N=92)**
Any	12 (13)
1	9 (9.8)
2	3 (3.3)
3	0
≥4	0

PSVT indicates paroxysmal supraventricular tachycardia.

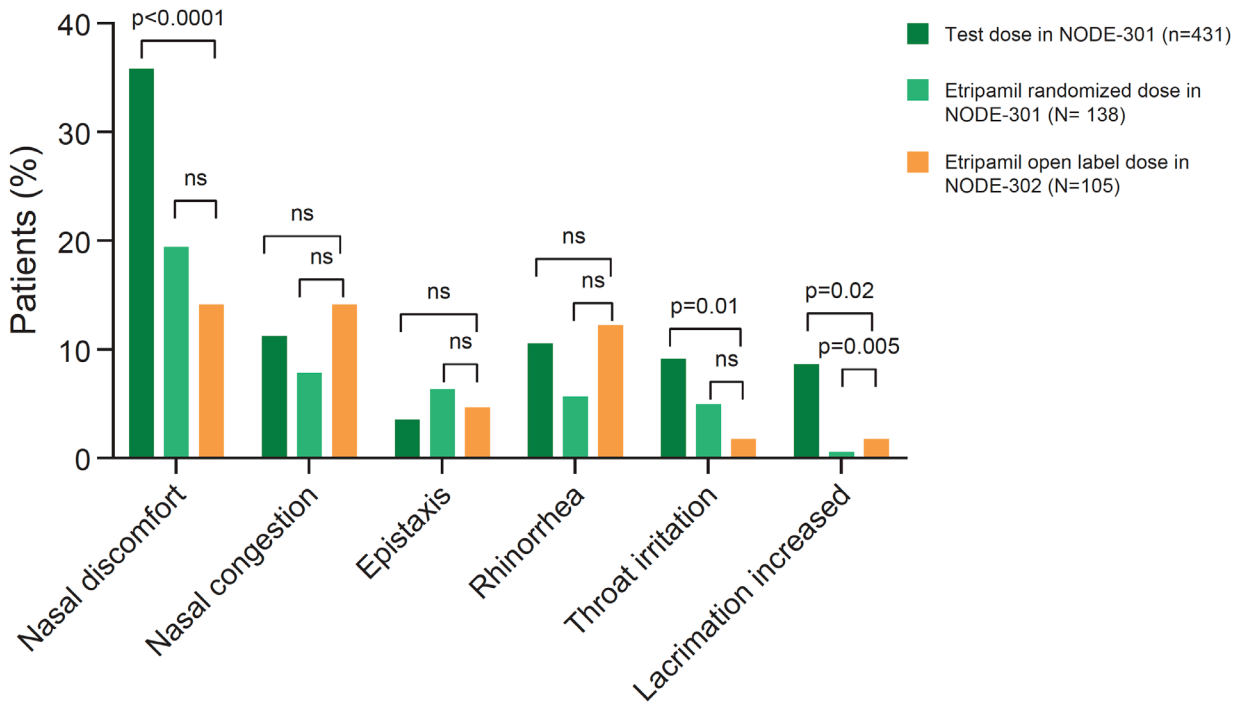
Table S4. Most Frequent (>1 Patient) TEAEs*

Preferred term	Safety population (N=105)
Patients with any TEAE	45 (42.9)
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)
Oropharyngeal pain	2 (1.9)
Headache	3 (2.9)
Dizziness	2 (1.9)
Paresthesia	2 (1.9)
Lacrimation increased	2 (1.9)
Palpitations	2 (1.9)
Atrial fibrillation	2 (1.9)

AE indicates adverse event; TEAE, treatment-emergent AE.

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

Figure S1. TEAEs localized to the drug administration site.



*ns = not significant