Supplemental Material

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2. Eligibility Criteria

Inclusion Criteria

Patients who meet all the following criteria will be eligible to participate in the study:

1. Male or female patients at least 18 years of age.
2. Electrographically documented history of paroxysmal supraventricular tachycardia (PSVT) (e.g., ECG obtained during an episode of PSVT, Holter monitoring, loop recorder, etc.). If the patient had a prior ablation for PSVT, the patient must have documented ECG evidence of PSVT post-ablation.
3. History of sustained episodes of PSVT (i.e., typically lasting approximately 20 minutes or longer).
4. Females of childbearing potential who are sexually active with a male partner who is not surgically sterile (i.e., vasectomy) must agree to use a highly effective form of contraception from the time of signed informed consent until 30 days after the last administration of the study drug. Females of childbearing potential should have a negative serum pregnancy test result at the Screening Visit and at the Final Study Visit, a negative urine pregnancy test at the Test Dose Randomization Visit, and must use a highly effective form of contraception between the visits.

The following categories define females who are NOT considered to be of childbearing potential:

- Premenopausal females with 1 of the following:
    a. Documented hysterectomy;
    b. Documented bilateral salpingectomy or tubal ligation; or
    c. Documented bilateral oophorectomy; or
- Postmenopausal females, defined as having amenorrhea for at least 12 months without an alternative medical cause.

5. Male patients, except those who are surgically sterile, must use a highly effective form of contraception during the three days after any study drug administration; and
6. Signed written informed consent.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Systolic blood pressure (SBP) <90 mm Hg after a 5-minute rest in sitting position at the Screening Visit or before the test dose. In patients treated with a chronic prophylactic drug for PSVT (e.g., beta-blockers, verapamil, diltiazem), the drug may be stopped for at least the equivalent of five half-lives, patients may be rescreened once, and chronic use of the drug cannot be restarted after randomization.

2. History of severe symptoms of hypotension, especially syncope, during episodes of PSVT.
3. History of atrial arrhythmia that does not involve the atrioventricular node as part of the tachycardia circuit (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia).
4. History of allergic reaction to verapamil.
5. Current therapy with digoxin or any Class I or III antiarrhythmic drug, except if these drugs are stopped at least the equivalent of 5 half-lives before the Test Dose Randomization Visit.
6. Current chronic therapy with oral amiodarone or oral amiodarone is taken within 30 days before the Test Dose Randomization Visit.
7. Evidence of ventricular pre-excitation (e.g., delta waves, short PR interval <100 msec, Wolff-Parkinson-White syndrome) on the ECG performed at the Screening Visit or before test dose administration.
8. Evidence of a second- or third-degree AV block on the ECG performed at the Screening Visit or before test dose administration.
9. History or evidence of severe ventricular arrhythmia (e.g., torsades de pointes, ventricular fibrillation, or ventricular tachycardia).
10. Current congestive heart failure defined by the New York Heart Association Class II to IV.
11. History of Acute Coronary Syndrome or stroke within 6 months of screening.
12. Evidence of hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN at the Screening Visit, unless due to Gilbert syndrome.
13. Evidence of End-Stage Renal Disease as determined by an estimated glomerular filtration rate assessed at the Screening Visit of <15 mL/min/1.73m^2 or requiring hemodialysis.
14. Females who are pregnant or lactating.
15. Evidence or history of any significant physical or psychiatric condition, which, in the opinion of the Investigator, could jeopardize the safety of patients or affect their participation in the study. Additionally, the Investigator has the ability to exclude a patient if for any reason the Investigator judges the patient is not a good candidate for the study or will not be able to follow study procedures.
16. Participation in any investigational drug or device study or the use of any investigational drug or device within 30 days of the Screening Visit; or
17. Previously enrolled in a clinical trial for etripamil and received study drug during a perceived episode of PSVT

Before randomization in the RAPID study, all patients will receive a test dose of an etripamil dosing regimen to evaluate tolerability and to train patients on the study procedures. Both doses of the etripamil dosing regimen must be administered for the test dose to be considered evaluable. A failure of the test dose is considered if patients meet any of the following criteria occurring after administration of either the first or second dose of etripamil NS 70 mg test dose:

a. Any symptoms consistent with clinically severe hypotension such as pre-syncope, medically significant light-headedness, syncope, nausea, or vomiting.

b. For patients with a pre-test dose SBP above 100 mm Hg:
   - Decrease in SBP ≥40 mm Hg after test dose or
   - Post-test dose SBP <80 mm Hg
c. For patients with a pre-test dose SBP between 90 mm Hg and 100 mm Hg (inclusive):
   - Post-test dose SBP <75 mm Hg
d. Third-degree AV block, Mobitz II second-degree AV block, or Wenckebach with bradycardia ≤40 bpm.
e. New, significant sinus bradycardia heart rate ≤40 bpm or sinus pauses (≥3 seconds), if considered by the investigator to put the patient's safety at risk if either were to occur while not under medical supervision.
f. Any new significant ventricular arrhythmia considered significant by the investigator; or
g. Atrial fibrillation, atrial flutter or atrial tachycardia (event lasting longer than 30 seconds).
h. Refusal of the second dose of the etripamil test dose regimen.

Patients who fail the test dose will proceed in the study as follows:

- If the investigator identifies a possible reversible cause of the initial test dose failure (e.g., concomitant medication such as beta-blocker), a rechallenge with a new test dose of the etripamil dosing regimen within a 14-day window from the initial test dose will be possible after elimination of the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Patients may be randomized if they pass the second test dose and the cause of the test dose failure is eliminated for the duration of the study; or
- If the investigator cannot identify a reversible cause of the initial test dose failure, or if the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and will complete a Final Study Visit. Patients who fail the test dose will be part of the Test Dose Only Population.

3. TSQM-9© and PSVT Symptoms Questionnaires

9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9)
The TSQM-9 is administered in the native language of the patients.
Patients are instructed to place a single checkmark next to the response that most closely corresponds to their experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
    - ☐ 1 Extremely Dissatisfied
    - ☐ 2 Very Dissatisfied
    - ☐ 3 Dissatisfied
    - ☐ 4 Somewhat Satisfied
    - ☐ 5 Satisfied
    - ☐ 6 Very Satisfied
    - ☐ 7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
    - ☐ 1 Extremely Dissatisfied
    - ☐ 2 Very Dissatisfied
    - ☐ 3 Dissatisfied
    - ☐ 4 Somewhat Satisfied
    - ☐ 5 Satisfied
    - ☐ 6 Very Satisfied
    - ☐ 7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
    - ☐ 1 Extremely Dissatisfied
    - ☐ 2 Very Dissatisfied
    - ☐ 3 Dissatisfied
    - ☐ 4 Somewhat Satisfied
    - ☐ 5 Satisfied
    - ☐ 6 Very Satisfied
    - ☐ 7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?
    - ☐ 1 Extremely Difficult
    - ☐ 2 Very Difficult
    - ☐ 3 Difficult

- ☐ 4 Somewhat Difficult
- ☐ 5 Easy
- ☐ 6 Very Easy
- ☐ 7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?
   - ☐ 1 Extremely Difficult
   - ☐ 2 Very Difficult
   - ☐ 3 Difficult
   - ☐ 4 Somewhat Difficult
   - ☐ 5 Easy
   - ☐ 6 Very Easy
   - ☐ 7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?
   - ☐ 1 Extremely Inconvenient
   - ☐ 2 Very Inconvenient
   - ☐ 3 Inconvenient
   - ☐ 4 Somewhat Convenient
   - ☐ 5 Convenient
   - ☐ 6 Very Convenient
   - ☐ 7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?
   - ☐ 1 Not at All Confident
   - ☐ 2 A Little Confident
   - ☐ 3 Somewhat Confident
   - ☐ 4 Very Confident
   - ☐ 5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?
   - □ 1 Not at All Certain
   - □ 2 A Little Certain
   - □ 3 Somewhat Certain
   - □ 4 Very Certain
   - □ 5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?
   - ☐ 1 Extremely Dissatisfied
   - ☐ 2 Very Dissatisfied
   - ☐ 3 Dissatisfied
   - ☐ 4 Somewhat Satisfied

- ☐ 5 Satisfied
- ☐ 6 Very Satisfied
- ☐ 7 Extremely Satisfied

PSVT Symptoms Questionnaire

As soon as possible, after completing dosing of the study drug during their PSVT episode, patients are asked to answer the following question below.

How long was it from the start of your PSVT episode until you took the study drug?

Please check the appropriate box:

- ☐ Less than 5 minutes
- ☐ Between 5 and 10 minutes
- ☐ Between 10 and 30 minutes
- ☐ Between 30 minutes and 1 hour
- ☐ Longer than 1 hour

As soon as possible, after their PSVT episode is over, patients are asked to complete the questionnaire below.

	1 **Did you have this symptom?**		***2*** **How severe was this symptom?** *If you marked "No" that you did not have the symptom, leave the question blank Please complete as soon as possible after you have completed the dosing of the study drug during your PSVT episode.*					***3*** **How much did the nasal spray worsen or improve this symptom?** *If you marked "No" that you did not have the symptom, leave this question blank. Please complete as soon as possible after your episode is over.*						
	Yes	**No**	**Mild 1**	**2**	**3**	**4**	**Severe 5**	**Very much worse**	**Much worse**	**Minimally worse**	**No change**	**Minimally improved**	**Much improved**	**Very much improved**
Rapid Pulse (my heart rate is very fast)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Palpitations (I can feel my heart pounding in my chest		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Feeling Dizzy or Lightheaded	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shortness of Breath (it is hard for me to catch my breath)	☐		☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐
Anxiety	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chest Tightness, Pain, or Pressure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fainting or Passing Out	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

4. Clinical Laboratory Analytes

Urine and Serum Pregnancy Test (for females of childbearing potential only)

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Gamma-glutamyl transferase	Bicarbonate
Aspartate aminotransferase	Calcium
Urea nitrogen	Glucose
Chloride	Potassium
Creatinine	Total bilirubin
Magnesium	Direct bilirubin
Inorganic phosphorus	Estimated glomerular filtration rate
Sodium	

Hematology

Hematocrit	Hemoglobin
Platelets	Erythrocyte count
Leukocyte cell count and differential	Neutrophils
Lymphocytes	Monocytes
Eosinophils	Basophils

Additional Hematology

Mean cell volume
Mean cell hemoglobin concentration
Mean cell hemoglobin

Urinalysis

Bilirubin	Urobilinogen
Glucose	Blood
Leukocyte esterase	Ketones
Nitrite	pH
Protein	Specific gravity

5. Supplemental Table 1.

Schedule of Procedures

Assessment	Screening Visit[1]	Test Dose Randomi-zation Visit[2]	Monthly Follow-up Visit[3]	Random-ized Treat-ment Period[4]	Random-ized Treat-ment Follow-up Visit	Open-Label Treat-ment Period [4]	Final Study Visit[5]	End of Study Telephone Follow-up Visit
Informed consent	X							
Eligibility	X[6]	X[7]	X[8]					
Contact the Telephone Coach[9]		X		X		X		
Demographics/medical history	X							
Concomitant medications	X	X	X		X		X	
Physical examination	X[10]						X	
Vital signs (blood pressure and heart rate)	X	X[11]			X		X	
Hematology, chemistry, and urinalysis[12]	X						X[13]	
Pregnancy test[14]	X	X			X		X	
12-lead ECG[15]	X	X					X[16]	
Test dose administration[17]		X						
Patient training on PSVT episode assessments[18]		X	X		X			
Randomization (via IRT)		X						
AEs		X	X	X	X	X	X	X
Dispense study kit[19]		X			X			
Ensure CMS data is downloaded and sent to cardiac monitoring core lab		X	X[20]		X		X	
Review the CMS report[21]		X			X		X	
Identify PSVT episode				X		X		
Apply and start CMS		X		X[22]		X[22]		
Perform VM		X		X		X		
Administer study drug and record time of dosing				X[23]		X[23]		
Complete patient questionnaires				X		X		
Evaluate medical intervention during the Treatment Period					X		X	
Collect study kit (used and unused)					X		X	

Identify the reason(s) for study completion or withdrawal							X	
Close case with IRT							X	

Note: Prospective study patients will be asked to sign the informed consent form before the commencement of any study-related assessments or procedures. Once the informed consent is signed, patients will be considered enrolled in the study.

1. Screening Visit can be conducted with Test Dose Randomization Visit to avoid an extra on-site visit in extenuating circumstances.
2. The Test Dose Randomization Visit must occur within 28 days after the Screening Visit for newly enrolled patients. It should occur at the time of reconsent for patients previously randomized in NODE-301 Part 1. The CMS identifier number will be recorded in the EDC system for the test dose. A rechallenge with a new test dose of etripamil NS 70 mg dosing regimen within a 14-day window from the initial test dose will be possible after eliminating the reversible cause (e.g., withdrawal of concomitant therapy with the appropriate washout period). Screening and Test Dose Randomization Visits can be incorporated into one visit for purposes of avoiding an extra on-site visit in extenuating circumstances.
3. Monthly Follow-up Visits to occur approximately monthly via a site visit or telephone (site visit preferred for patients who have an episode of PSVT terminated by VM).
4. Randomized Treatment Period occurs from randomization until the patient has an episode of PSVT treated with study drug. Open-Label Treatment Period occurs from after Randomized Treatment Follow-up Visit until the patient has an at-home episode treated with Open-Label drug.
5. Final Study Visit to occur within seven days after the Open-label Treatment Period or within seven days of the test dose administration for patients who fail the test dose.
6. Confirmation of eligibility at Screening includes confirmation of PSVT diagnosis. Acceptable source documents to confirm the PSVT diagnosis are provided in the MoOP.
7. Additional eligibility criteria apply to pass the test dose at the Test Dose Randomization Visit only.
8. Eligibility assessments at the Monthly Follow-up Visits based on a review of the patient's concomitant medications or changes in health status.
9. If possible. The telephone coach will guide the patient through the study procedures. For the Test Dose Randomization Visit only, the telephone coach should be contacted once the 10 minutes of baseline recording with the CMS is complete. If the patient cannot reach the telephone coach, they may proceed with the printed and electronic guides.
10. Including height and weight.
11. Vital signs will be obtained within 10 minutes pre-test dose and every 5 minutes (±1 minute) for 45 minutes post first test dose.
12. Blood/urine samples can be analyzed locally for preliminary enrollment if Screening/Test Dose Randomization Visits are combined; samples are **also** sent to the Central lab. Central lab results will **allow** enrollment in the study.
13. Blood and urine tests will be performed on all patients who pass the test dose and are randomized.
14. For females of childbearing potential. A serum pregnancy test is required at the Screening Visit and the Final Study Visit. A urine test is needed for the Test Dose Randomization Visit and the Randomized Treatment Follow-Up Visit.
15. The paper speed for these recordings should be 25 mm/sec. A continuous on-screen ECG monitoring (at least 2-leads) is required from the beginning until the end of the test dose for the Test Dose Randomization Visit.
16. A 12-lead ECG will be performed on all patients who pass the test dose and are randomized.

17. Before randomization, all patients will be trained on VMs and will receive a test dose of etripamil regimen (an initial dose of etripamil NS 70 mg followed by a second dose of etripamil NS 70 mg not earlier than 10 minutes and not later than 15 minutes after the first dose) to evaluate tolerability. The test dose procedures are described in the MoOP. Patients who pass the test dose will be randomized. If the patient fails the first test dose and the Investigator can identify a potentially reversible cause for the failure, a second test dose may be administered within a 14-day window from the initial test dose. If the investigator cannot identify a reversible cause or the potential cause cannot be modified (e.g., necessary antihypertensive drug to control blood pressure), patients will not be randomized and complete a final study visit. Patients who fail the test dose will be part of the test dose-only population. During each patient's test dose randomization visit, the test dose CMS ECG data will be reviewed by the cardiac monitoring core laboratory, and a report will be sent to the site. The operational aspects of the use of the CMS during the test dose are described in the MoOP.
18. Randomized patients will be trained on how to identify and report symptoms, use of the Telephone Coach, set up and use of the CMS, performance of VMs, self-administration of study drug (as described in the MoOP), recording time of study drug administration, use of a patient diary, and reporting AEs to the sites during the study for evaluation. A caregiver may assist in these procedures.
19. The study kit will include the study drug (2 devices of placebo or etripamil NS), a CMS, a study identification card, patient's study instructions, and other study-related material. Patients will also be provided with patient questionnaires to be completed after experiencing a PSVT episode. At the Randomized Treatment Follow-up Visit, open-label etripamil will be provided with the CMS device (sites to ensure the device has been reset) and new patient questionnaires.
20. Download of CMS data during Follow-Up Visit if patient applied device without dosing study drug (e.g., VM-terminated PSVT).
21. The interpretation of the CMS ECG will be provided by the cardiac monitoring core laboratory to the site in a report based on the mobile system's proprietary arrhythmia detection algorithms and automatic ECG collection. During each patient's test dose randomization visit, the cardiac monitoring core laboratory will generate a summary test dose report within approximately 1 to 2 hours of receiving the ECG data. The site will use this report to determine if the patient passes or fails the test dose and if the eligibility criteria to be randomized in the study have been met. During the Randomized Treatment Period and the Open-Label Treatment Period, the cardiac monitoring core laboratory will generate a summary report within 48 hours of receiving ECG data. The operational aspects are described in the MoOP. These reports will be sent to the site and the medical monitor.
22. The CMS recording during an episode of SVT should continue for at least 5 hours, regardless of treatment outcome.
23. During the Randomized Treatment Period and the Open-Label Treatment Period, study drug should only be administered if the VM does not resolve the patient's symptoms. The patient will push the CMS event marker button to record the dosing time immediately before self-administering the study drug intranasally as instructed. If symptoms of the SVT episode have not resolved within 30 minutes after the start of study drug administration, patients may seek appropriate medical care.

AE, adverse event; CMS, cardiac monitoring system; ECG, electrocardiogram; EDC, electronic data capture; IRT, interactive response technology; MoOP, manual of operations and procedures; NS, nasal spray; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; VM, vagal maneuver.