Supplementary materials

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Safety endpoints

Safety variables will include clinical adverse events (AEs), vital signs, and arrhythmias and conduction disorders detected on surface electrocardiogram (ECG) or Cardiac Monitoring System (CMS) recordings.

Summarization of all AEs, treatment emergent adverse events (TEAEs), and TEAEs 24h will include patient incidence of the following:

* Any AE
* TEAEs: defined as AEs with the first onset or worsening of an existing AE occurring after administration of study drug, AEs considered related to the study drug, and AEs with a start date / time up to 12 hours prior to study drug administration
* TEAEs 24h: defined as AEs with a start date or date of worsening occurring 0 to 24 hours study drug administration, and AEs with a start date / time up to 12 hours prior to study drug administration
* AEs by maximum severity
* Drug-related AEs
* Drug-related AEs by maximum severity
* Serious adverse events (SAEs)
* Drug-related SAEs
* AEs leading to death
* AEs leading to study drug discontinuation
* Drug-related AEs leading to study drug discontinuation
* AEs with a start date occurring 0 to 48 hours after drug administration (for all AEs only)
* AEs with a start date occurring 0 to 7 days after drug administration (for All AEs only)
* AEs of special interest (AESI) in the 24 hours after etripamil administration
  + Tachyarrhythmias
  + Bradyarrhythmias
  + AV Block – any degree
  + Hypotension and/or syncope
* AEs in subgroups of interest

Investigators rated the severity (intensity) of each AE as mild, moderate, or severe, and categorized each AE as to its potential relationship to study drug using the categories of not related, unlikely related, possibly related, probably related, or definitely related. AEs listed as possibly, probably, or definitively related were classified as related to the study drug; AEs listed as not related or unlikely related were classified as not related.

Efficacy endpoints

Efficacy variables will be collected as secondary or exploratory analyses.

The secondary efficacy endpoints are:

* Number of emergency department visits, or other medical intervention
* Number of hospital admissions (including inpatient and outpatient hospitalizations)
* Characteristics of patients who receive ablation
* Concomitant PSVT medication usage
* Improvement in patient quality of life, as measured by the patient-reported outcome scales (Brief Illness Perception Questionnaire, Cardiac Anxiety Questionnaire, Short Form (36) Health Survey), and the patient Baseline/monthly PSVT survey
* Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication
* Mean and median time to conversion post etripamil NS administration
* Proportion of patients who convert at 3, 5, 10, 15, 20, 30, and 60 minutes after etripamil administration

Exploratory endpoints are:

* Frequency of PSVT episodes, and use of etripamil for those episodes, as captured by the Monthly PSVT and Per Episode Surveys
* Number of PSVT episodes a patient experiences
* Frequency of PSVT episodes
* Number of PSVT episodes terminated by vagal maneuvers
* Patient-reported PSVT episode characteristics as captured by the Per Episode Survey

Inclusion criteria

A patient will be eligible for study participation if they meet all of the following criteria:

* Diagnosis of PSVT by a medical professional and reports having at least one previous episode of PSVT
  + For clarity, PSVT refers to episodic SVT that includes the AV node as a critical part of reentrant circuit
* Is at least 18 years of age
* Signed NODE-303 written informed consent
* Women of child-bearing potential must be willing to use at least 1 form of contraception during the trial and must be willing to discontinue from the study should they become or plan to become pregnant. Postmenopausal females are defined as having amenorrhea for at least 12 months prior to screening without an alternative medical cause
* Willing and able to comply with study procedures

Exclusion criteria

A patient will be excluded from the study if they meet any of the following criteria:

* A history of atrial arrhythmia that does not involve the AV node as part of the tachycardia circuit (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia)
* Patients with a history of these tachycardias who are also diagnosed with PSVT are eligible
* History of allergic reaction to verapamil
* Current therapy with digoxin, or any Class I or III antiarrhythmic drug
* Patients may be eligible if these drugs are stopped at least five half-lives before the administration of etripamil. The only exception is oral amiodarone, which must be stopped 30 days before enrollment
* History or evidence of ventricular pre-excitation, e.g., delta waves, Wolff-Parkinson-White syndrome.
* History or evidence of a second- or third-degree AV block.
* History or evidence of severe ventricular arrhythmia (e.g., torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia)
* Symptoms of congestive heart failure New York Heart Association Class II to IV
* SBP < 90 mmHg at screening, baseline, or any follow-up visit.
* Severe symptoms of hypotension experienced during PSVT episodes
* Significant physical or psychiatric condition including alcoholism or 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.
* History of syncope due to an arrhythmic etiology at any time, or history in last 5 years of unexplained syncope
* Is pregnant or breastfeeding
* Previously enrolled in a clinical trial for etripamil and received study drug or participation in any clinical trial for other investigational products or medical devices within 30 days of screening
* History of ACS or stroke within 6 months of screening
* Evidence of renal dysfunction as determined by an estimated glomerular filtration rate assessed at the screening visit as follows:
* < 60mL/min/1.73m2 for patients <60 years of age
* < 40mL/min/1.73m2 for patients ≥60 and <70 years of age
* < 35mL/min/1.73m2 for patients ≥70 years of age

Central review mandate and scope

The central review will be conducted by the study medical monitor who will review ECG CMS recordings and capture findings for 1 hour following a perceived PSVT episode treated with etripamil. Review will be performed on the CMS PDF reports and ECG CMS tracings are also be reviewed in an aliquout of 20% for consistency. ECG CMS tracings are reviewed by the medical monitor in all cases which present with 1st degree AV block to confirm presence and duration (PR measurement) and in any situation in which ECG abnormalities may make it necessary per the medical reviewer. For 1st degree AV block, screening ECGs will also be consulted to determine preexistence.

In the event a CMS report cannot be unequivocally reviewed, the reason will be captured among the following options and all other fields will be left blank:

1. ECG CMS data not collected

2. Empty file

3. Uninterpretable data (e.g., mostly artifacts or too short for interpretation)

4. Data not pertaining to current treated episode (e.g., duplicate report)

The objective of the central review is to review and identify all relevant data in ECG recordings during 1-hour following treated episodes to determine if they meet protocol specified criteria and definitions, as follows:

a. Determine the initial diagnosis, before IP is taken, to confirm initial rhythm as one of the following 5 options:

i. Sinus rhythm

ii. PSVT

iii. Atrial fibrillation

iv. Atrial flutter

v. Atrial tachycardia

b. If a PSVT is present as initial diagnosis:

i. Determine whether participants converted to sinus rhythm maintained for > 30 seconds within one hour of the first available relevant event marker (see conventions below), or of CMS signal start time if event marker is not available or not relevant.

ii. If the PSVT terminated within 1 hour of relevant event marker or CMS signal start time, determine time of conversion taking the following in consideration:

1. Participants will be censored as non-converted in case signal is lost or becomes uninterpretable while the patient is in PSVT if interpretable signal is not recovered prior to end of 1 hour.

2. Participants who have converted during signal loss will be considered to have converted at the time signal with sinus rhythm is captured again if this occurs within 1 hour of first event marker if present or start of CMS signal.

c. Identify occurrence, type, and duration of ECG abnormalities other than initial diagnosis, described in the protocol as safety endpoints, for up to 1 hour following first available relevant event marker or CMS signal start, among the following three main categories:

i. Tachyarrhythmias lasting longer than 30 seconds:

1. Atrial fibrillation, including onset & offset times if present

2. Atrial flutter, including onset & offset times if present

3. Atrial tachycardia, including onset & offset times if present

4. Non-sustained ventricular tachycardia (defined as > or = 3 ventricular wide

consecutive beats), and whether present at time of PSVT conversion

5. Sustained ventricular tachycardia (defined as consecutive wide ventricular beats

or QRS complexes of ≥120 msec at >100 bpm lasting longer than 30 seconds), and

whether present at time of PSVT conversion

6. PSVT recurrences, including onset & offset times, if present

ii. AV blocks (AVB):

1. First degree AVB lasting longer than 30 seconds. Unless AVB first degree is present at screening ECG, onset & offset times will be captured.

2. Mobitz I AVB second degree, with onset and offset times captured (in place of / where EDC inappropriately asks for time at which HR was 39 bpm or less and again 40 bpm or more). Any evidence of bradycardia should be captured in the comments section.

3. Mobitz II AVB second degree, with times of first and last blocked P waves

4. 3rd degree AVB, with time of last conducted P wave and first conducted P wave

after conduction resumes.

iii. Bradyarrhythmias:

1. Any pause equal or greater than 3 seconds.

2. Sinus bradycardia defined as any heart rate less than 40 bpm lasting longer than 30 seconds.

Arbitration process

The medical monitor performing the review will determine the initial diagnosis and ECG abnormality findings based on review of the CMS reports. In case of doubt, observations will be discussed with the Medical Director and the Chief Medical Officer. In case of discordance or remaining doubts on the interpretation, CMS reports will be reviewed by an external expert electrophysiology consultant who will contribute to the final decision to be entered in the database. External expert observations will be documented and signed off by the consultant; emails will be considered appropriate proof of signature and will be filed in the folder with the tracker. To the extent possible, CMS service provider will be asked to modify their interpretation in the pdf report.

Supplementary Table 1. Schedule of Procedures

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| --- | --- | --- | --- | --- | --- |
|  | Screening visit  (within 30 days of baseline)a | Baseline visita | Treatment periodc | Follow-up visits  (within 14 days of treated episode)d | Final study visit |
| Informed consent | X |  |  |  |  |
| Eligibility | X | X |  | X |  |
| Demographics / medical history | X |  |  |  |  |
| Concomitant medications | X | X |  | X | X |
| Physical exam | X |  |  |  |  |
| Vital signse | X |  |  | X | X |
| Hematology, chemistry, urinalysis, urine drug screenf | X |  |  |  |  |
| Pregnancy test | X |  |  |  |  |
| On-site safety ECG | X |  |  |  |  |
| Patient training |  | X |  | Xg |  |
| Dispense study kith |  | X |  | X |  |
| Apply and start ECG CMS |  |  | X |  |  |
| Perform VM |  |  | X |  |  |
| Self-administer drugi |  |  | X |  |  |
| PROsj |  | X | X |  |  |
| TSQM-9 |  |  | X |  |  |
| Patient remindersk |  |  | X |  |  |
| Return used study drug to site |  |  |  | X | X |
| Review ECG CMS data |  |  |  | X | X |
| Adverse events |  | X |  | X | X |
| Collect ECG CMS |  |  |  |  | X |
| End of study eCRF completion |  |  |  |  | X |

aScreening and baseline visits could be incorporated into one visit for purposes of avoiding an extra on-site visit in extenuating circumstances.

bBaseline visit could be conducted with screening visit for purposes of avoiding an extra on-site visit in extenuating circumstances.

cTreatment period assessments were done by the patient in an at-home setting.

dFollow-up visits could be conducted within up to 60 days of a treated episode in extenuating circumstances.

eVital signs included blood pressure, heart rate, and weight. Height was taken at the screening visit only.

fBlood / urine samples could be analyzed locally for purposes of preliminary enrolment if screening/baseline visits were combined; samples also were sent to the central laboratory. Central laboratory results allowed enrollment in study.

gAt follow-up visits, sites re-trained patients who were having questions with their ECG CMS or PRO systems.

hStudy kit at baseline included ECG CMS device and materials, two study drug kits, study identification card and any paper training or PRO materials required or requested. Study kits at follow-up included two study drug kits, additional ECG CMS materials, and any paper training or PRO materials required or requested.

iPatients self-administered one dose, waited 10 minutes, and self-administered a repeat dose if PSVT symptoms persisted.

jPROs were administered via Phone or Tablet application. PROs included a) baseline survey to be done on site at baseline; b) the BIPQ, CAQ, and SF-36 done within 48 hours of baseline and every 6 months thereafter; c) a monthly survey done each month after baseline; d) a per episode survey done for each episode regardless of whether or not a patient took study drug; e) the TSQM-9 done after each episode where the patient took study drug.

kSites called patients who missed two consecutive PRO surveys to retrain and engage the patient.

BIPQ, Brief Illness Perception Questionnaire; CAQ, Cardiac Anxiety Questionnaire; eCRT, electronic case report form; EGC, electrocardiogram; PRO, patient-reported outcome; SF-36, Short Form (36) Health Survey; TSQM-9, Treatment Satisfaction Questionnaire for Medication®-9; VG, vagal maneuver