Etripamil Nasal Spray Reduces Heart Rate in Patients With Paroxysmal Supraventricular Tachycardia Prior to Conversion to Sinus Rhythm

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Background

- Paroxysmal supraventricular tachycardia (PSVT) is characterized by intermittent episodes of tachycardia with sudden onset and termination.[1-3]
  - PSVT may involve reentry within the atrioventricular (AV) node (AV nodal reentrant tachycardia) or through the AV node (AV reentry).
  - The acute onset of elevated heart rate (HR) during PSVT often leads to clinical symptoms including palpitations, dizziness, light-headedness, anxiety and shortness of breath, which may require medical intervention.
- Etripamil (E) is a first in class, rapid, short-acting, non-dihydropyridine calcium channel blocker that is self-administered intranasally that is being developed to terminate episodes of PSVT in a medically unsupervised at-home setting.
- The NODE-301 study evaluated self-administration of etripamil nasal spray 70 mg in a medically unsupervised (generally at home) setting for acute PSVT termination.
- Here, we present a post hoc analysis of the effects of etripamil on HR in PSVT before conversion to sinus rhythm (SR) in NODE-301.

Objectives

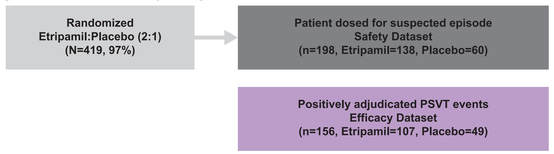
- To evaluate the effect of etripamil on HR during episodes of SVT prior to conversion to SR
- To evaluate the correlation of HR with patient-reported outcomes (PROs)

Methods

Study Design

- NODE-301 (NCT03464019) was a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of self-administration of etripamil versus placebo nasal spray in patients with PSVT
  - 156 subjects experienced a vagal maneuver-refractory, symptomatic episode of confirmed PSVT; 107 subjects self-administered etripamil and 49 administered placebo nasal spray with 2:1 randomization (**Figure 1**).
- Each PSVT episode was documented by an ambulatory cardiac monitoring system (Preventice BodyGuardian® Heart, Eagan, MN, USA) that was placed on the chest after symptoms began.

Figure 1. NODE-301 Study Design



PSVT, paroxysmal supraventricular tachycardia.

Study Population

- NODE-301 study enrolled adult patients aged 18 years or older who had an electrocardiographically (ECG) documented history of PSVT with episodes of PSVT lasting 20 minutes or longer.
- ***Assessments*** As part of the post-hoc analysis, additional time periods were observed (e.g., 60 minutes) in addition to the primary endpoint observation window of 5 hours.
- HR data were captured in 1-minute increments from baseline (average of 4 values before drug administration) until 1 minute before SVT converted to SR (confirmed by the ambulatory monitor and adjudicated by an independent blinded committee).
- Mean change from baseline was defined as the average of non-missing values at 3, 2, and 1 minute prior to drug administration to the value at a post-dose time point.
- Change in baseline was analyzed using a mixed model with repeated measures including treatment, time point, and treatment-by-time point interaction as fixed effects, and baseline HR as a covariate; the covariance structure was compound symmetry.
- Maximal change in HR was assessed as the difference from the lowest HR value measured in PSVT from baseline during an SVT episode to the highest.
- Adequate HR data during SVT were available for 150 patients (etripamil, N=102; placebo, N=48).
  - Six patients were not included in this analysis: 4 patients (etripamil, n=3; placebo, n=1) converted within 1 minute, and 2 patients treated with etripamil experienced a monitoring system defect.
- PROs were collected shortly after an SVT episode to measure treatment satisfaction via the Treatment Satisfaction Questionnaire for Medication 9 (TSQM-9®).
  - The TSQM-9 is composed of 9 questions with responses on a scale of 1 (extremely dissatisfied) to 7 (extremely satisfied), which were converted to a 0- to 100-point score for analysis where 0 was most dissatisfied and 100 was most satisfied; a higher score indicated greater satisfaction with a medication.
    - Patient-reported satisfaction with treatment effectiveness, assessed by calculating the TSQM-9 score for the effectiveness domain using the first 3 TSQM-9 questions.
    - Patient-reported relief of symptoms was assessed by taking the score on TSQM question 2 "How Satisfied are you with the way the medication relieves your symptoms?"

Results

- In this post hoc analysis of the effects of etripamil on HR in PSVT before conversion to SR, demographics and baseline characteristics were generally well-balanced between treatment groups (**Table 1**).
  - Among patients treated with etripamil, mean±standard deviation (SD) age was 57.2±12.6 years, most patients were female (67.6%), and the majority were White (87.3%).

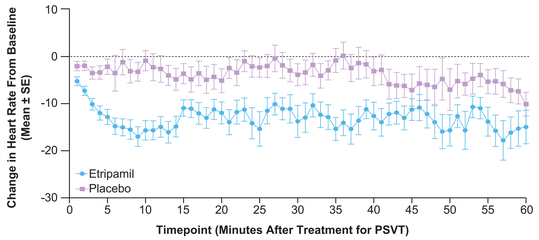
Table 1. Demographics and Baseline Characteristics

	Etripamil (N=102)	Placebo (N=48)
Age (years)		
Median Q1, Q3	60.5 (52.0, 65.0)	57.0 (46.5, 65.5)
Sex, n (%)		
Female	69 (67.6)	32 (66.7)
Male	33 (32.4)	16 (33.3)
Number of ER visits for PSVT events		
Median (Q1, Q3)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)
Number of PSVT events in the past year		
Median (Q1, Q3)	4.0 (2.0, 10.0)	6.0 (3.0, 10.0)
Age at PSVT confirmation		
Median (Q1, Q3)	58.9 (49.9, 65.0)	56.7 (43.8, 65.6)
Body mass index		
Median (Q1, Q3)	27.2 (23.2, 31.8)	26.8 (23.7, 32.2)
Current use of CCB, n (%)	28 (27.5)	13 (27.1)
Current use of BB, n (%)	37 (36.3)	21 (43.8)

BB, beta-blocker; CC, calcium channel blocker; ER, emergency room; PSVT, paroxysmal supraventricular tachycardia.

- At baseline, mean (± standard error [SE]) HR for etripamil- and placebo-treated patients was 179±2.8 and 174±4.0 beats per minute (bpm), respectively, and were not significantly different.
- Patients treated with etripamil had a significantly greater reduction in mean HR during PSVT from baseline compared with placebo-treated patients (P<0.0001; **Figure 2**).
  - This difference in HR appeared within the first minute (-5 bpm ±0.9), reached its maximum at 10 minutes (-16 bpm ±2.1), and was sustained through the 60 minute observation period.
- A statistically significant difference in HR was reached between etripamil treatment and placebo at 3 minutes (P<0.03), 10 minutes (P<0.0001), 30 minutes (P<0.0002), and 40 minutes (P<0.004), but not at 60 minutes.

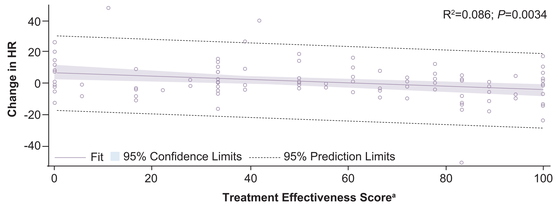
Figure 2. Mean Change in HR From Baseline



PSVT, paroxysmal supraventricular tachycardia; SE, standard error.

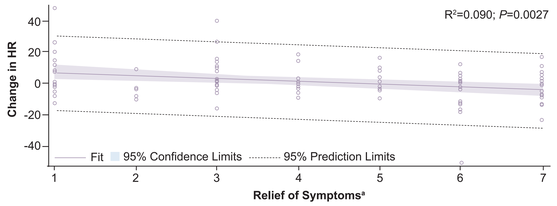
- Among all patients treated with etripamil (includes converters and non-converters to SR), maximal change in HR from baseline was positively but weakly correlated with PROs of:
  - Satisfaction of treatment effectiveness (R^2=0.086; P=0.0034; **Figure 3**)
  - Satisfaction with relief of symptoms (R^2=0.090; P=0.0027; **Figure 4**).

Figure 3. Maximal Change in HR From Baseline vs. Patient-Reported Treatment Effectiveness



[a]Ratings to the composite of effectiveness questions (0=most dissatisfied for effectiveness, 100=most satisfied for effectiveness).
HR, heart rate.

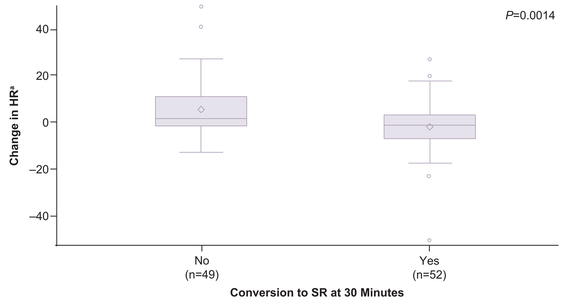
Figure 4. Maximal Change in HR From Baseline vs. Relief of Patient-Reported Symptoms



[a]Ratings to the TSQM-9 question 2 (1= most dissatisfied, 7=most satisfied).
HR, heart rate. TSQM-9,

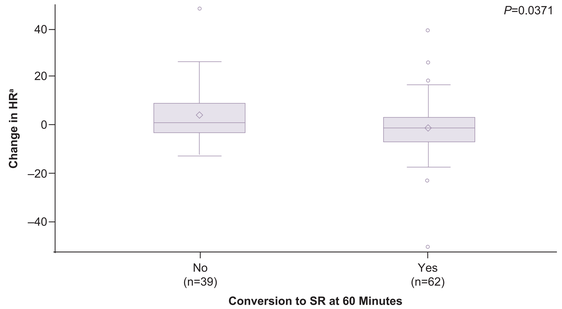
- The maximal change in HR from baseline during PSVT after treatment with etripamil was significantly greater (P=0.0014) in patients who converted to SR within 30 minutes than in those who remained in SVT beyond 30 minutes (**Figure 5**), and in patients who converted to SR within 60 minutes than in those who remained in SVT beyond 60 minutes (P=0.0371; **Figure 6**).

Figure 5. Maximal Change From Baseline in HR Among Etripamil-Treated Patients Converting to SR at <30 and >30 Minutes



[a]Box plot shown here presents median (middle line in box), mean (diamond), first and third quartiles (ends of box), maximum and minimum values (whiskers), and outlines (circles).
HR, heart rate; SR, sinus rhythm.

Figure 6. Maximal Change From Baseline in HR Among Etripamil-Treated Patients Converting to SR at <60 and >60 Minutes



[a]Box plot shown here presents median (middle line in box), mean (diamond), first and third quartiles (ends of box), maximum and minimum values (whiskers), and outlines (circles).
HR, heart rate; SR, sinus rhythm.

Conclusions

- Self-administration of intranasal etripamil rapidly and significantly decreased HR in PSVT prior to conversion to SR, and had a treatment effect that was maintained over 40 minutes.
- Patients treated with etripamil had a significantly greater reduction in mean HR during PSVT from baseline compared with placebo-treated patients.
- Maximal change in HR during PSVT from baseline was positively correlated with patient-reported relief of symptoms and treatment effectiveness.
- A greater maximal change in HR from baseline during PSVT was associated with a greater likelihood of PSVT conversion within 30 minutes of etripamil administration.
- These findings provide additional insights into the potential efficacy of etripamil for self-management of PSVT.
- These observations may have potential implications for the future study of etripamil for ventricular rate reduction and symptom relief during atrial fibrillation.

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Disclosures

JI, BS, PS, BC, ASP, BM, AV, and AJC were study investigators. MC and BM serve as consultants to Milestone Pharmaceuticals. SS and FP are employees of Milestone Pharmaceuticals.

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