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NODE-303: Multi-Center, Multi-National, Open-Label, Safety Study of Etripamil Nasal Spray for Patients With Paroxysmal Supraventricular Tachycardia

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Disclosures

James E. Ip, MD:

- Received compensation as study investigator and steering committee member for Milestone Pharmaceuticals
- Received honoraria/speaking/consulting fees for Abbott Medical, Boston Scientific, and Medtronic Inc.
- Membership on advisory committee and/or steering committee for Abbott Medical and Medtronic Inc.
- Membership on data safety monitoring committee for Boston Scientific

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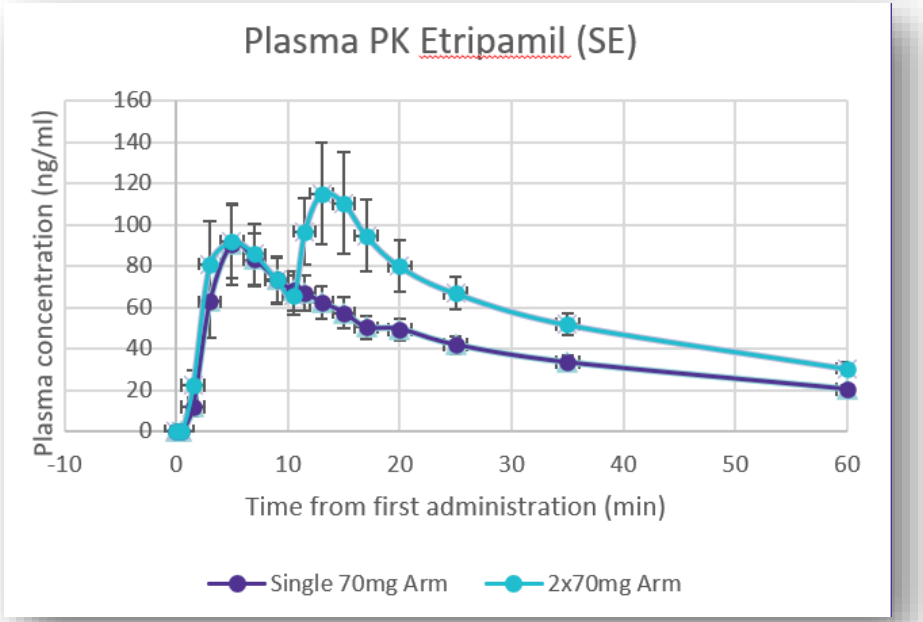
Etripamil: Potential New Treatment for PSVT

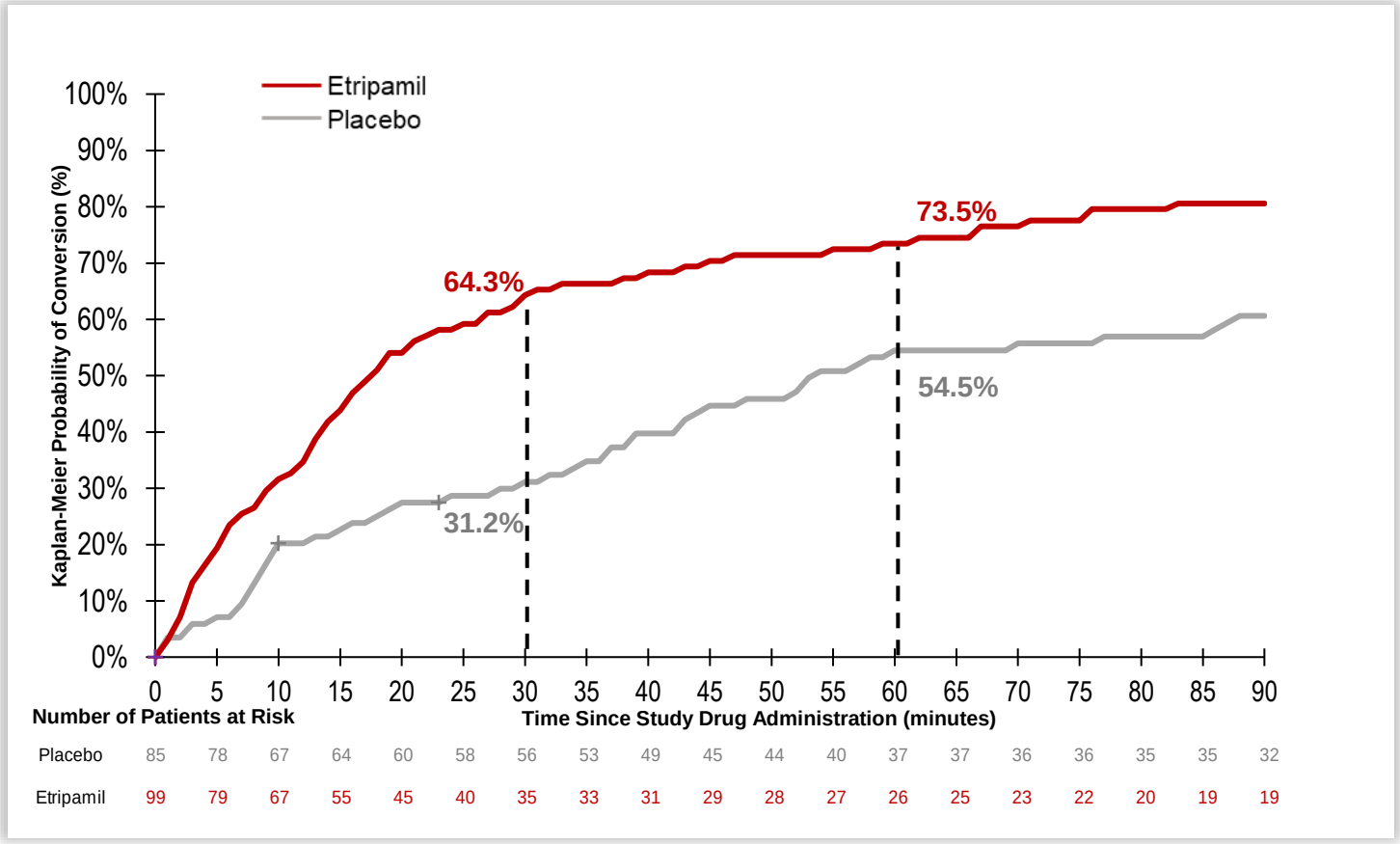
- Novel, investigational, L-type channel calcium channel blocker
- Formulated for intranasal spray with:
  - Rapid onset of action (T_{max} ≤7 minutes)
  - Metabolism: inactivation by blood esterases
- Developed to satisfy unmet need for self-administered therapy that is convenient & safe outside the healthcare setting
- Effective at rapidly terminating single episodes of AV nodal–dependent PSVT
  - Three phase 3 studies: NODE-301 Part 1, RAPID, NODE-302



Stambler BS, et al., *J Am Coll Cardiol*. 2018.
Wight D, et al. *J Am Coll Cardiol.* 2022 Mar, 79 (9_Supplement) 43.
Ip JE, et al. *Lancet*. 2023 July.
Ip JE, et al. *Clin Pharmacol Drug Dev*. 2024 Feb.
NODE-PK-101, -103, data on file.

Error bars = standard error (SE). PSVT = paroxysmal supraventricular tachycardia. PK = pharmacokinetic.

RAPID: Conversion of Adjudicated PSVT to NSR at 30 and 60 min



Median time to conversion: **17.2 min** **vs** **53.5 min**

Test dose required:

- During Sinus Rhythm
- Continuous ECG Monitoring
- Serial BP Measurements every 5 min

1.3% test dose failure in RAPID study

BP = blood pressure. ECG = electrocardiography. NSR = normal sinus rhythm. PSVT = paroxysmal supraventricular tachycardia.

NODE-303 Phase 3 Study Design

Real-world design:
- No test dose
- No exclusion of AF/AFL history
- Multiple episodes (up to four)

Screening visit

Key inclusion criteria
- Patients ≥18 years old
- Documented PSVT
- Episodes lasting ≥20 min

Key exclusion criteria
- Evidence of ventricular pre-excitation
- 2nd- or 3rd-degree AV block
- History of severe symptoms of hypotension or syncope during PSVT

Treatment period

Treated PSVT episode
- Patient recognizes symptoms
- Applies cardiac monitor (ECG)
- Attempts VM
- Administers etripamil 70 mg intranasally
- If symptoms persist for 10 min, dose etripamil 70 mg again[a]
- Keep cardiac monitor for at least 1 hr

Follow-up visit
Additional study drug dispensed

Additional PSVT episodes (up to 4 in total) and follow-up visits

End of study

Final visit
Study completion, discontinuation, or after 4th episode

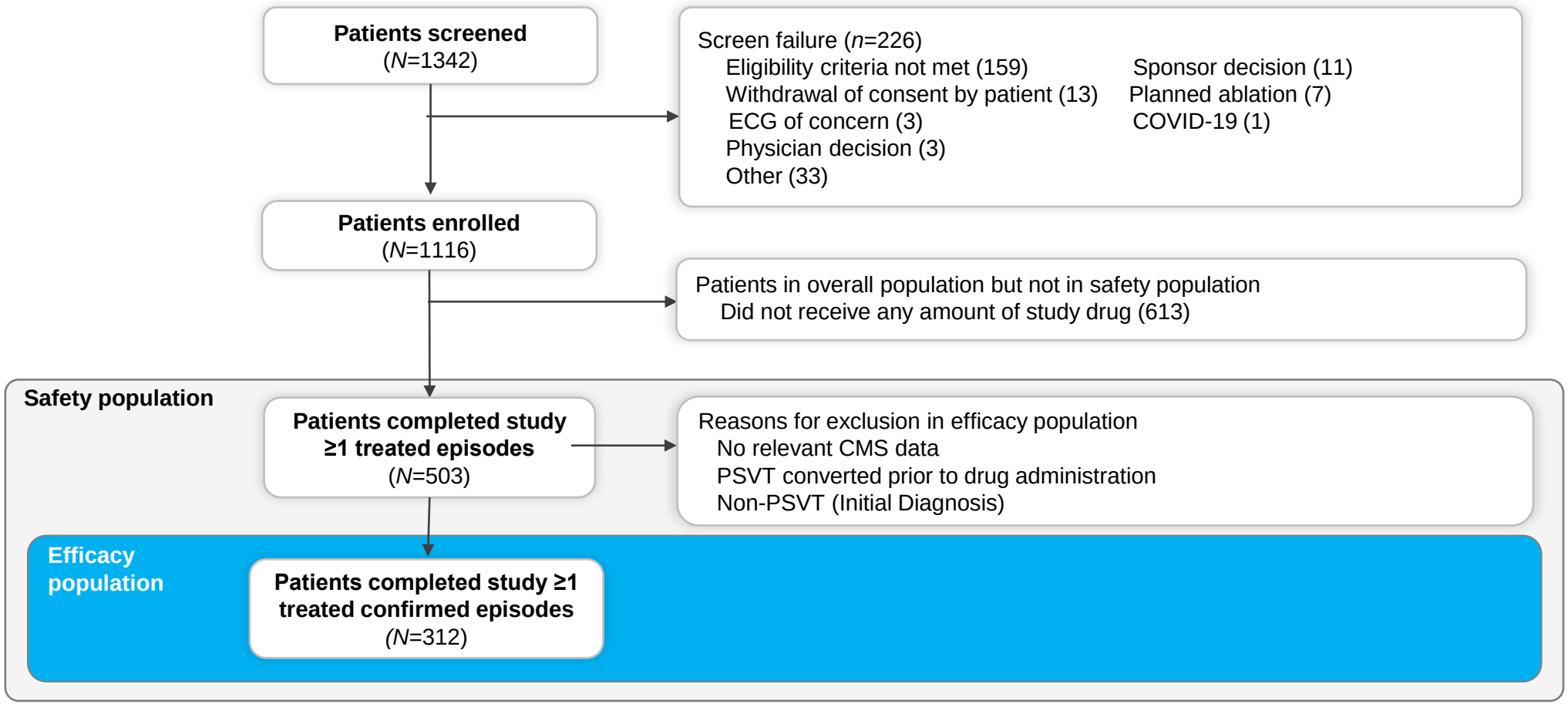
Outcome measures

Safety assessments
- AEs
- SAEs
- Arrhythmias and conduction disorders detected on ECG

Efficacy assessments
- Termination of PSVT
- Frequency of additional medical interventions
- Patient-reported outcomes

[a]Approximately 21 months after the study started, the protocol was amended to allow a repeat 70-mg dose to be self-administered if symptoms persisted 10 minutes following the first dose. If the symptoms of PSVT have not resolved within 20 minutes after study drug administration, the patient may seek appropriate medical care as needed. AE = adverse event. AF = atrial fibrillation. AFL = atrial flutter. AV = atrioventricular. ECG = electrocardiography. PSVT = paroxysmal supraventricular tachycardia. SAE = serious adverse event. SR = sinus rhythm. VM = vagal maneuver.

Patient Disposition and Analyses Populations



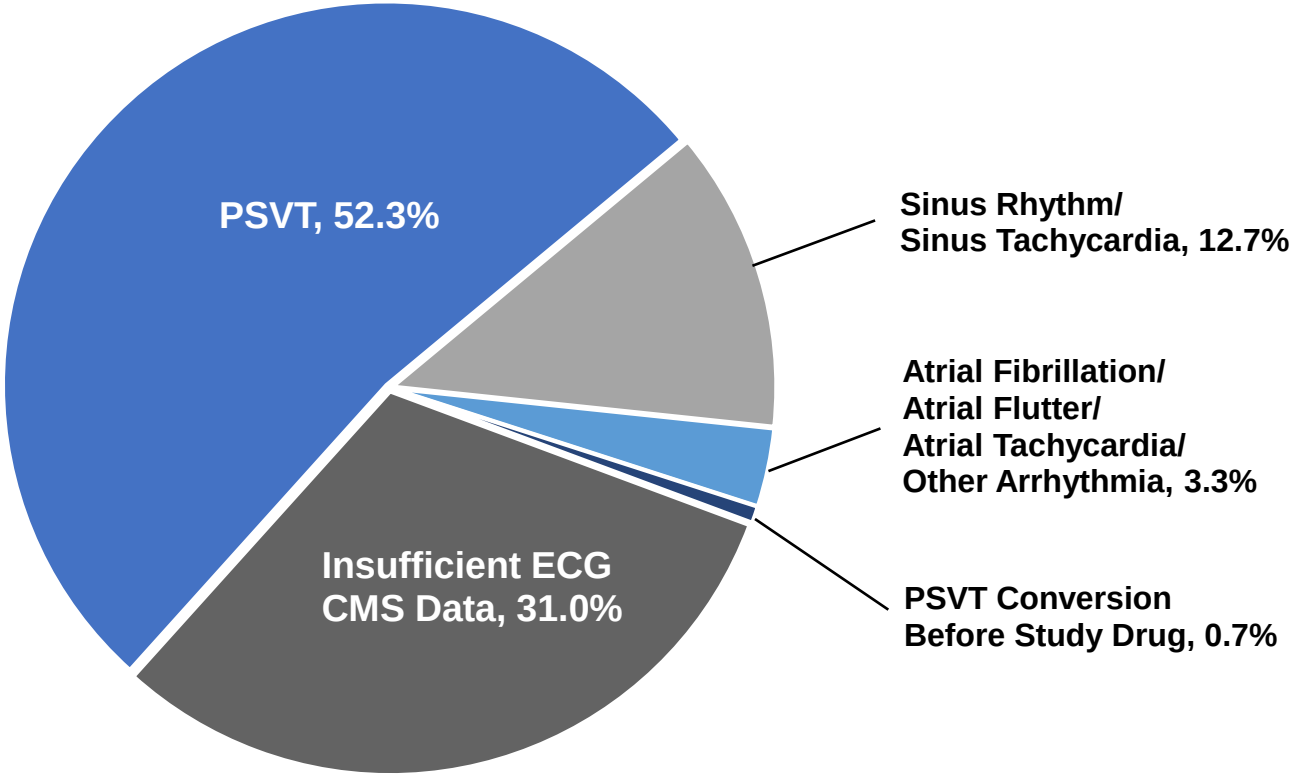
CMS = cardiac monitoring system. ECG = electrocardiography. PSVT = paroxysmal supraventricular tachycardia.

Demographics & Baseline Characteristics (Safety Population)

	Mean (SD) or Patients for Categorical Variables, *n* (%)
Age, y	54.9 (13.6)
Sex, *n* (%)	
Female	344 (68.4)
Male	159 (31.6)
Region, *n* (%)	
North America	353 (70.2)
South America	150 (29.8)
Age at first PSVT diagnosis, y	47.7 (16.8)
Time since first PSVT diagnosis, y	7.0 (9.2)
PSVT episodes in past year, *n*	9.8 (17.6)
Patient-reported emergency department visits for PSVT since diagnosis, *n*	3.9 (5.7)
Patients with concomitant medications of interest, *n* (%)[a]	
β-blocker or calcium channel blocker	**355 (70.6)**
β-blocker only[b]	238 (47.3)
Calcium channel blocker only[c]	68 (13.5)
β-blocker and calcium channel blocker	49 (9.7)
NDHP calcium channel blocker (verapamil, diltiazem)	92 (18.3)

[a]Drugs acting on the atrioventricular node that were started at any time and were taken at any time after the date of informed consent until the end of the follow-up period. [b]β-blocker only category does not include calcium channel blockers. [c]Calcium channel blocker only category does not include β-blockers. NDHP = non-dihydropyridine. PSVT = paroxysmal supraventricular tachycardia. SD = standard deviation.

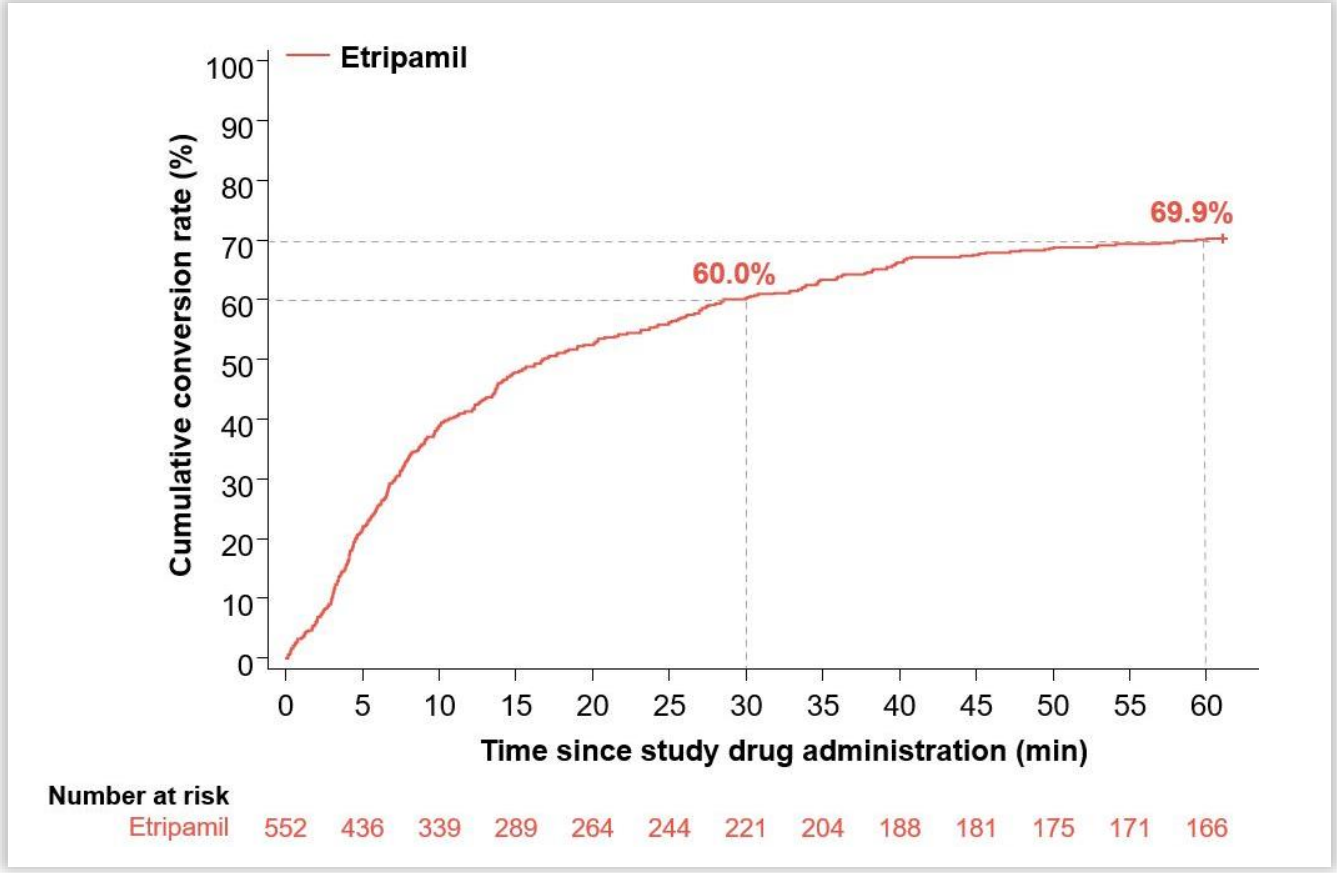
Rhythms Captured on CMS During Perceived PSVT Episodes



- 503 patients treated 1054 episodes as perceived PSVT
  - 220 pts treated 1 episode
  - 118 pts treated 2 episodes
  - 62 pts treated 3 episodes
  - 103 pts treated 4 episodes
- 552 episodes were confirmed as PSVT and included in the efficacy population

CMS = cardiac monitoring system. ECG=electrocardiography. PSVT = paroxysmal supraventricular tachycardia.

Conversion of PSVT to SR: All Episodes (Efficacy Population) Secondary Efficacy Assessments



KM Estimate of PSVT Conversion to Sinus Rhythm	By 30 Minutes	By 60 Minutes
NODE-301	53.7	63.7
NODE-302	60.2	75.1
RAPID	64.3	73.5
NODE-303	**60**	**69.9**

Median time to conversion:
17.0 min (95% CI, 13.9–22.3)

CI = confidence interval. KM = Kaplan Meier. PSVT = paroxysmal supraventricular tachycardia. SR = sinus rhythm.

Additional Secondary Endpoints

Kaplan-Meier Analyses of Confirmed PSVT to SR Conversion at 60 Minutes by Episode (Efficacy Population)

	All Episodes	Episode 1 (*n*=312)	Episode 2 (*n*=151)	Episode 3 (*n*=71)	Episode 4 (*n*=18)
Kaplan-Meier Estimate of Patients Converted to SR Within 60 min, %[a]	**69.9**	**70.5**	**73.5**	**57.7**	**77.8**
Time to Conversion, min					
Q1 (95% CI)	6.0 (5.0, 6.8)	6.6 (5.1, 7.5)	4.9 (4.2, 6.6))	6.0 (3.3, 9.1)	6.0 (0.3, 13.9)
Median (95% CI)	17.0 (13.9, 22.3)	18.3 (14.2, 25.6)	14.0 (9.7, 24.2)	19.1 (9.8, -)	15.6 (6.0, 33.7)
Q3 (95% CI)	- (-, -)[b]	- (58.1, -)[b]	- (36.4, -)[b]	- (-, -)[b]	34.7 (16.3, -)[b]

[a]Patients who converted during signal loss were considered to have converted at the time signal with sinus rhythm was captured again if this occurred within 1 hour of the first event marker if present or start of CMS signal. Patients were censored as non-converted if signal was lost or became uninterpretable while the patient was in PSVT if interpretable signal was not recovered within 1 hour. [b]Did not occur within the observation window.
CI = confidence interval. CMS = cardiac monitoring system. PSVT = paroxysmal supraventricular tachycardia.

Overview of Treatment-Emergent Adverse Events (Safety Population)

TEAE Category (Safety Population *N*=503)	Events, *n*	Patients, *n* (%)
Any TEAE	997	301 (59.8)
Severe	43	31 (6.2)
Any TEAE 24 h	776	269 (53.5)
Severe	22	16 (3.2)
Serious TEAE	33	26 (5.2)
Drug related	0	0
Leading to death[a]	4	4 (0.8)
Serious TEAE 24 h	5	5 (1.0)
Drug related	0	0
Leading to death	0	0
Drug-related TEAE	719	250 (49.7)
Severe	19	14 (2.8)
Drug-related TEAE 24 h	706	249 (49.5)
Severe	19	14 (2.8)
TEAE leading to study drug discontinuation	40	26 (5.2)
Drug related	24	12 (2.4)
TEAE 24 h leading to study drug discontinuation	31	18 (3.6)
Drug related	24	12 (2.4)
Any clinical AESI 24 h	22[b]	17 (3.4)[b,c]

[a]TEAEs leading to death were not related to etripamil and include acute myocardial infarction, cardio-respiratory arrest, septic shock and high-grade B cell lymphoma. [b]AESIs were identified by the Investigator and do not include those identified from the CMS data. [c]An additional clinical AESI (mild hypotension) was identified in one additional patient post-database lock.
AESI=AE of special interest. TEAE=treatment-emergent adverse event, TEAE 24h=TEAE occurring ≤24h after study drug.

Summary of Drug-Related TEAEs Leading to Study Drug Discontinuation

System Organ Class Preferred Term	Drug-Related TEAEs* (*N*=503)	
	No. of Events	*n* (%)
Any TEAE	**24**	**12 (2.4)**
Gastrointestinal disorders	**1**	**1 (0.2)**
Oral discomfort	1	1 (0.2)
General disorders and administration site conditions	**1**	**1 (0.2)**
Facial pain	1	1 (0.2)
Nervous system disorders	**2**	**2 (0.4)**
Syncope[a]	1	1 (0.2)
Hypoaesthesia	1	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	**19**	**9 (1.8)**
Nasal discomfort	7	7 (1.4)
Epistaxis	3	3 (0.6)
Nasal congestion	3	3 (0.6)
Rhinalgia	2	2 (0.4)
Cough	1	1 (0.2)
Rhinorrhea	1	1 (0.2)
Sneezing	1	1 (0.2)
Throat irritation	1	1 (0.2)
Vascular disorders	**1**	**1 (0.2)**
Hypotension[b]	1	1 (0.2)

*TEAE defined as AE with a start date occurring after administration of study drug
TEAE= treatment-emergent adverse event

[a]One patient with reported syncope 5 min after etripamil administration, however, investigation showed no reported loss of consciousness, judged as no syncope by study sponsor. [b]One patient experienced an event of hypotension 1 hour and 6 min after etripamil administration while in PSVT in the ER (BP 72/27 mm Hg). Patient restored to NSR after cardioversion. The investigator considered the event of hypotension as severe in intensity and probably related to etripamil. The study sponsor considered the event of hypotension as unlikely related to etripamil due to elapsed time between event and drug administration based on the half-life of etripamil.

Most Common (≥5%) Treatment-Emergent Adverse Events Within 24 h After Etripamil Administration (Safety Population)

TEAE 24 h	Single Dose (70 mg) (*N*=428)		Optional Repeat Dose (2 × 70 mg) (*N*=75)		Total Safety Population (*N*=503)	
System organ class Preferred term	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Any TEAE 24 h	652	228 (53.3)	124	41 (54.7)	776	269 (53.5)
Gastrointestinal disorders	24	21 (4.9)	5	5 (6.7)	29	26 (5.2)
Nausea	5	5 (1.2)	4	4 (5.3)	9	9 (1.8)
Nervous system disorders	65	42 (9.8)	5	4 (5.3)	70	46 (9.1)
Headache	32	23 (5.4)	4	3 (4.0)	36	26 (5.2)
Respiratory, thoracic, and mediastinal disorders	485	198 (46.3)	97	39 (52.0)	582	237 (47.1)
Nasal discomfort	189	126 (29.4)	43	26 (34.7)	232	152 (30.2)
Nasal congestion	80	59 (13.8)	13	11 (14.7)	93	70 (13.9)
Rhinorrhea	76	54 (12.6)	18	12 (16.0)	94	66 (13.1)
Epistaxis	39	33 (7.7)	6	4 (5.3)	45	37 (7.4)

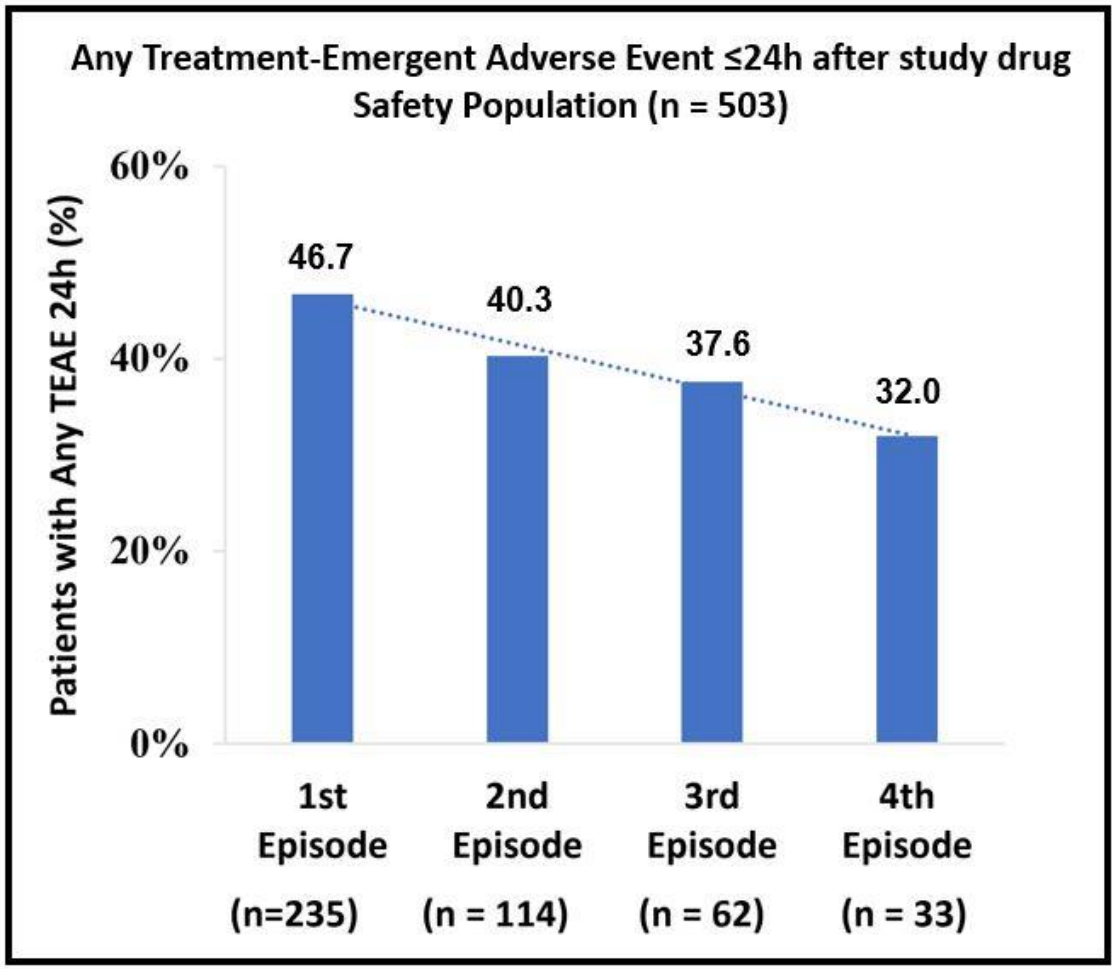
Data are presented for TEAEs 24 h that occurred in ≥5% of patients (by preferred term) in the total safety population. Within each system organ class and within each preferred term, patients with more than one event are counted once only. A TEAE 24 h was defined as an AE starting or worsening within 24 hours after study drug administration, or an AE that started within 12 hours prior to study drug administration. AE = adverse event. TEAE = treatment-emergent adverse event.

TEAEs of Special Interest (Safety Population)

	Single Dose (70 mg) (*N*=428)		Repeat Dose (2 × 70 mg) (*N*=75)		Total Safety Population (*N*=503)	
System Organ Class Preferred Term	**Events, *n***	**Patients, *n* (%)**	**No. of Events**	***n* (%)**	**No. of Events**	***n* (%)**
Any AEs	20	15 (3.5)	3	3 (4.0)	23	18 (3.6)
Cardiac disorders	6	3 (0.7)	3	3 (4.0)	9	6 (1.2)
Sinus arrest (≥3 seconds)	2	1 (0.2)	1	1 (1.3)	3	2 (0.4)
Atrioventricular block, first degree	1	1 (0.2)	1	1 (1.3)	2	2 (0.4)
Atrioventricular block, second degree	2	1 (0.2)	0	0	2	1 (0.2)
Atrioventricular block, third degree	0	0	0	0	0	0
Atrial flutter	0	0	1[a]	1 (1.3)	1	1 (0.2)
Atrial fibrillation	1[b]	1 (0.2)	0	0	1	1 (0.2)
Nervous system disorders	12	10 (2.3)	0	0	12	10 (2.0)
Dizziness	11[c]	9 (2.1)	0	0	11	9 (1.8)
Syncope	1[d]	1 (0.2)	0	0	1	1 (0.2)
Vascular disorders	2	2 (0.5)	0	0	2	2 (0.4)
Hypotension	2[e]	2 (0.5)	0	0	2	2 (0.4)

One transient third-degree heart block occurred after IV adenosine. [a]Moderate severity. [b]Not related to study drug. [c]Two events of dizziness were of moderate severity. [d]One event of syncope was severe. [e]One event of hypotension was mild and one event of hypotension was severe. AE = adverse event. IV = intravenous. TEAE = treatment-emergent adverse event.

Downward Trend in Treatment-Emergent Adverse Events Within 24 h With Repeat Episodes



TEAE = treatment-emergent adverse event.

NODE-303: Summary and Conclusions

- NODE-303 was the first study to evaluate treatment of **multiple episodes of PSVT** with single and optional repeat-dose etripamil, self-administered outside of the healthcare setting as prompted by PSVT symptoms, **without a prior medically supervised test dose**
- The safety profile of etripamil in NODE-303 was similar to that observed in previous randomized trials of etripamil
  - Most treatment-emergent AEs on the day of self-administration (TEAEs 24 h) were transient, mild, or moderate, and localized to the site of etripamil administration, most commonly nasal discomfort, nasal congestion, rhinorrhea, and epistaxis
  - There were no serious drug-related TEAEs
- Efficacy of conversion of PSVT and restoration of SR was demonstrated over multiple episodes (up to 4) to a similar degree and with a similar time to median conversion compared with prior trial data
- The results of this study are consistent with previous clinical studies and support the potential benefit of self-administration of etripamil in treating PSVT in a **medically unsupervised setting without the need for prior test dosing**

AE = adverse event. PSVT = paroxysmal supraventricular tachycardia. SR = sinus rhythm. TEAE = treatment-emergent adverse event.

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