Etripamil Nasal Spray For Acute Termination Of Spontaneous Episodes Of Paroxysmal Supraventricular Tachycardia.

NODE-301 Trial

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Disclosures

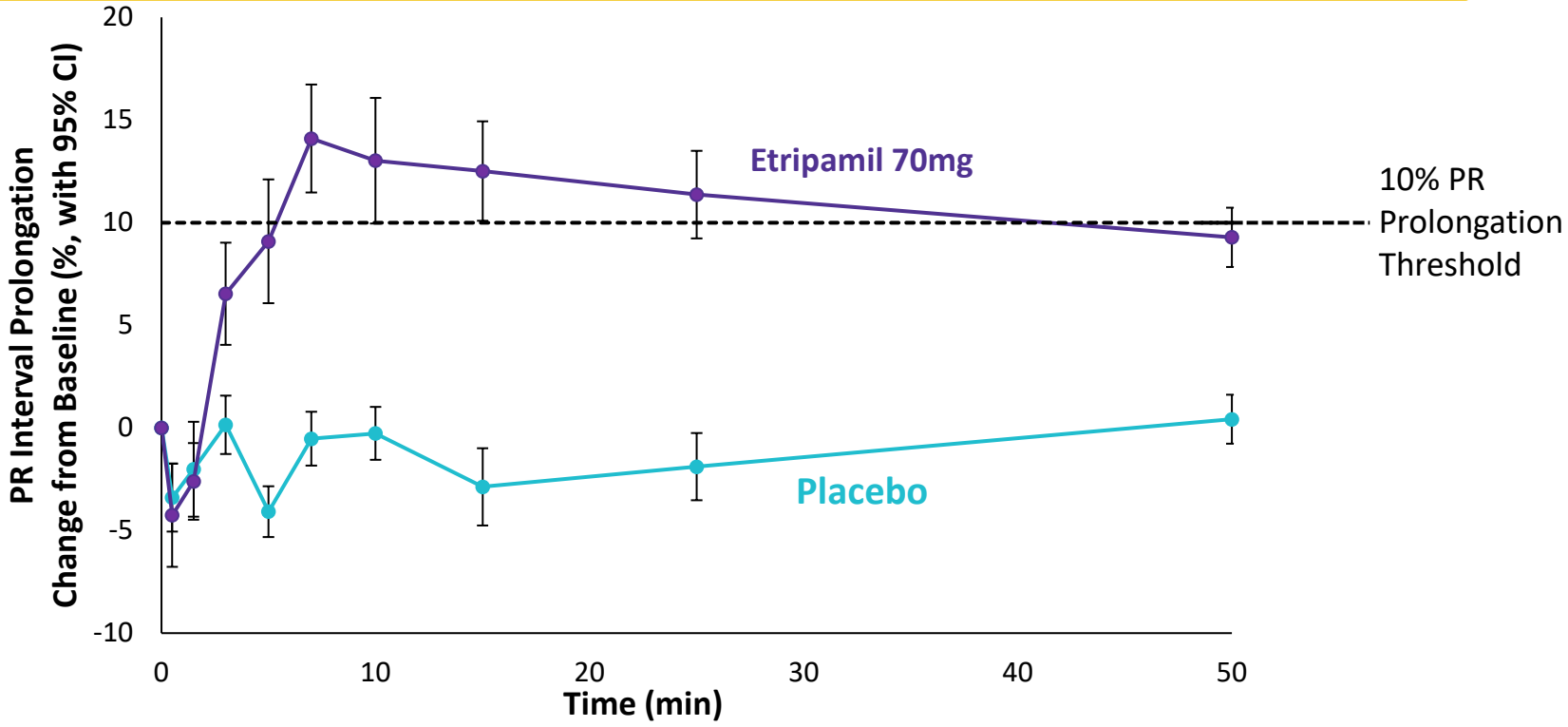
- ***B Stambler***: Honoraria, Consulting Fees, Contracted Grants for PIs - Milestone.
- The **NODE-301** trial and these analyses were funded by Milestone Pharmaceuticals.
- The trial was conducted and coordinated by Medpace.

Etripamil

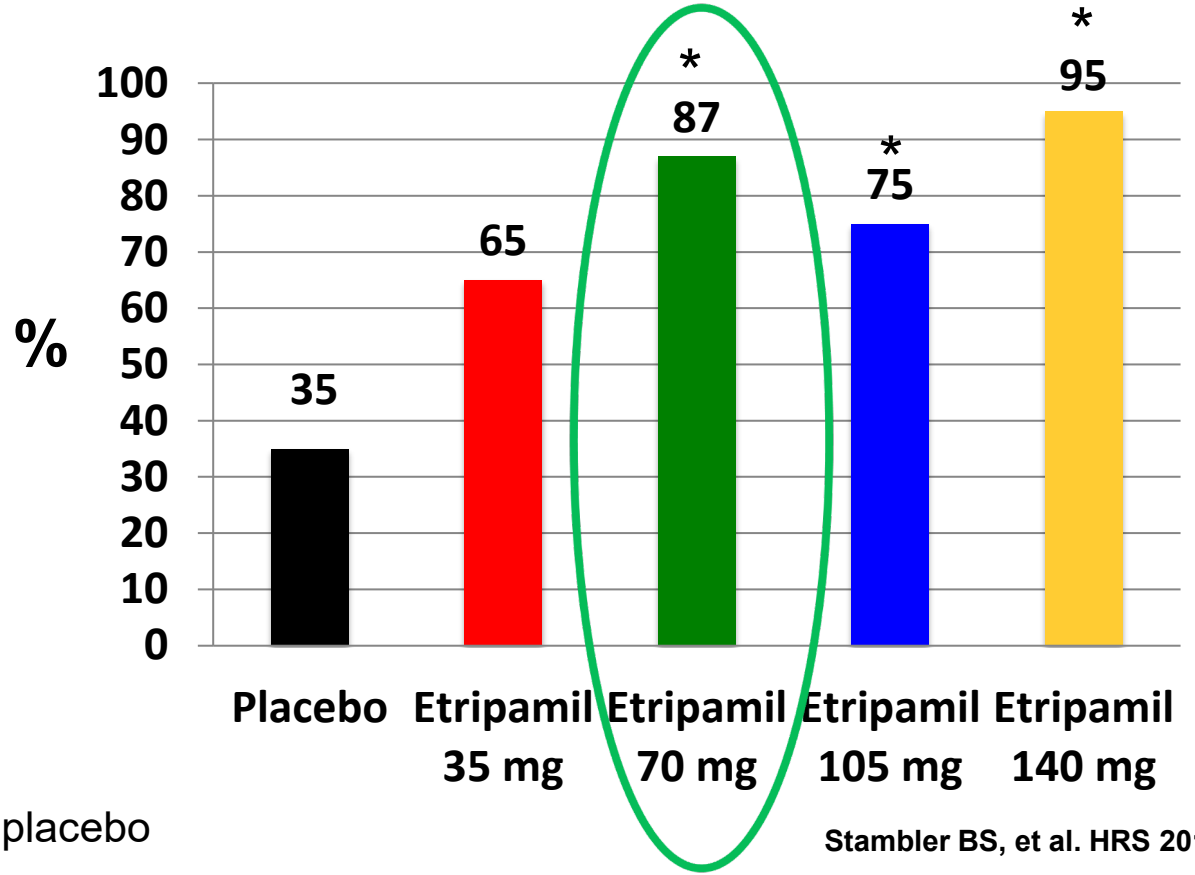
- Novel, L-type calcium channel blocker
- Administered as a nasal spray
- Being developed as a self-administered therapy to terminate AV nodal-dependent PSVT outside of the emergency room or hospital.

NODE-102 Etripamil Nasal Spray Pharmacological Study

Effective pharmacologic activity of etripamil occurs between 5 and 45 minutes



Induced PSVT Conversion Rate within 15 minutes



*p<0.05 vs placebo

Stambler BS, et al. HRS 2017 Late Breaking Clinical Trials

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MULTI-CENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF ETRIPAMIL NASAL SPRAY 70 MG FOR TERMINATION OF *SPONTANEOUS EPISODES* OF PSVT

ClinicalTrials.gov ID: 0346401

ELIGIBILITY CRITERIA

Subjects who met all of the following inclusion criteria were eligible to participate:

- ECG-documented history of sustained episodes of PSVT (lasting ≥20 min);
- Male or female, aged ≥18 years;
- Signed written informed consent.

77 sites in US and Canada

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Key Exclusion Criteria

- History of a non-AV nodal dependent tachycardia
  - Atrial tachycardia, flutter, or fibrillation
  - Ventricular tachycardia or fibrillation, torsades de pointes
- History of severe symptomatic hypotension or syncope during PSVT
- Systolic blood pressure < 90 mm Hg at screening visit
- Ventricular pre-excitation syndrome (WPW)
- Second- or third-degree AV block on screening ECG
- Class I or III AAD or digoxin use <5 half-lives prior to randomization visit
- Amiodarone use within 30 days of randomization visit
- Current NYHA class II-IV heart failure
- Stroke in the last 6 months
- Failure of a safety test dose of etripamil

Etripamil Test Dose in Sinus Rhythm

- Failure of the medically supervised, self-administered test dose of etripamil:
  - Any symptoms consistent with clinically severe hypotension (pre-syncope, lightheadedness, syncope, nausea, vomiting)
  - Decrease in SBP ≥40 or SBP <75-80 mm Hg after test dose
  - 3rd AV block, Mobitz II 2nd AV, Mobitz I with HR < 40 bpm
  - Sinus bradycardia ≤40 bpm or sinus pauses ≥3 seconds
  - Significant ventricular arrhythmias (>6 PVCs over 45 seconds)
  - Atrial fibrillation (>30 seconds)

Study Design

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Objective: Superiority of etripamil over placebo in terminating PSVT events in the outpatient setting

Randomized
Etripamil:Placebo (2:1)
(N=419, 97%)

Patient dosed for suspected episode
Safety Dataset
(N=198, Etripamil=138, Placebo=60)

Positively-Adjudicated PSVT events
Efficacy Dataset
(N=156, Etripamil=107, Placebo=49)

Test Dose
Active drug while in SR
(N=431)

Documented diagnosis of PSVT with a history of episodes lasting ≥ 20 minutes

PSVT = Paroxysmal Supraventricular Tachycardia; SR = Sinus Rhythm;

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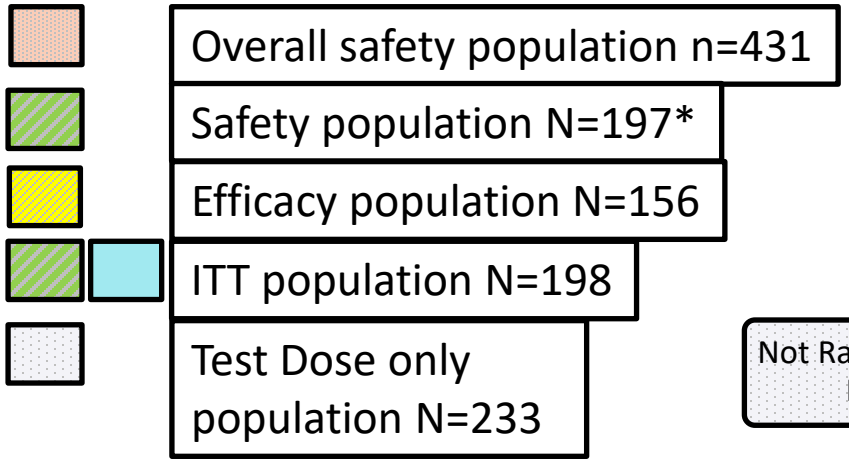
Consort Flow Diagram



07/18/18 – 01/15/20

* 1 pt lost to follow up (documented PSVT without final visit)

Demographics

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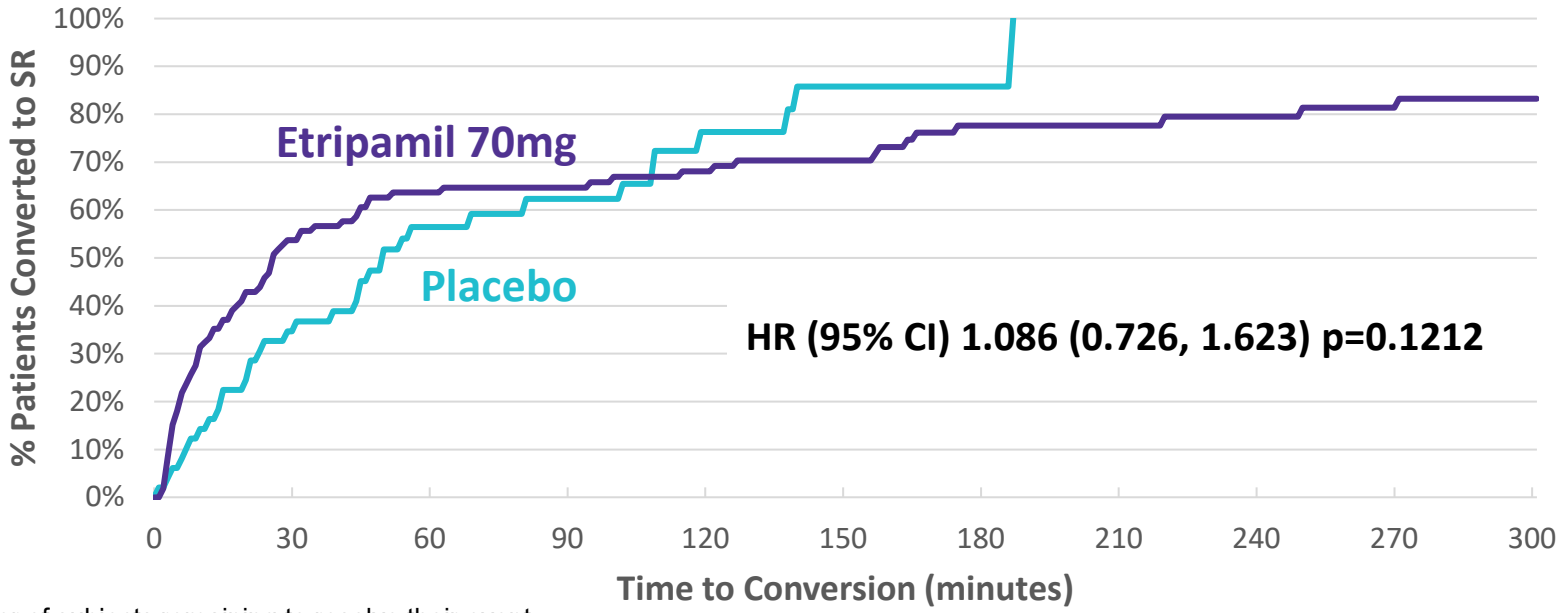
	Efficacy Population		Overall Safety Population (N=431)
	Etripamil (N=107)	Placebo (N=49)	
Age, years	56.9	54.3	**55.2**
Gender			
Male, n (%)	34 (31.8)	16 (32.7)	**158 (36.7)**
Female, n (%)	73 (68.2)	33 (67.3)	**273 (63.3)**
PSVT Duration, yrs	1.5	1.3	**1.4**
# PSVT in past yr	7.4	11.3	**7.8**
Lifetime ED visits	2.7	3.4	**2.8**
BMI, kg/m^2	28.32	28.78	**29.17**

ED = emergency department

NODE-301 Primary Endpoint – Time to Conversion

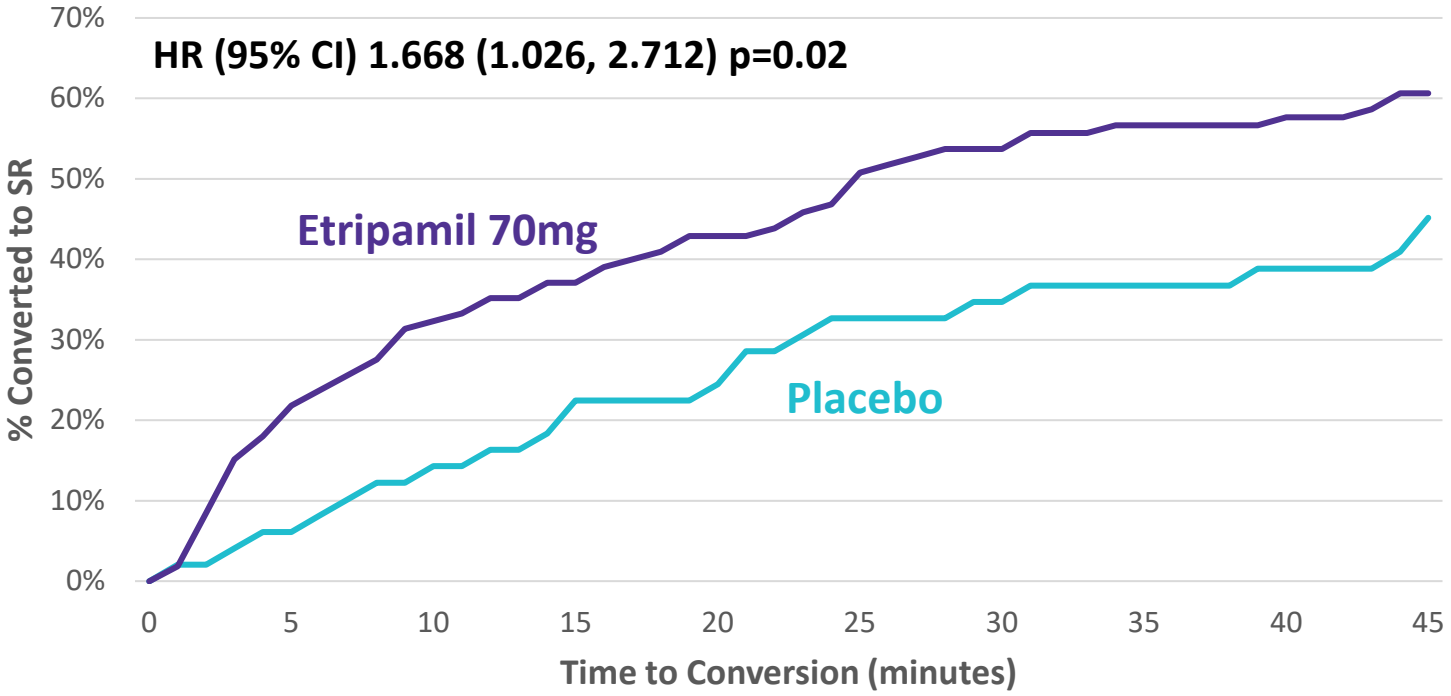
Kaplan-Meier analysis of time to conversion of positively-adjudicated PSVT episodes over 5 hours



Number of subjects remaining to resolve their event

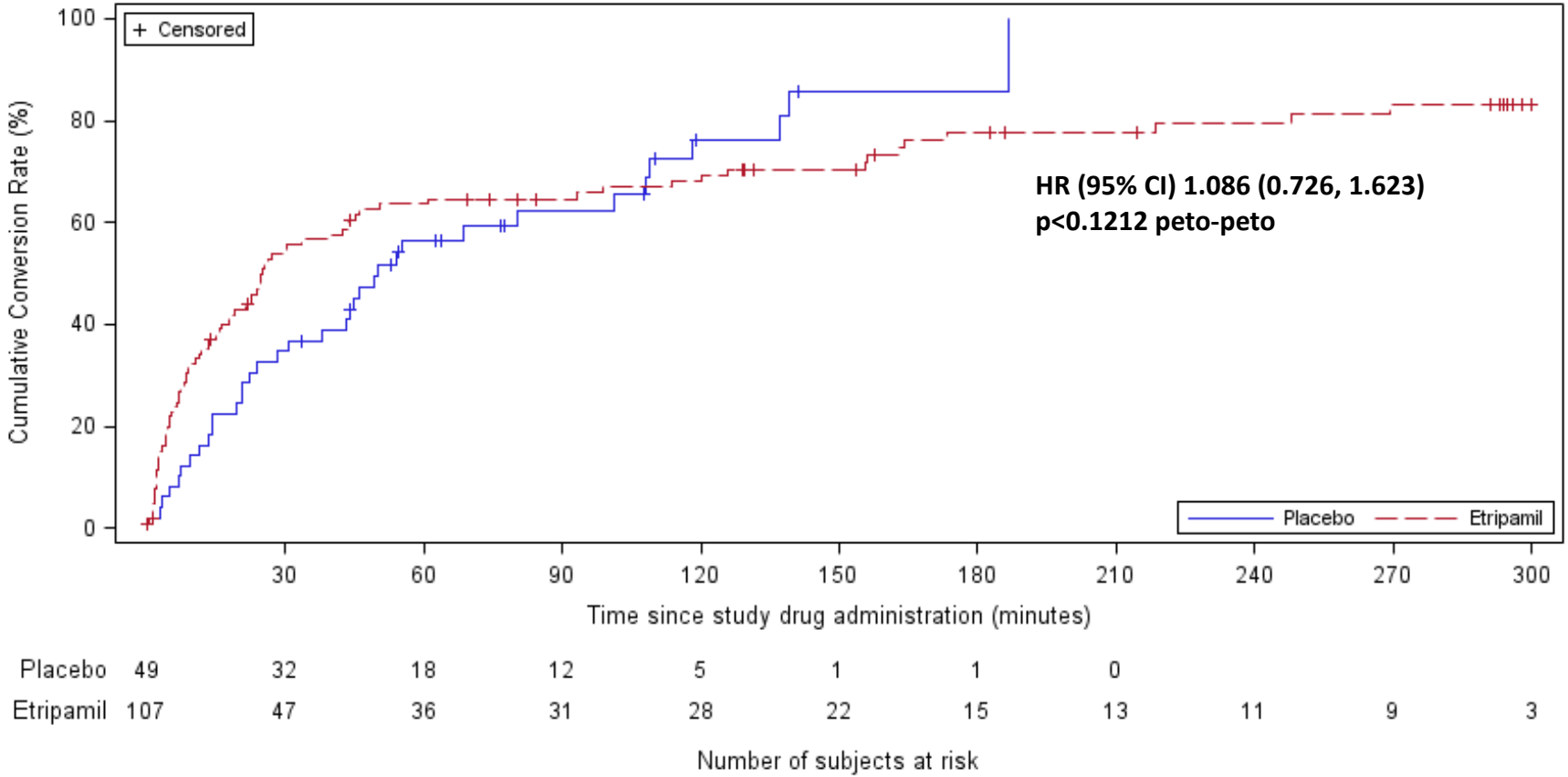
Placebo	49	32	18	12	5	1	1	0			
Etripamil	107	47	36	31	28	22	15	13	11	9	3

NODE-301 Efficacy – Time to Conversion over 45 Minutes



- *Median time to conversion: 25 vs. 50 minutes (Etripamil vs. Placebo)*

Time to Conversion of an Adjudicated PSVT Episode up to Hour 5



NODE-301 Safety Analysis

Treatment Emergent Adverse Events	Etripamil (N=138)	Placebo (N=60)
Nasal discomfort	27 (19.6)	4 (6.7)
Nasal congestion	11 (8.0)	2 (3.3)
Epistaxis	9 (6.5)	0 (0.0)
Rhinorrhea	8 (5.8)	1 (1.7)
Throat irritation	7 (5.1)	1 (1.7)
Headache	4 (2.9)	0 (0.0)
Sneezing	3 (2.2)	0 (0.0)
Atrioventricular (AV) block first degree	2 (1.4)	0 (0.0)
Dysgeusia	2 (1.4)	1 (1.7)
Sinus congestion	1 (0.7)	2 (3.3)
Rhinalgia	1 (0.7)	1 (1.7)
Ventricular tachycardia	1 (0.7)	1 (1.7)
Lacrimation increased	1 (0.7)	1 (1.7)
Burning sensation	1 (0.7)	0 (0.0)
Presyncope	1 (0.7)	0 (0.0)

Summary

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- Etripamil nasal spray (70 mg dose) did not meet the primary endpoint of conversion of PSVT over 5 hours.
- During the first 45 minutes, etripamil had a clinically meaningful treatment effect, consistent with the drug's pharmacology.
- Etripamil had an acceptable safety profile when self-administered by patients during PSVT in a medically unsupervised setting.