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Self-Administered Etripamil Nasal Spray Rapidly Terminated Spontaneous Paroxysmal Supraventricular Tachycardia (PSVT): Analysis of Open-Label Treatment in the RAPID Study

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Disclosure

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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The trial was conducted and coordinated by Medpace and IQVIA.

Etripamil is an investigational drug and is not approved for use by the FDA.

Etripamil Is a Novel Treatment for PSVT

- Etripamil, a **potential new treatment for PSVT**, is an investigational, L-type **calcium channel blocker**, formulated as an intranasal spray[1,2]:
  - Onset of action ≤7 minutes
  - Metabolized by blood esterases
- Etripamil is being developed as a safe and convenient therapy for PSVT to be **self-administered outside the healthcare setting**
- Effectively terminates AV nodal–dependent PSVT episodes
  - NODE-301 (Part 1) , NODE-302, RAPID, and NODE-303[3-5]

Error bars represent standard error (SE).

AV, atrioventricular; PK, pharmacokinetics; PSVT, paroxysmal supraventricular tachycardia. 1. Stambler BS, et al. *J Am Coll Cardiol*. 2018;72:489-497. 2. Ip JE, et al. *Clin Pharmacol Drug Dev*. 2024;13:367-379. 3. Stambler BS, et al. *Lancet*. 2023;402:118-128. 4. Stambler BS, et al. *Circ Arrhythm Electrophysiol*. 2022;15:e010915. 5. Ip JE, et al. *J Am Coll Cardiol*. 2024:S0735-1097(24)06670-1.

RAPID trial: Study Design

Key inclusion criteria:
- ≥18 years of age
- ECG-documented PSVT
- Sustained PSVT episode ≥20 minutes

Key exclusion criteria:
- Ventricular pre-excitation
- 2º or 3º AV block
- Severe ventricular arrhythmia

Test dose
- Etripamil (70 mg) followed by repeat dose (70 mg) after 10 minutes during SR

1:1 randomization period
- Etripamil 70 mg dose + optional repeat 70 mg dose if symptoms persist
- Placebo dose + optional repeat dose if symptoms persist

Open-label period[a]

Etripamil 70 mg dose + optional repeat 70 mg dose if symptoms persist

(ECG CMS for 5 hours after etripamil administration)

14 days

Final study visit

(PE, VS, laboratory test, PT, ECG data review)

Primary efficacy endpoint:

Time to conversion of an *adjudicated PSVT episode* to SR within 30 minutes of study drug administration

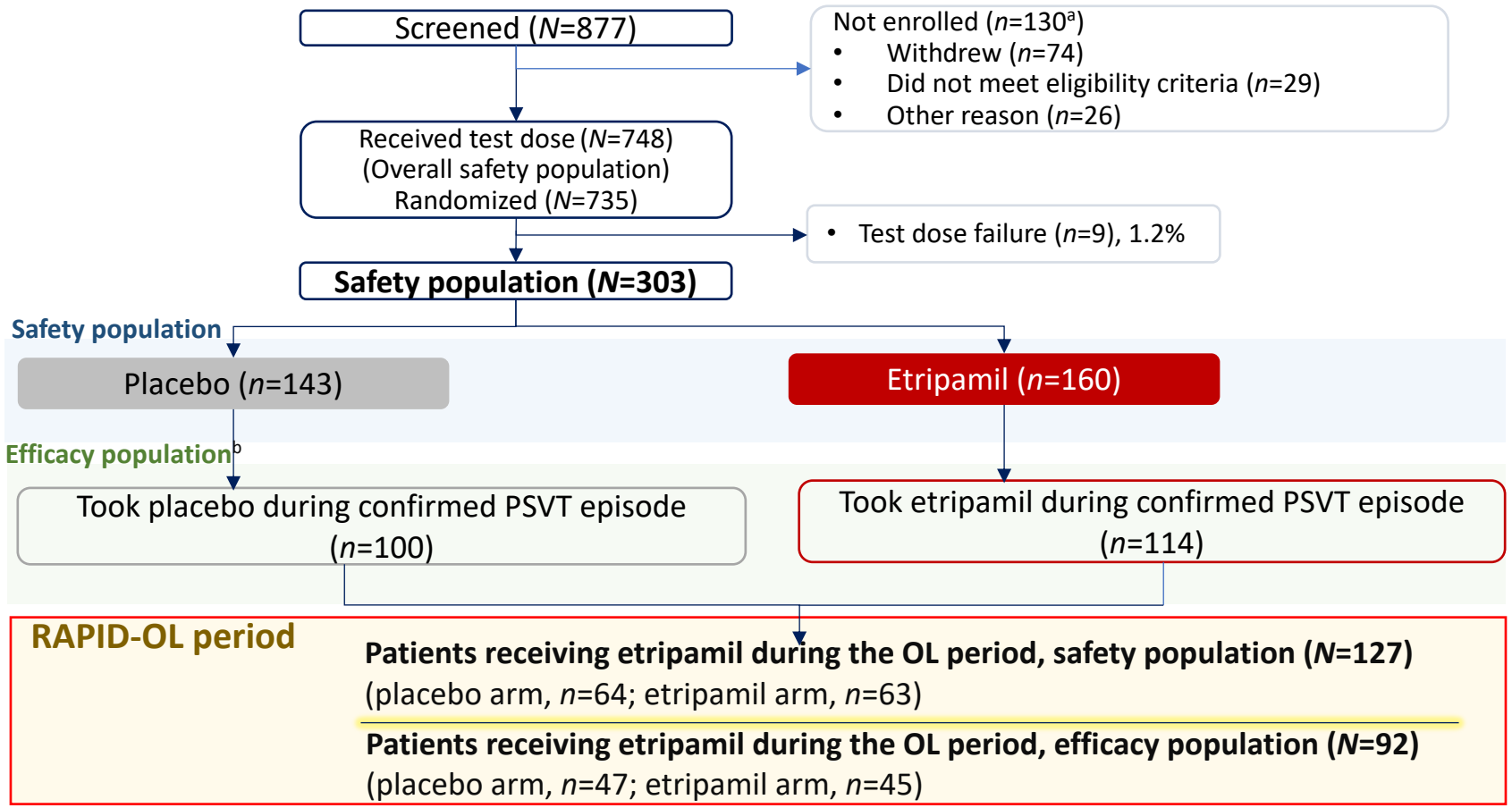
[a]All randomized patients who did not experience any adverse events after etripamil administration for a perceived PSVT episode were included in the open-label treatment.

AV, atrioventricular; PK, pharmacokinetics; PSVT, paroxysmal supraventricular tachycardia. 1. Stambler BS, et al. *J Am Coll Cardiol*. 2018;72:489-497. 2. Ip JE, et al. *Clin Pharmacol Drug Dev*. 2024;13:367-379. 3. Stambler BS, et al. *Lancet*. 2023;402:118-128. 4. Stambler BS, et al. *Circ Arrhythm Electrophysiol*. 2022;15:e010915. 5. Ip JE, et al. *J Am Coll Cardiol*. 2024:S0735-1097(24)06670-1.

Patient Disposition

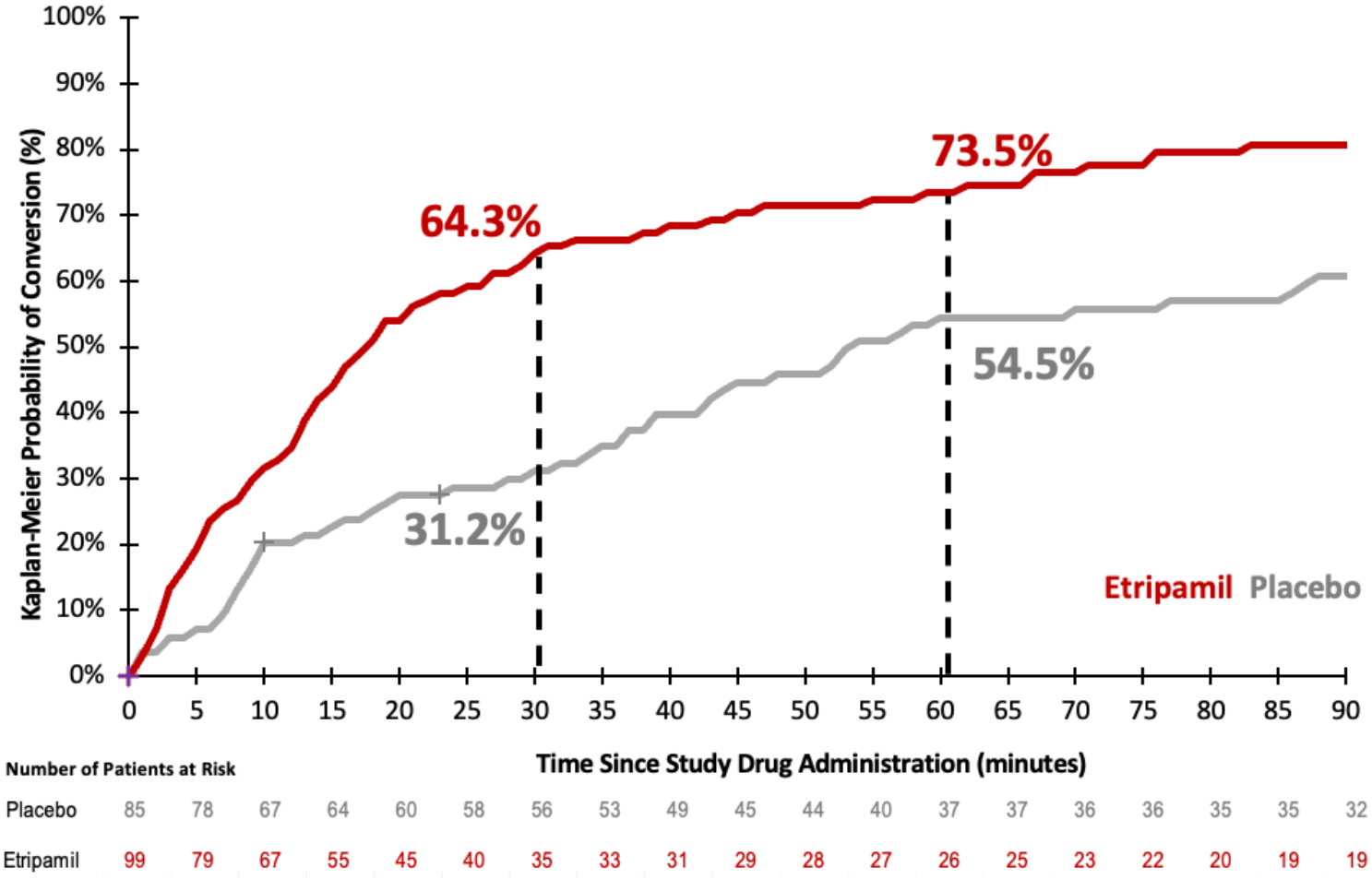
Safety population
- All randomized patients who took the study drug to treat a perceived PSVT episode

Efficacy population
- All randomized patients who took the study drug to treat an episode of confirmed PSVT by the Adjudication Committee



[a]One patient was classified as a screen failure after receiving a test dose. [b]30 patients were included in the efficacy population from the RAPID Extension study. OL, open-label; PSVT, paroxysmal supraventricular tachycardia.

RAPID Trial: Conversion of PSVT to SR at 30 and 60 Minutes Superior with Etripamil



Median time to conversion:
17.2 vs 53.5 minutes

30m: **HR 2.6** [1.7, 4.2]; p<0.001
60m: **HR 1.9** [1.3, 2.7]; p<0.001

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CI, confidence interval; HR, hazard ratio; PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm.

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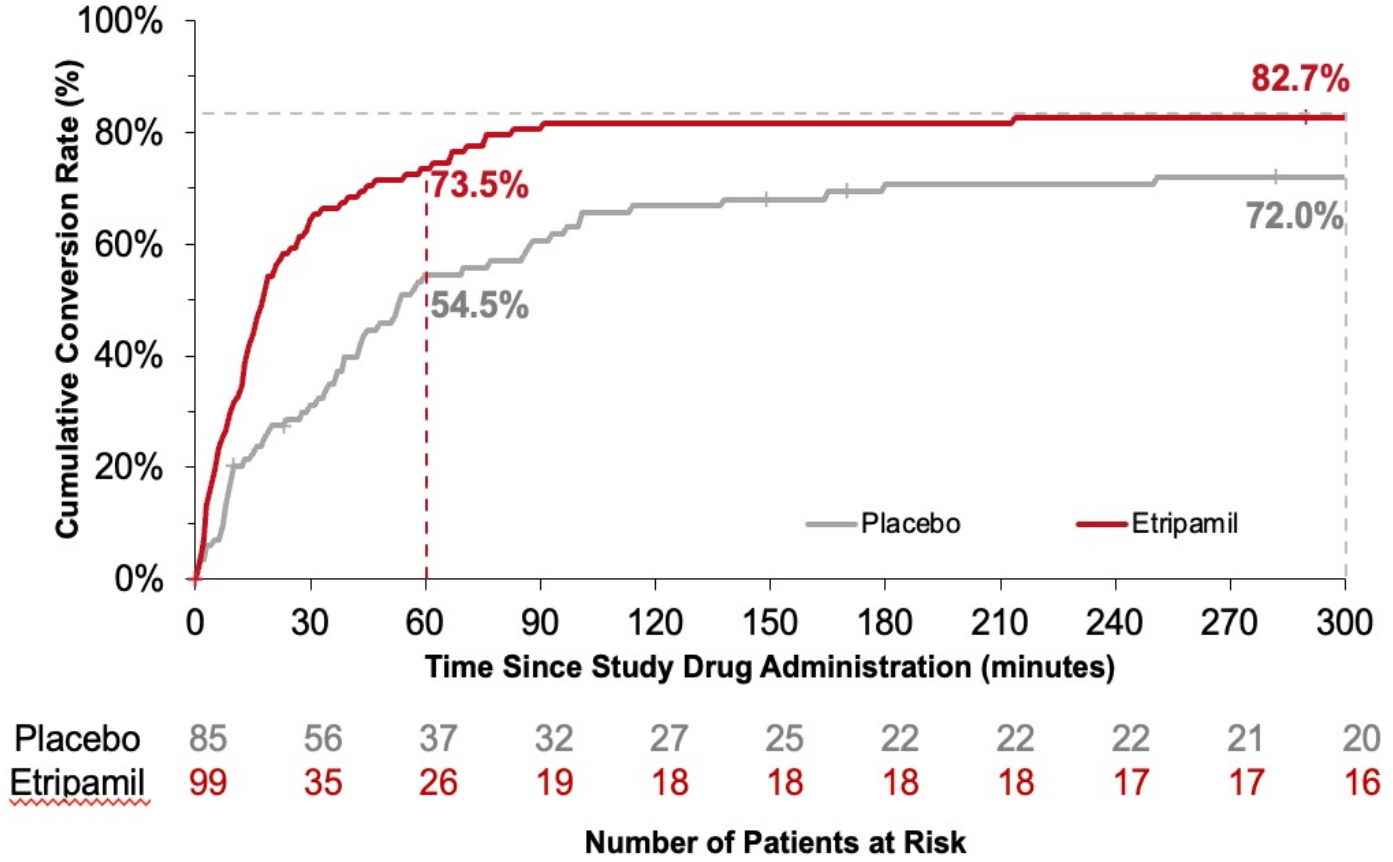
RAPID Trial: Conversion of PSVT to SR at 1 and 5 Hours Superior with Etripamil



1 hour: **HR 1.9** [1.3, 2.7]; p <0.001

5 hour: **HR 1.7** [1.2, 2.4]; p <0.001

CI, confidence interval; HR, hazard ratio; PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm.

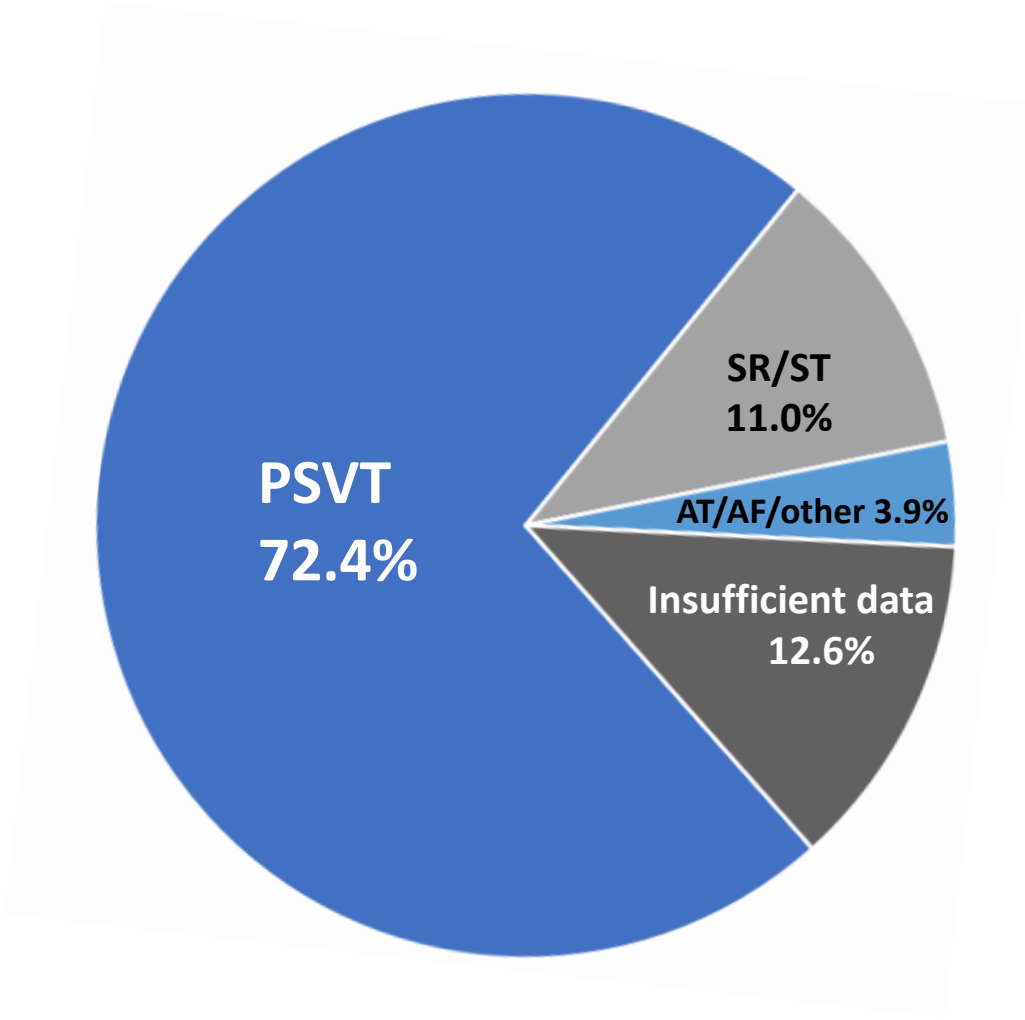
Results From the **Open-Label** Period of the RAPID and RAPID Extension Studies

Baseline Characteristics (Open-Label[a])

Characteristics	Overall (*N*=127)
Age (years), mean (SD)	55.8 (12.6)
Female, *n* (%)	91(71.7)
Race, *n* (%)	
American Indian/Alaska Native	1 (0.8)
Asian	3 (2.4)
Black/African American	4 (3.1)
White	117 (92.1)
Other	2 (1.6)
Age at confirmation of PSVT (years), mean (SD)	54.2 (13.0)
Duration of PSVT (years), mean (SD)	2.1 (4.6)
Number of patient-reported PSVT episodes in the past year, mean (SD)	9.8 (21.7)
Concomitant medications of interest, *n* (%)[b]	
β-blockers or CCB	84 (66.1)
β-blockers only	43 (33.9)
CCB only	30 (23.6)
β-blockers and CCB	11 (8.7)
Patients with past ablation, *n* (%)	13 (10.1)

[a]The safety population includes all patients who administered open-label etripamil for a perceived episode of PSVT. [b]A single patient may have reported taking more than one type of medication.
CCB, calcium channel blocker; PSVT, paroxysmal supraventricular tachycardia; SD, standard deviation.

ECG Adjudication of Perceived Episodes

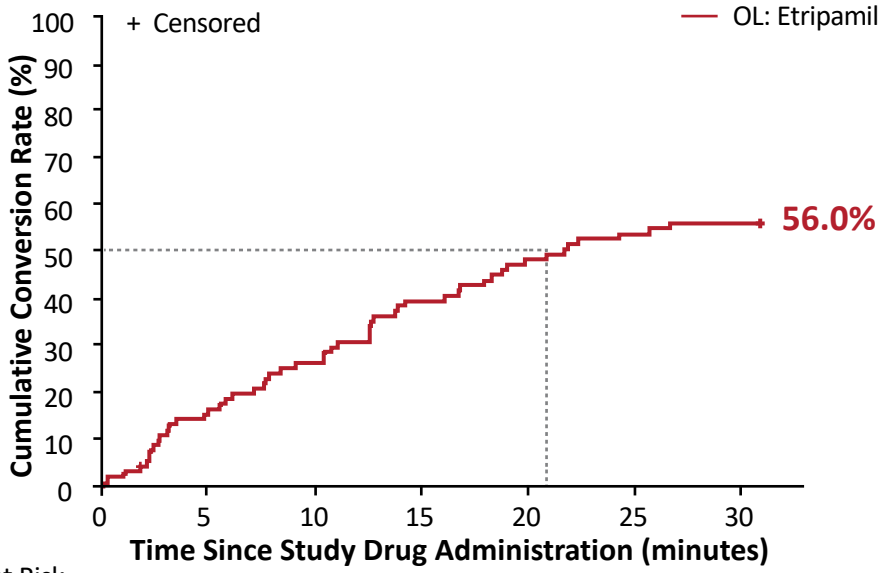


- Safety population (*N*=127)
- Efficacy population (*N*=92)

AF, atrial fibrillation; AT, atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm; ST, sinus tachycardia.

Primary Endpoint: Conversion of Adjudicated PSVT to Sinus Rhythm

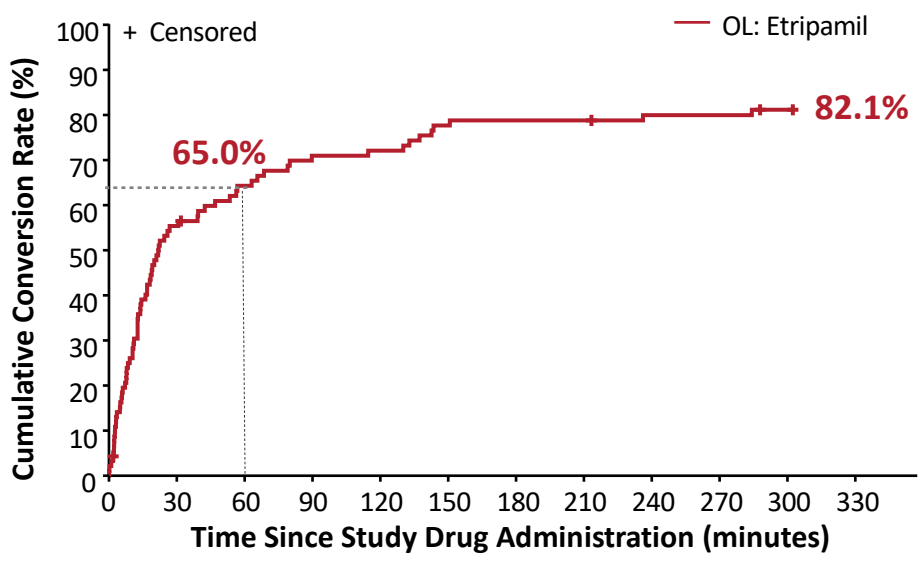
Open-Label 30-Minute Endpoint



Number at Risk

OL: Etripamil	92	77	67	55	47	42	40

Open-Label 300-Minute Endpoint



OL: Etripamil	92	40	31	25	24	19	18	18	16	16	14	0

Median time to conversion at 30 minutes: **21.7 minutes** (14.3, 42.2)

OL, open-label; PSVT, paroxysmal supraventricular tachycardia.

Safety Analysis: Treatment-Emergent Adverse Events

- Treatment-emergent adverse events (TEAEs) = adverse events occurring ≤24 hours after etripamil administration

	RAPID + RAPID Extension Open-Label Period	RAPID + RAPID Extension Randomized		
Category, *n* (%)	**Etripamil Dose (*N*=127)**	**Placebo Dose (*N*=143)**	**Etripamil Dose (*N*=160)**	
Patients with any TEAEs	46 (36.2)*	28 (19.6)	83 (51.9)*	**P*=0.0079
Maximum severity of any TEAEs				
Mild	28 (22.0)	21 (14.7)	60 (37.5)	
Moderate	18 (14.2)	6 (4.2)	22 (13.8)	
Severe	0	1 (0.7)	1 (0.6)	
Drug-related TEAEs	44 (34.6)**	20 (14.0)	77 (48.1)**	***P*=0.0212
Drug-related TEAEs by maximum severity				
Mild	30 (23.6)	19 (13.3)	57 (35.6)	
Moderate	14 (11.0)	1 (0.7)	19 (11.9)	
Severe		0	1 (0.6)	

- **No** open-label follow-up adverse events (OLFAEs) resulted in study drug discontinuation or death
- **No** severe or serious OLFAEs or drug-related OLFAEs

Drug-Related Adverse Events

- Most common (≥5%) AEs were nasal discomfort, nasal congestion, rhinorrhea, and epistaxis, consistent with the most frequent adverse events reported in the randomized study

	RAPID + RAPID Extension Open-Label Period	RAPID + RAPID Extension Randomized	
Category, *n* (%)	**Etripamil Total (*N*=127)**	**Placebo Dose (*N*=143)**	**Etripamil Dose (*N*=160)**
Patients with drug-related AEs	44 (34.6)*	20 (14.0)	77 (48.1)*
Respiratory, thoracic, and mediastinal disorders			
Nasal discomfort	19 (15.0)	10 (7.0)	39 (24.4)
Nasal congestion	11 (8.7)	1 (0.7)	23 (14.4)
Rhinorrhea	11 (8.7)	4 (2.8)	17 (10.6)
Epistaxis	8 (6.3)	3 (2.1)	9 (5.6)
Adverse events of special interest			
Syncope[a]	1 (0.8)	0	0
Dizziness[a]	1 (0.8)	1 (0.7)	1 (0.6)

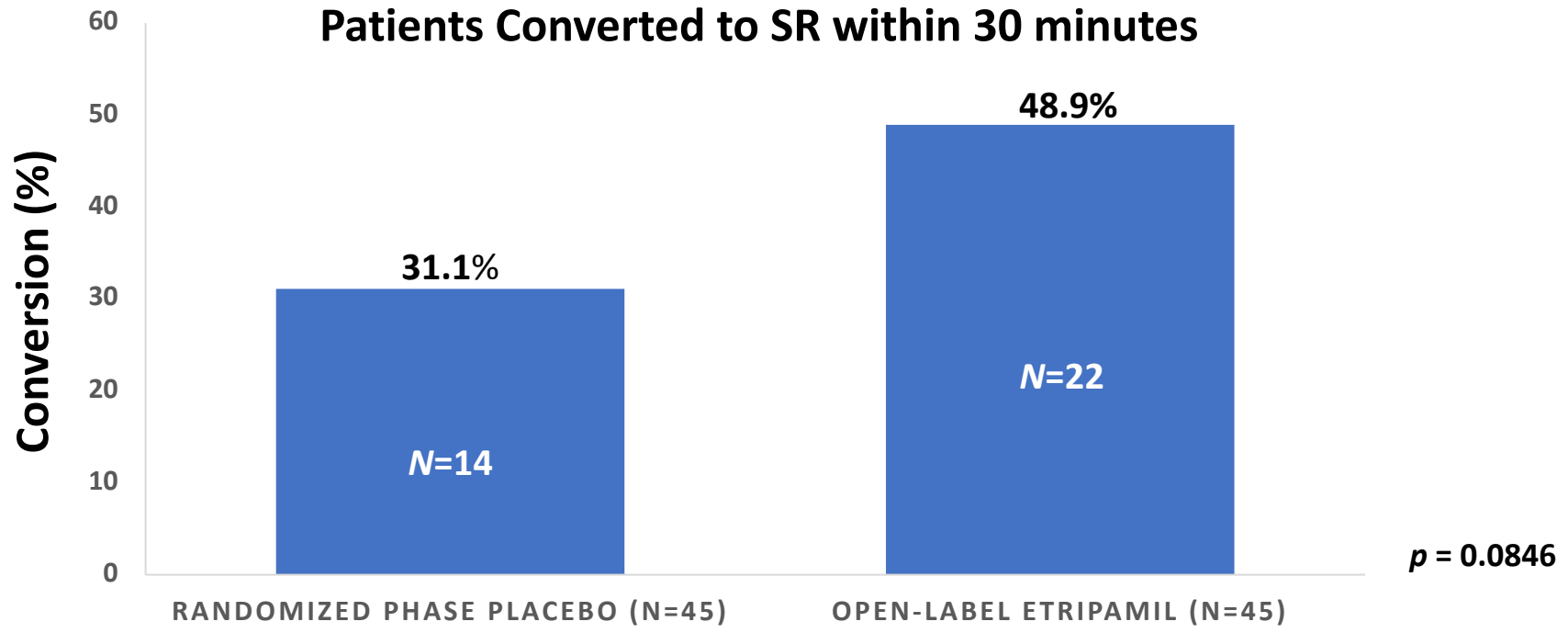
*p = 0.0212

- No episodes of hypotension, atrioventricular block, or pauses noted in the open-label period

[a]Considered mild and possibly related to etripamil. AE, adverse event.

Cross-Over Analysis of Confirmed PSVT Episodes

- A cross-over analysis was performed for patients who treated a confirmed PSVT episode with placebo during the randomization period and etripamil during the open-label period



P value is obtained from the Wilcoxon test.
PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm.

Conclusions: RAPID Open-Label Treatment

- The RAPID trial showed a **robust treatment effect of etripamil** to rapidly convert PSVT to SR in a medically unsupervised setting
- Etripamil showed a **consistent safety** profile in the RAPID-OL trial, similar to that observed in previous randomized trials of etripamil
- **All OLFAEs were mild or moderate** in severity and were localized to the site of etripamil administration
  - Common OLFAEs included nasal discomfort, nasal congestion, rhinorrhea, and epistaxis
  - There were **no serious drug-related adverse events** (i.e., no hypotension, AV block, pauses)
  - Significantly fewer AEs reported compared to first randomized dose
- Etripamil was efficacious in converting PSVT and restoring SR in the OL period with more than 50% of the patients converting to SR within 30 minutes of study drug administration
- Efficacy and safety outcomes from the RAPID-OL trial support the **potential benefit of self-administration of etripamil in treating PSVT in a medically unsupervised setting**

OL, open-label; OLFAE, open-label follow-up adverse event; PSVT, paroxysmal supraventricular tachycardia; SR, sinus rhythm.

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- **Data Safety Monitoring Committee**

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THANK YOU!