

Combined Efficacy, Safety, and Test Dose Tolerability of Etripamil for Acute Paroxysmal Supraventricular Tachycardia (PSVT) Across Multiple Clinical Trials



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Background

- Paroxysmal supraventricular tachycardia (PSVT) affects 1 in 300 people in the U.S. and leads to ~50,000 emergency room (ER) visits annually.¹
- Management of PSVT episodes often requires visits to a healthcare facility for intravenous medications (e.g. adenosine) or electrical cardioversion, resulting in frequent ER visits, increased healthcare costs, and patient inconvenience.
- Previous clinical trials have consistently demonstrated etripamil's favorable safety and efficacy in restoring sinus rhythm (SR) during PSVT episodes.²⁻⁷

Objective

- To analyze the efficacy, safety, and test-dose tolerability of etripamil across PSVT clinical studies.

Methods

- This analysis involved a targeted, systematic review of randomized controlled trials (RCTs) and open-label studies evaluating etripamil in adult patients with documented PSVT. Studies were selected based on their focus on self-administered etripamil for acute episode termination, with inclusion criteria encompassing patients ≥18 years with a history of PSVT confirmed by electrocardiography (ECG).
- Key studies included: Phase 2: NODE-1. Phase 3: NODE-301 (Parts 1 and 2, including RAPID and its extensions), NODE-302, and NODE-303 (open-label extensions) (Table 1).
- Efficacy endpoints were assessed using Kaplan-Meier (KM) estimates for the time to conversion from PSVT to SR, defined as the restoration of SR for at least 30 seconds confirmed by ECG.
- Safety data were descriptively summarized, focusing on treatment emergent adverse events (TEAEs) occurring within 24 hours of administration (TEAE24h), serious AEs, and discontinuations due to AEs.

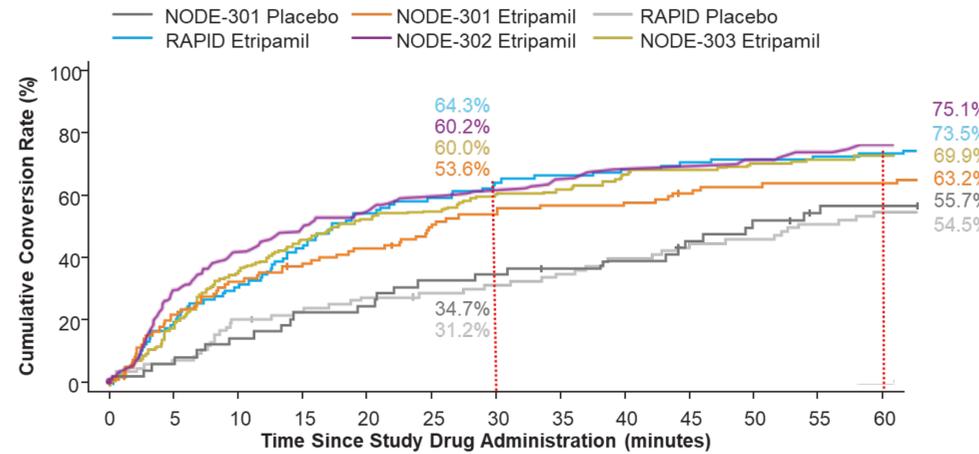
Table 1. Studies Evaluating the Efficacy and Safety of Etripamil for SVT

Study	ClinicalTrials.gov ID	Phase	Design*	Dates	Location	Ref.
NODE-1	NCT02296190	2	DB RCT (1:1 randomized)	03/2015 - 12/2016	U.S., Canada	[2]
NODE-301 Part 1	NCT03464019	3	DB RCT (2:1 randomized)	06/2018 - 01/2023	U.S., Canada	[3]
NODE-301 Part 2, RAPID	NCT03464019	3	DB RCT (1:1 randomized)	10/2020 - 07/2022	U.S., Canada, Europe	[4]
RAPID (Extension)	NCT03464019	3	DB RCT (1:1 randomized)	07/2022 - 02/2023	U.S., Canada, Europe	[5]
RAPID (Open Label)	NCT03464019	3	Open-label	10/2020 - 07/2022	U.S., Canada, Europe	[5]
RAPID (Open Label Extension)	NCT03464019	3	Open-label	07/2022 - 02/2023	U.S., Canada, Europe	[5,6]
NODE-302	NCT03635996	3	Open-label	06/2018 - 10/2020	U.S., Canada	[7]
NODE-303	NCT04072835	3	Open-label	09/2019 - 01/2023	U.S., Canada, South America	[8,9]

DB=double blind; RCT=randomized control trial; Ref=reference; US= United States. *1:1 and 2:1 indicates the etripamil to placebo randomization ratio in RCTs. Note: All studies sponsored by Milestone Pharmaceuticals, Inc.

Results

Figure. Kaplan-Meier Estimates of Time to Conversion of PSVT to Sinus Rhythm at 30 and 60 Minutes Across Phase 3 Etripamil Studies



Study	552	436	339	289	264	244	221	204	188	181	175	171	166
NODE-303 Etripamil	552	436	339	289	264	244	221	204	188	181	175	171	166
NODE-302 Etripamil	188	128	106	91	82	74	71	64	59	57	53	48	45
RAPID Etripamil	99	79	67	55	45	40	35	33	31	29	28	27	26
RAPID Placebo	85	78	67	64	60	58	56	53	49	45	44	40	37
NODE-301 Etripamil	107	82	71	65	59	50	47	44	43	39	37	36	36
NODE-301 Placebo	49	46	42	38	37	33	32	30	29	25	22	19	18

- Among 622 etripamil-exposed patients experiencing PSVT episodes, the KM estimate for conversion to SR within 30 minutes of drug administration was **59.6%** (range across studies 53.6% to 64.3%) (Figure).
- At **60 minutes** post-administration, etripamil conversion rates varied from **63.2% to 75.1%** across individual studies (Figure).
- The **median time to conversion** was **18.5 minutes** (95% CI: 15.7 to 21.0 minutes)

Discussion

- These results position etripamil as a potential therapy for PSVT management, potentially empowering patients to self-treat episodes and substantially reducing the reliance on emergency healthcare services.

Limitations

- This work represents a descriptive, targeted systematic review and does not include rigorous statistical analysis.
- The generation of high-quality Real-world evidence (RWE) outside of clinical trial settings is needed.
- Future use of etripamil and subsequent research will enable more robust meta-analyses.

References

1. Rehorn M, et al. J Cardiovasc Electrophysiol. 2021. 2. Stambler BS, et al., J Am Coll Cardiol. 2018. 3. Stambler BS, et al. Circ Arrhythm Electrophysiol. 2022. 4. Stambler, BS et al. Lancet. 2023. 5. Data on file, Milestone Inc. 6. Ip et al., Presented at HRS. 2024. 7. Ip JE, et al. J Am Heart Assoc. 2023. 8. Ip JE, et al., J Am Coll Cardiol. 2023. 9. Ip, JE, et al. J Cardiovasc Electrophysiol. 2025.

Table 2. Treatment Emergent Adverse Events within 24 hours (TEAE24h) ≥5% Incidence In Any Group of Self-Administered Etripamil, Safety Population

Category	Randomized, Double-Blind, Placebo-Controlled Trials		Open-Label Studies	
	Placebo (n= 223)	Etripamil Exposed (n= 321)	Etripamil Exposed (n= 735)	
	No. of events	n (%)	No. of events	n (%)
Any TEAE24h	78	51 (22.9)	373	169 (52.6)
Serious TEAE24h	3	3 (1.3)	0	0
Nasal Discomfort	15	14 (6.3)	92	87 (27.1)
Nasal Congestion	3	3 (1.3)	46	44 (13.7)
Rhinorrhea	4	4 (1.8)	39	37 (11.5)
Throat Irritation	3	3 (1.3)	22	22 (6.9)
Epistaxis	2	2 (0.9)	20	20 (6.2)

- Safety data from etripamil-exposed patients (N=321 in RCTs, N=735 in open-label studies) and 223 placebo recipients showed a favorable profile as the majority of TEAE24h were mild and transient, primarily related to the nasal administration route (Table 2).

Table 3. Test-dose Tolerability

Patients Who Received at Least One Test Dose of Etripamil While in SR (n= 1,107)	
Test Dose Tolerability	
Test Dose Failure*, n (%)	16 (1.4)
Reasons for Test Dose Failure, n	
Atrial Tachycardia	1
Dizziness	1
Hypotension	5
Incomplete administration of study drug	2
Nasal Discomfort	2
Premature Ventricular Contractions	5

*Intolerance requiring discontinuation. SR= Sinus Rhythm

Conclusions

- There was **consistent efficacy of etripamil** across study phases, designs, and geographic regions (in >600 unique treated patients), with treatment demonstrating greater conversion rates for symptomatic PSVT episodes compared with placebo arms. The median time to conversion from PSVT to SR with etripamil, **18.5 minutes**.
- The **safety profile was favorable and consistently shown** in >1050 etripamil-exposed patients, characterized by predominantly mild, transient, and localized adverse events.
- The low rate of test-dose failures (1.4%) among >1,100 patients in SR further indicates the **consistent tolerability** of etripamil.

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