Impact of Investigational, at-Home, Self-administered, Intranasal Etripamil on the Need for Additional Medical Intervention in Patients With Supraventricular Tachycardia

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Background

- Paroxysmal supraventricular tachycardia (PSVT) is a heart rhythm disorder characterized by the sudden onset and termination of episodes of abnormally high heart rates.[1] Clinical symptoms include heart palpitations, shortness of breath, dizziness, chest pain, and anxiety.[2]
- PSVT incurs a substantial economic burden, in part due to its impact on healthcare costs including a frequent need for medical interventions and emergency department (ED) visits.[3,4]
- Current treatments, including intravenous (IV) calcium channel blockers and IV adenosine, are effective for terminating PSVT episodes[5] but are not feasible for self-administration in an outpatient setting due to the requirement for IV access. A rapidly acting therapy that patients could self-administer would give patients the ability to terminate acute PSVT without the need for direct medical supervision.
- Etripamil is a fast-acting, non-dihydropyridine L-type intranasal calcium channel blocker with a mechanism of action similar to other non-dihydropyridine calcium channel blockers. Etripamil slows atrioventricular (AV) nodal conduction and prolongs AV nodal refractoriness by inhibiting calcium ion influx through L-type calcium channels. The drug is designed to be rapidly inactivated by esterases that are ubiquitous in human blood. Etripamil nasal spray (NS) is intended for patients with AV-nodal dependent PSVT episodes when a vagal maneuver (VM), a technique sometimes used to treat rapid heartbeat conditions, is ineffective (as is often the case).[7]
- The NODE-301 studies evaluated the efficacy and safety of the novel, fast-acting, investigational intranasal calcium channel blocker etripamil for conversion of PSVT in an at-home setting. This pre-specified, pooled analysis assessed the impact of etripamil on the need for additional medical intervention.

Methods

- NODE-301 part 1 and RAPID (NODE-301 part 2) were event-driven, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of etripamil in patients experiencing a PSVT episode in an at-home setting.
- The primary results of NODE-301 part 1[6] and the study design of RAPID[8] have been published. In Part 1, 419 patients were randomized to etripamil 70 mg or placebo. In RAPID, 692 patients were randomized to etripamil 70 mg or placebo with a repeat dose if symptoms persisted.
- The RAPID study includes an open-label treatment period.
- After identifying symptoms of an episode of PSVT, patients in the RAPID study performed a sequence of steps, including performing a VM and, if the VM was unsuccessful, self-administering etripamil. Self-administration of the study drug regimen during a PSVT episode was as follows: an initial dose of etripamil NS 70 mg followed by a second dose 10 minutes later if the patient continued to experience PSVT symptoms (patients who were symptom-free before 10 minutes did not repeat dosing).
- The efficacy population was defined as all randomized patients who use the study drug to treat a positively adjudicated episode of PSVT.
- Reduction in medical intervention in favor of etripamil was previously observed in the NODE-301 part 1:
  - 26.5% of patients with placebo vs 14% with etripamil (*P*=0.053).
  - ED visit — 24.5% placebo vs 12.1% etripamil (*P*=0.051).
  - Patients who received placebo went to the ED earlier than those who received etripamil.
- Neither RAPID nor NODE-301 part 1 was powered to detect a difference in medical interventions separately; thus a pooled analysis was predefined.
- In this prespecified, pooled analysis, the proportion of patients receiving medical intervention for PSVT after administering etripamil or placebo was examined in a data set pooled between RAPID and NODE-301 part-1.
- Secondary efficacy endpoints include:
  - Proportion of patients seeking additional medical intervention over 5 hours following the study drug.
  - All medical interventions in the ED or at home.
  - Proportion of patients requiring additional medical intervention in the ED over 24 hours following the study drug.
  - Use of IV adenosine, calcium channel blocker or beta blocker IV or any route, physician-assisted VM, cardioversion, or other procedures.

Results

Table 1. Self-administered Study Drug for Confirmed PSVT

	NODE-301 Part 1	RAPID (NODE-301 Part 2)	Pooled
Self-administered placebo	49	85	134
Self-administered etripamil	107	99	206
Overall self-administered	156	184	340

Abbreviation: PSTV, paroxysmal supraventricular tachycardia.

- Demographics included mean age 54.8 years, 69.6% female, and mean 8.2 PSVT episodes in the prior year.
- Of patients in optional second-dose arms in the efficacy population (n=155), 57/72 (79.2%) using placebo and 55/83 (66.3%) using etripamil took a second dose.

Table 2. Additional Medical Intervention Within 5 Hours of Treatment

	Placebo	Etripamil	*P* value*
NODE-301 Part 1	13/49 (26.5%)	15/107 (14.0%)	0.053
RAPID	21/85 (24.7%)	15/99 (15.2%)	0.103
Pooled	34/134 (25.4%)	30/206 (14.6%)	0.013

**P* value obtained from a chi-square test.
Additional medical intervention included oral or lintravenous medications.

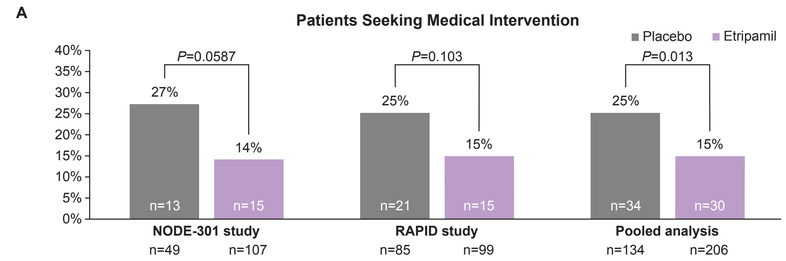
- There was a low frequency (7/71, 9.9%) of additional medical intervention in the open-label portion of the RAPID study.
- Across randomized patients, 340 treated an episode with placebo (n=134) or etripamil (n=206) (Table 1).
  - 34 (25.4%) randomized to placebo and 30 (14.6%) randomized to etripamil received additional intervention (oral or intravenous medications) (*P*=0.013) (Table 2).
  - 30 (22%) on placebo and 28 (14%) on etripamil required an ED visit for an episode of PSVT (*P*=0.035), a 39% relative risk reduction.
- Fewer patients sought rescue medical intervention with etripamil within 5 hours of treatment.
- Fewer patients sought treatment at the ED within 24 hours of treatment.
  - 18/85 (21.2%) placebo vs 14/99 (14.1%) etripamil (*P*=0.206) in RAPID.
  - Most received IV adenosine (10 placebo and 9 etripamil).
- A small fraction (6/71, 8.5%) sought treatment at an ED in the open-label portion of RAPID.
- An effective VM was observed in only ~5% cases.

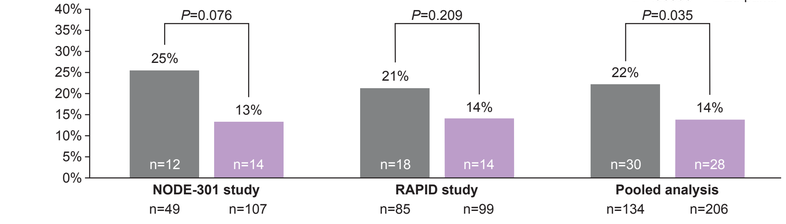
Table 3. Summary of ED Visits and Treatments in RAPID

	Placebo	Etripamil	Open-Label
Total patients	18/85 (21.2)	14/99 (14.1)	6/71 (8.5)
P value		0.209	
Type of treatment received*			
No treatment	1	1	0
Cardioversion	0	0	0
Adenosine IV	10	9	5
CCB any route	2	2	2
CCB oral	0	1	0
CCB IV	0	1	1
CCB unknown route	2	1	1
BB any route	2	1	1
BB oral	0	0	0
BB IV	1	1	0
BB unknown route	1	0	1
VM	0	0	0

Abbreviations: BB, beta blocker; CCB, calcium channel blocker; IV, intravenous; VM, vagal maneuver.
*Some patients didn't have a treatment reported, so data are excluded/missing. Patients may have had more than one treatment.

Figure 1. Patients Seeking Medical Intervention (A) and Patients with Emergency Department Visits (B)





Safety

The most common adverse events were localized to the nasal administration site. No serious adverse events were related to drug. Safety and tolerability data were consistent with those observed in prior trials.

Conclusions

- Relative to placebo, etripamil was associated with a significant reduction in use of the ED for medical intervention (*P*=0.035; 14% of etripamil patients vs 22% of placebo patients in the prespecified RAPID and NODE-301 Part 1 pooled analysis), reflecting a 39% relative risk reduction.
- Etripamil — on-demand, self-administered outside of the medically supervised setting — could potentially lessen the burden of PSVT.

References

1. Bibas L, Levi M, Essebag V. Diagnosis and management of supraventricular tachycardias. *CMAJ*. 2016;188(17-18): E466-E473. doi: 10.1503/cmaj.160079.
2. Stambler BS, Plat F, Sager P, et al. Etripamil nasal spray relieves symptoms and reduces emergency room interventions in patients with paroxysmal supraventricular tachycardia (PSVT). Presented at American College of Cardiology Annual Scientific Session & Expo, May 15-17, 2021. Virtual.
3. Sacks NC, Cyr PL, Preib MT, et al. Healthcare resource use and expenditures in patients newly diagnosed with paroxysmal supraventricular tachycardia. *Am J Cardiol*. 2020;125(2):215-221. doi: 10.1016/j.amjcard.2019.10.015.
4. Chew DS, Sacks NC, Emden MR, et al. Trends in health care resource use and expenditures in patients with newly diagnosed paroxysmal supraventricular tachycardia in the United States. *Am Heart J*. 2021;233:132-140. doi: 10.1016/j.ahj.2020.12.012.
5. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2016 ;133(14) :e506-74. doi : 10.1161/CIR.0000000000000311.
6. Stambler BS, Plat F, Sager PT, et al. First randomized, multicenter, placebo-controlled study of self-administered intranasal etripamil for acute conversion of spontaneous paroxysmal supraventricular tachycardia (NODE-301). *Circ Arrhythm Electrophysiol*. 2022;15(12):e010915. doi: 10.1161/CIRCEP.122.010915.
7. Stambler BS, Ip JE, Plat F, et al. Very low efficacy of vagal maneuvers in terminating paroxysmal supraventricular tachycardia: results from the NODE-301 study. *Heart Rhythm*. 2022; 19: S211.
8. Stambler BS, Plat F, Sager PT, et al. Rationale for and design of a multicenter, placebo-controlled, phase 3 study to assess efficacy and safety of intranasal etripamil for the conversion of paroxysmal supraventricular tachycardia. *Am Heart J*. 2022;253:20-29. doi: 10.1016/j.ahj.2022.06.005.