#AHA22

Self-administered Etripamil for Termination of Spontaneous Paroxysmal Supraventricular Tachycardia: Primary Analysis from the RAPID Study

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American Heart Association.

Disclosures

James E. Ip, MD:

- Received compensation as study investigator and steering committee member for Milestone Pharmaceuticals.
- Received honoraria/speaking/consulting fee 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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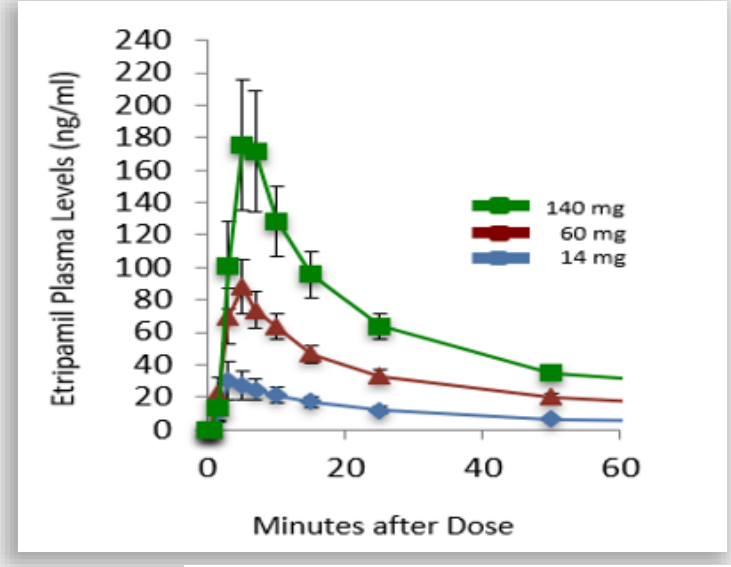
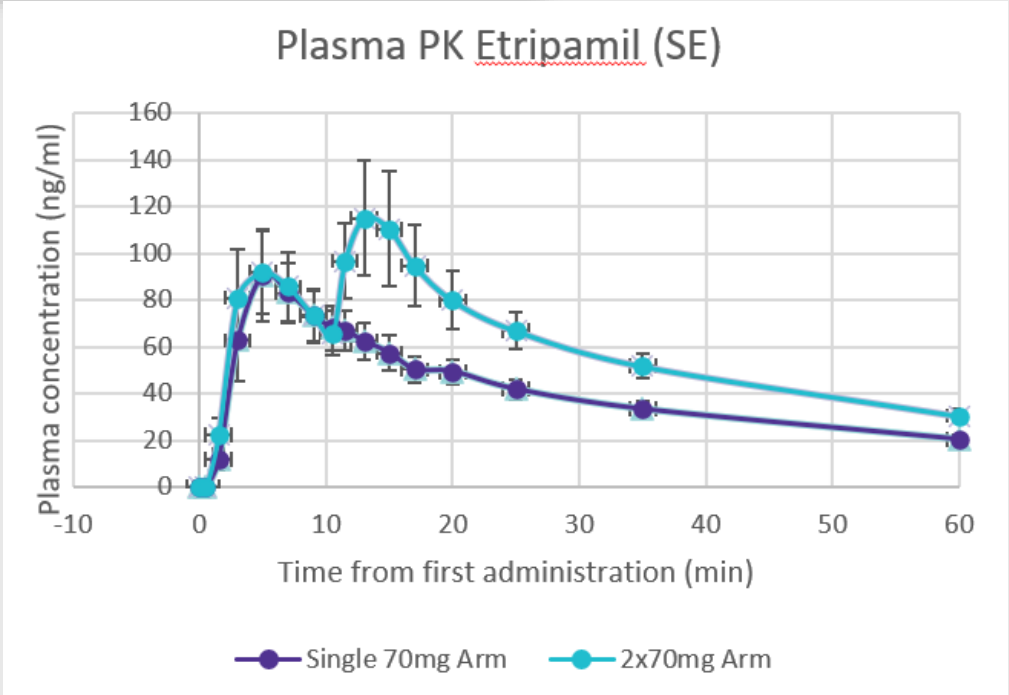
The trial was conducted and coordinated by *Medpace* and *IQVIA*.

Etripamil: Potential New Treatment for PSVT

- **Novel, investigational, L-type calcium channel blocker**
- **Formulated for intranasal spray with:**
  - **Rapid onset of action (T_{max} ≤ 7 min)**
  - **Short-lasting: inactivated by blood esterases**
- **Developed to satisfy unmet need for self-administered therapy that is convenient & safe outside healthcare setting**
- **Effective at rapidly terminating AV nodal-dependent PSVT**



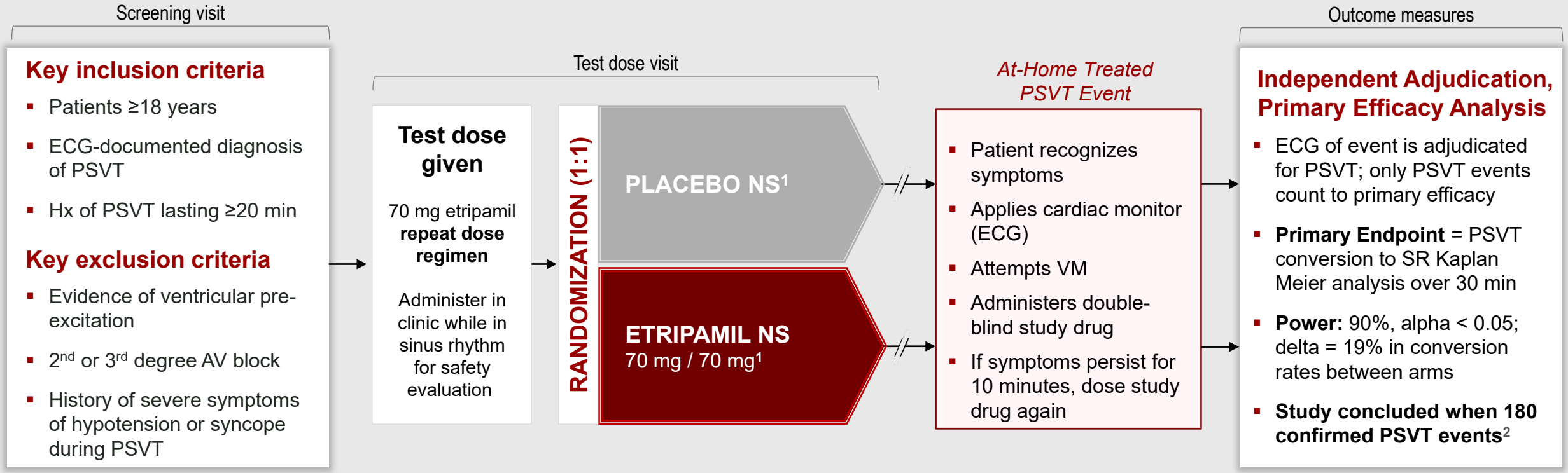


PSVT= paroxysmal supraventricular tachycardia. PK = pharmacokinetic. Error bars = standard error (SE).

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.* manuscript in preparation.
NODE-PK-101, -103, data on file.

RAPID Phase 3 Clinical Study Design

Objective: Evaluate the efficacy and safety of etripamil nasal spray in patients experiencing a PSVT episode in an at-home setting



1. Second dose of study drug self-administered if SVT episode does not resolve within 10 minutes after first dose
2. Includes 29 events of single-dose double-blind study drug administration from NODE-301 Part 1 patients who experienced an event after event lock in that study; all blinds maintained.

ECG = electrocardiogram; AV = atrioventricular; PSVT = paroxysmal supraventricular tachycardia; Hx = history; SR = sinus rhythm; VM = vagal maneuver; NS = nasal spray.

Stambler, BS *et al.* Am Ht. J (2022)

RAPID Study Patient Populations

Overall safety population[1]
N = 706

Test dose[1]
N = 706

14 not randomized,
(9 test dose failures, 5 Other)

Randomized[2]
N = 692

102 discontinued by time of RAPID data cut.[3]
335 no treated PSVT episode at time of RAPID data cut;[3] continuing in RAPID Extension study, blind maintained.

Safety population[4]
N = 255

Placebo
n = 120

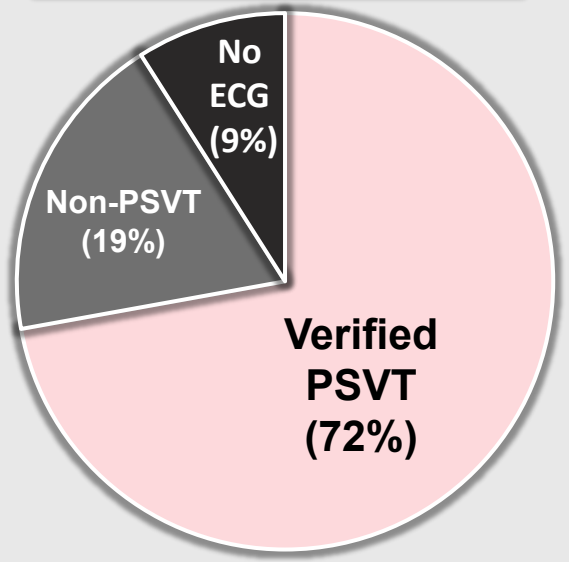
Etripamil
n = 135

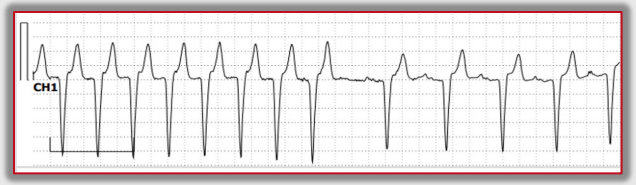
Efficacy population[5]
N = 184

PSVT treated with placebo
n = 85

PSVT treated with etripamil
n = 99

Blinded Adjudication of Safety Population



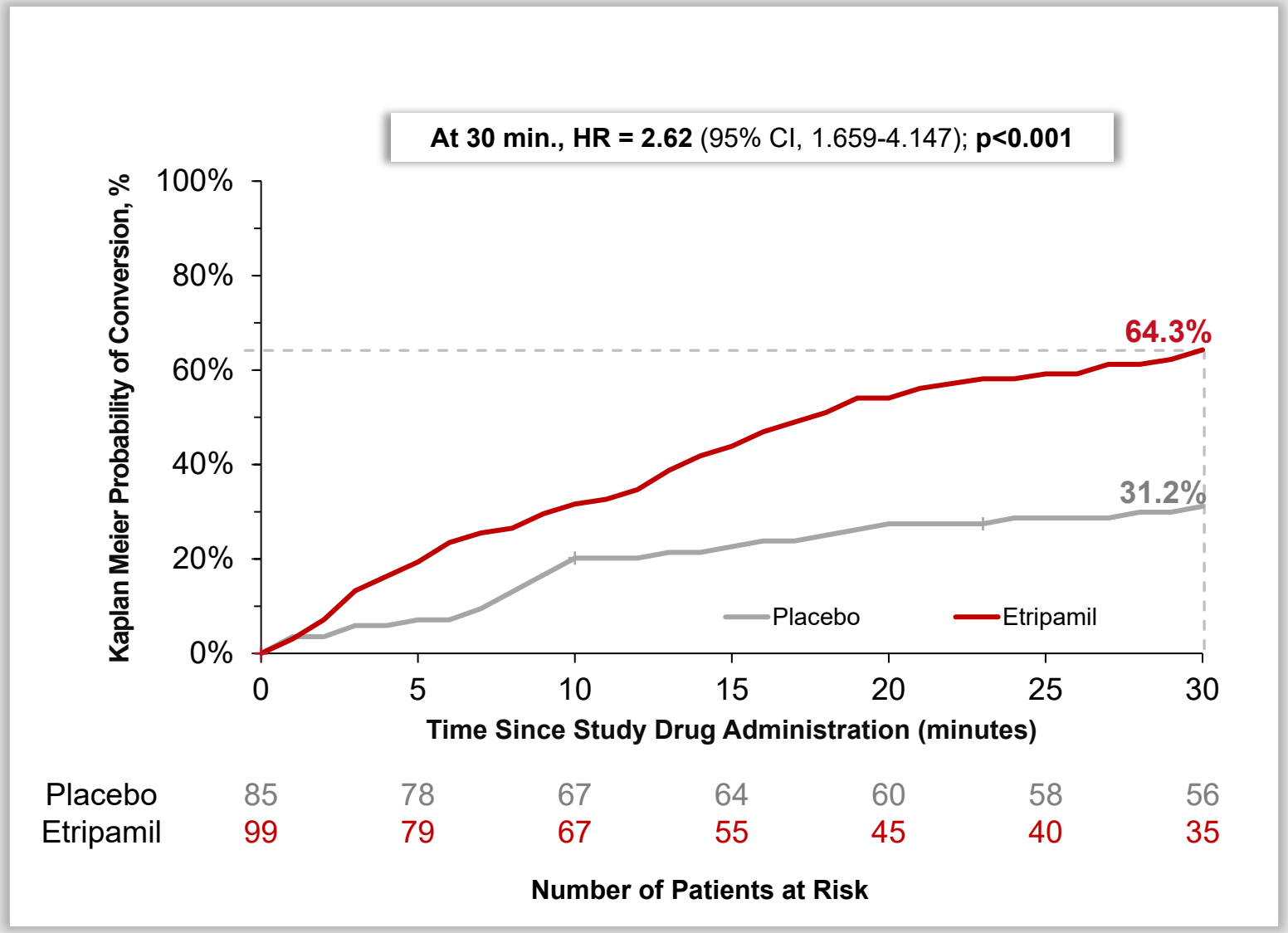


[1] Received test dose of etripamil (34 received 1 x 70 mg, 672 received 2 x 70 mg)
[2] 34 randomized to single-dose regimen in NODE-301 Part 1; 658 randomized to optional repeat-dose regimen (repeat dose if symptoms persisted after 10 minutes) in RAPID.
[3] July 20, 2022
[4] Took randomized drug during episode of perceived PSVT, 34 received a single-dose drug regimen, 221 received an optional repeat-dose regimen (2nd dose if symptoms persisted after 10 min)
[5] Took randomized drug during episode of verified PSVT confirmed by independent adjudication, 29 received single-dose regimen, 154 received optional repeat dose-regimen (repeat dose if symptoms persisted after 10 min)

Demographics & Baseline Characteristics (Safety Population)

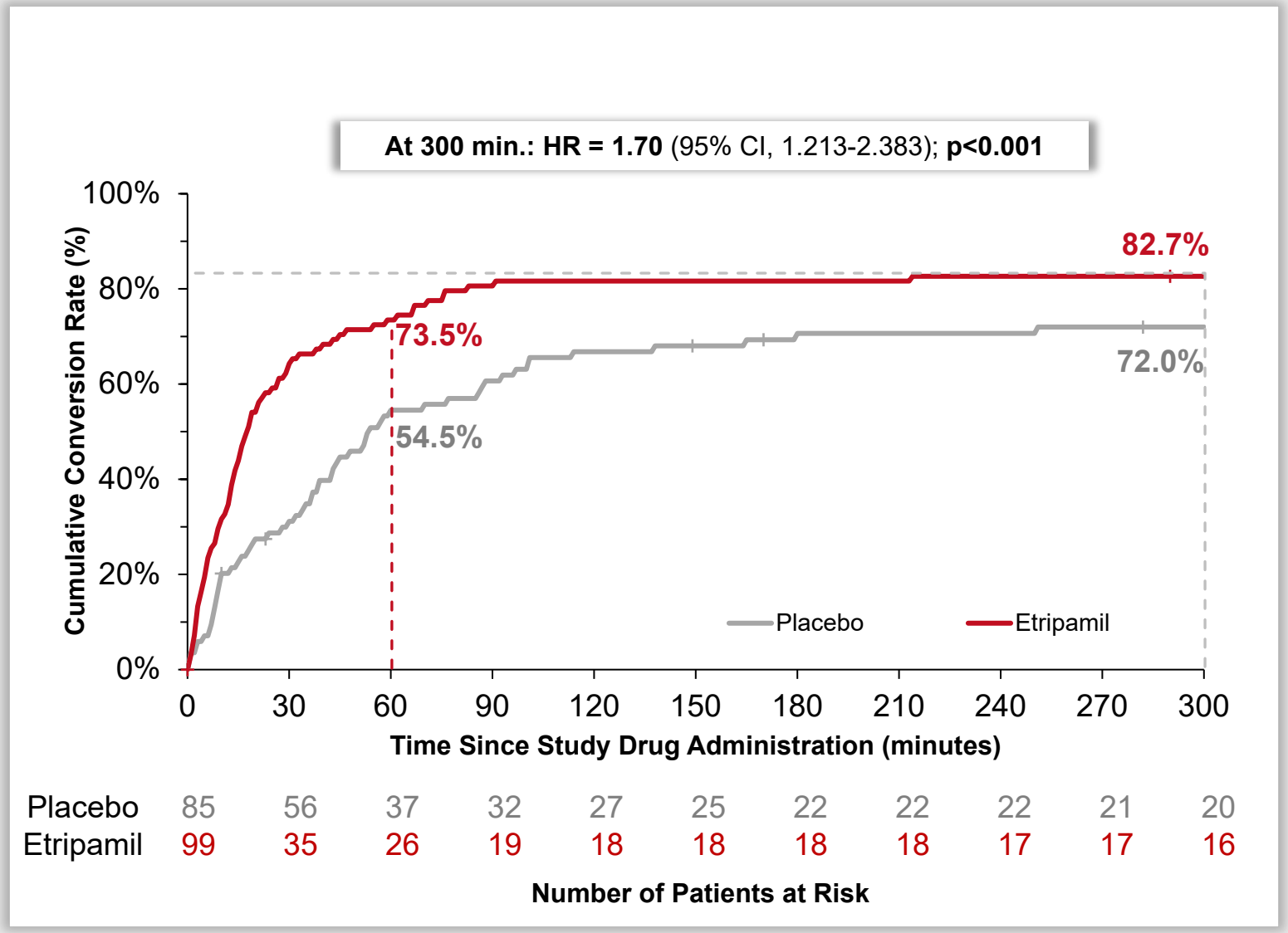
	Placebo (N=120)	Etripamil (N=135)	Overall (N=255)
Age, years			
Mean (SD)	**56.2** (12.0)	**52.4** (14.0)	**54.2** (13.2)
Median (range)	**58.0** (21, 78)	**52.0** (19, 82)	**55.0** (19, 82)
Sex, female, n (%)	**88** (73.3)	**93** (68.9)	**181** (71.0)
Race, n (%)			
American Indian or Alaska native	**0**	**1** (0.7)	**1** (0.4)
Asian	**4** (3.3)	**2** (1.5)	**6** (2.4)
Black or African American	**3** (2.5)	**4** (3.0)	**7** (2.7)
White	**110** (91.7)	**126** (93.3)	**236** (92.5)
Other	**3** (2.5)	**2** (1.5)	**5** (2.0)
PSVT confirmation duration, years			
Mean (SD)	**1.7** (3.8)	**2.2** (5.3)	**2.0** (4.7)
Median (range)	**0.5** (0.0, 32.2)	**0.3** (-0.7, 30.7)	**0.4** (-0.7, 32.2)
PSVT episodes in past year			
Mean (SD)	**10.8** (22.9)	**6.3** (13.9)	**8.4** (18.8)
Median (range)	**5.0** (0.0, 200.0)	**3.0** (0.0, 150.0)	**4.0** (0.0, 200.0)
Lifetime emergency department visits for PSVT			
Mean (SD)	**3.9** (11.2)	**4.6** (15.5)	**4.3** (13.6)
Median (range)	**2.0** (0.0, 120.0)	**2.0** (0.0, 160.0)	**2.0** (0.0, 160.0)
Concomitant medications, n (%)			
Beta blocker or calcium channel blocker	**80** (66.7)	**86** (63.7)	**166** (65.1)
Beta blocker only	**40** (33.3)	**45** (33.3)	**85** (33.3)
Calcium channel blocker only	**29** (24.2)	**30** (22.2)	**59** (23.1)
Beta blocker and calcium channel blocker	**11** (9.2)	**11** (8.1)	**22** (8.6)

Primary Endpoint: Conversion of Adjudicated PSVT to NSR at 30 min



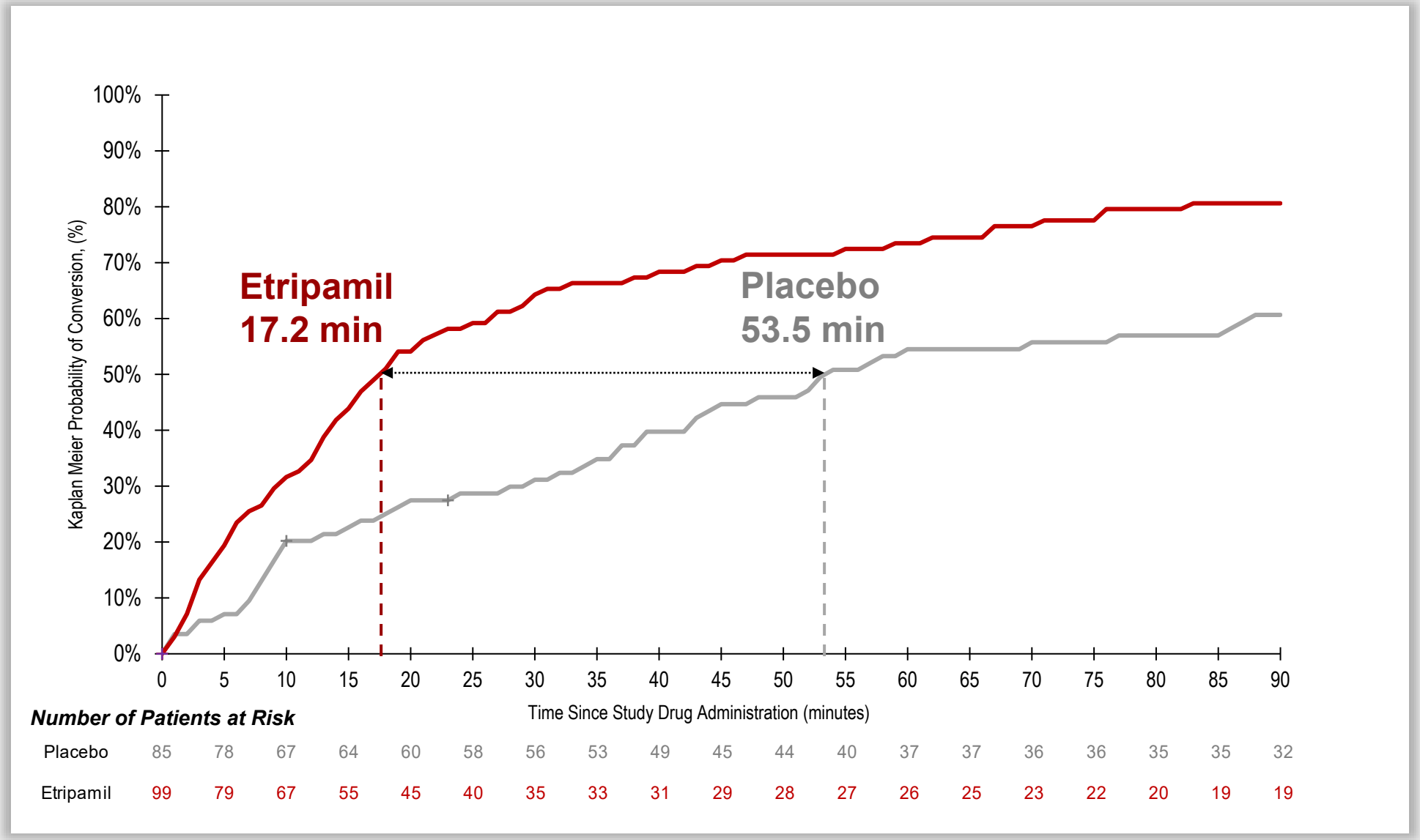
"+" symbol on graph indicates censoring for signal loss (n=4 over 30 minutes). PSVT = paroxysmal supraventricular tachycardia. NSR = normal sinus rhythm. HR = hazard ratio.

300-Minute Endpoint: Conversion of Adjudicated PSVT to NSR



"+" symbol on graph indicates censoring for signal loss (n=4 over 30 minutes). PSVT = paroxysmal supraventricular tachycardia. NSR = normal sinus rhythm. HR = Hazard Ratio

Median Time to Conversion of PSVT to NSR, Reduced in Etripamil Arm Compared to Placebo

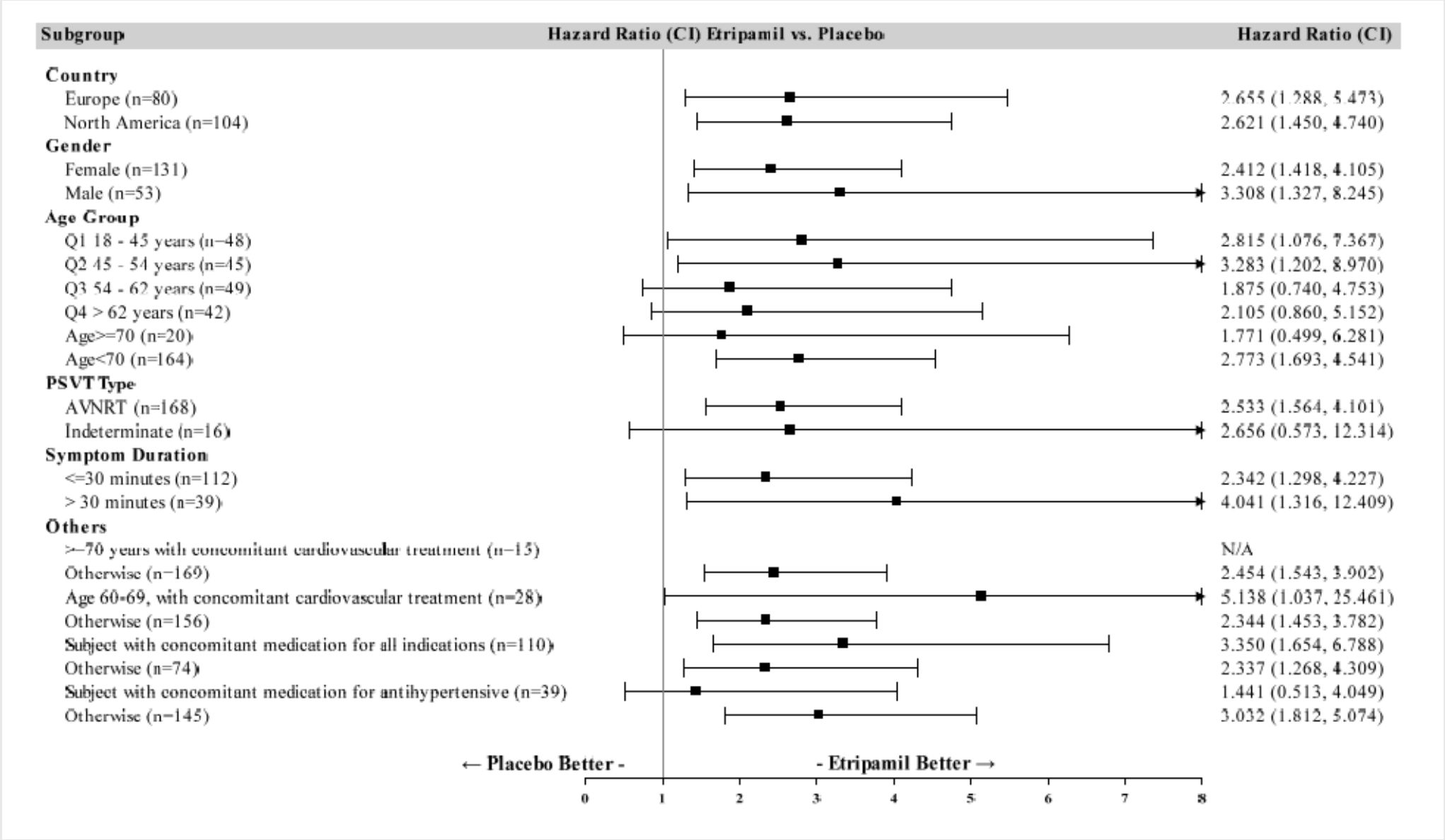


Number of Patients at Risk

Placebo	85	78	67	64	60	58	56	53	49	45	44	40	37	37	36	36	35	35	32
Etripamil	99	79	67	55	45	40	35	33	31	29	28	27	26	25	23	22	20	19	19

"+" symbol on graph indicates censoring for signal loss (n=4 over 30 minutes). PSVT = paroxysmal supraventricular tachycardia. NSR = normal sinus rhythm.

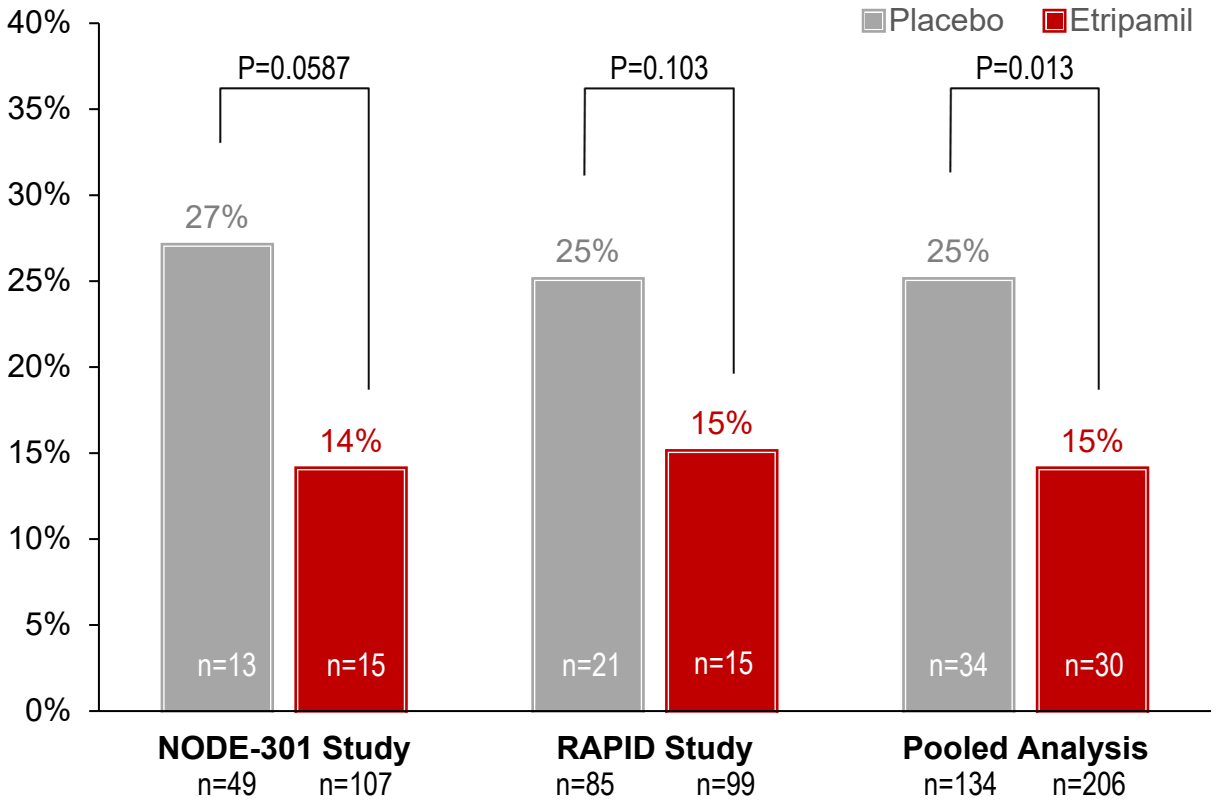
Subgroup Analyses: Responders At 30 Minutes



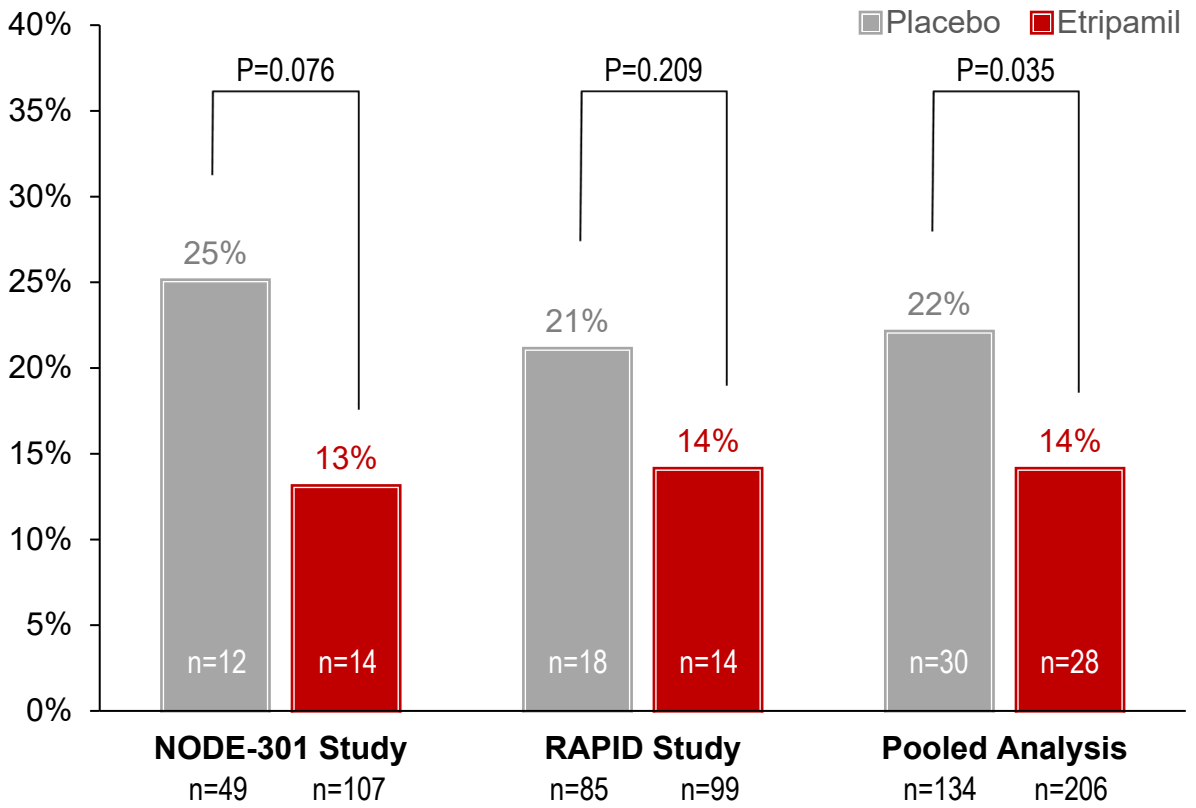
Responder = conversion of PSVT to normal sinus rhythm. Age groups are not inclusive of the lower bound: Q2 45-54, includes patients >45 years old; Q3 54-62, includes patients >54 years old. PSVT = paroxysmal supraventricular tachycardia; AVNRT = atrioventricular nodal reentrant tachycardia. Q = quartile.

Secondary Endpoints: Medical Interventions, Emergency Department Utilization

Patients Seeking Medical Intervention



Patients with Emergency Department Visits



Pooling of data and analyses were prespecified in RAPID statistical analysis plan. Statistical analyses performed by Chi-square test for each study data set and pooled data set.

RAPID Safety – Direct ECG CMS Reading[1]

	Placebo Randomized Dose[2] N=116	Etripamil Randomized Dose[2] N=128
Non-sustained ventricular tachycardia	**19** (16.4)	**18** (14.1)
Sustained ventricular tachycardia (≥ 30 seconds)	**1** (0.9)[3]	**0**
PSVT Recurrence	**5** (4.3)	**4** (3.1)
Atrial Fibrillation ≥ 30 seconds	**4** (3.5)	**1** (0.8)
Atrial Tachycardia ≥ 30 seconds	**1** (0.9)	**2** (1.6)
Prolonged PR, for duration of ≥ 30 seconds	**1** (0.9)	**2** (1.6)
Pause ≥ 3 seconds	**1** (0.9)[4]	**1** (0.8)[4]
Atrial Flutter ≥ 30 seconds	**1** (0.9)	**0**
Sinus Bradycardia ≤ 40 bpm	**1** (0.9)	**0**
PVC greater than 6 PVCs within 45 seconds	**0**	**0**
2nd Degree AV Block - Mobitz I AV Block	**0**	**0**
2nd Degree AV Block - Mobitz II AV Block	**0**	**0**
3rd Degree AV Block	**0**	**0**

[1] Expert cardiac electrophysiologist adjudication committee evaluated all ECG recordings for each patient in the Safety Population, pre- and post-drug administration. All adjudications performed blinded to treatment assignment.
[2] Safety Population patients with full 5-hour ECG recordings available.
[3] Blinded-expert ECG readings were indeterminate between supraventricular tachycardia with a wide-QRS vs. ventricular tachycardia; for conservatism, rated as the latter. Of note, this tachycardia was present prior to administration of placebo.
[4] Cases of pauses observed only after rescue treatment with IV adenosine.
CMS = cardiac monitoring system.

RAPID Safety Analysis

	Placebo Randomized Dose[1] N=120	Etripamil Randomized Dose[1] N=135
Subjects with any randomized-period TEAE, n (%)	**20** (16.7)	**68** (50.4)
Maximum severity, and n (%) of subjects with any randomized-period TEAE		
Mild	**15** (75.0%)	**46** (67.6%)
Moderate	**4** (20.0%)	**21** (30.9%)
Severe	**1** (5.0%)	**1** (1.5%)
Subjects with SAE	**1** (0.8)	**0**
Subjects with SAE related to study drug	**0**	**0**
Subjects with AE leading to death	**0**	**0**
Subjects with Drug-related AE leading to study discontinuation	**0**	**3** (2.2)[2]

[1] Safety Population.
[2] Three events were: (a) frequent PVCs and couplets after PSVT termination; (b) non-sustained VT after PSVT termination (4 beats); and (c) possible allergic reaction, treated with oral Benadryl.
TEAE timing – up to 24 hours following drug administration. TEAE = treatment-emergent adverse event; SAE = serious adverse event; AE = adverse event; PVC = premature ventricular complex; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia.

RAPID Safety – Adverse Events

Subjects with Randomized-period TEAE, Incidence >5%, n (%)	Placebo Randomized Dose[2] (n=120)	Etripamil Randomized Dose[2] (n=135)
Nasal discomfort	**6** (5.0)	**31** (23.0)
Nasal congestion	**1** (0.8)	**17** (12.6)
Rhinorrhea	**3** (2.5)	**12** (8.9)
Epistaxis	**2** (1.7)	**8** (5.9)[3]

Subjects with Randomized-period TEAE,[1] n (%)	Placebo Randomized Dose[2] (n=120)	Etripamil Randomized Dose[2] (n=135)
Syncope	**0.0**	**0.0**
Loss of Consciousness	**0.0**	**0.0**
Pre-Syncope	**0.0**	**0.0**
Dizziness	**0.0**	**1** (0.7)[4]

[1] Adverse events specifically acquired as adverse events of interest, as potentially representing lowered blood pressure.
[2] Safety population.
[3] Six of 8 rated as mild, 2 of 8 rated as moderate.
[4] Rated as mild.
TEAE timing – up to 24 hours following drug administration.
TEAE = treatment-emergent adverse event.

RAPID Study: Summary and Conclusions

- RAPID study achieved primary efficacy endpoint of terminating PSVT with self-administered etripamil, using symptom-based optional repeat dosing (HR 2.62, $p < 0.001$)
  - Conversion of PSVT to sinus rhythm: 64.3% at 30 minutes, 73.5% at 60 minutes
- Median Time to Conversion, 17.2 minutes in Etripamil arm *vs* 53.5 minutes in Placebo arm
- Favorable safety and tolerability data are consistent with prior etripamil trials
  - No new safety signals or AEs with a 2nd dose of etripamil
  - Majority of AEs were mild, local, and transient
- Pooled analysis with NODE-301 showed a significant reduction in ED utilization and medical intervention
- Results demonstrate a potential management strategy for patients to self-treat episodes with etripamil in a medically unsupervised setting
- Ongoing analysis of RAPID open-label period and NODE-303 trial will provide more insights into the safety and efficacy of etripamil for recurrent episodes of PSVT

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- **Study Participants**
- **Participating study sites / Principal Investigators / Study Coordinators across 9 countries**
- **Adjudication Committee members**

  José Dizon, MD, (Chair)

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- **Clinical Operational Support**

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THANK YOU!

American Heart Association.