Milestone PHARMACEUTICALS

Corporate Overview

April 2021

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Chief Executive Officer

Disclaimers

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Milestone (Nasdaq: MIST) - Corporate Highlights

Phase 3 Cardiovascular Company

Targeting Large Areas of Unmet Need

PSVT

Atrial Fibrillation with Rapid Ventricular Rate

Additional pipeline opportunities under consideration

Paradigm-Changing Approach

Etripamil - novel calcium channel blocker

IP protection until 2036

Potential to shift the treatment setting from the Emergency Department to patient self-management

Recent Events Position for Future Success

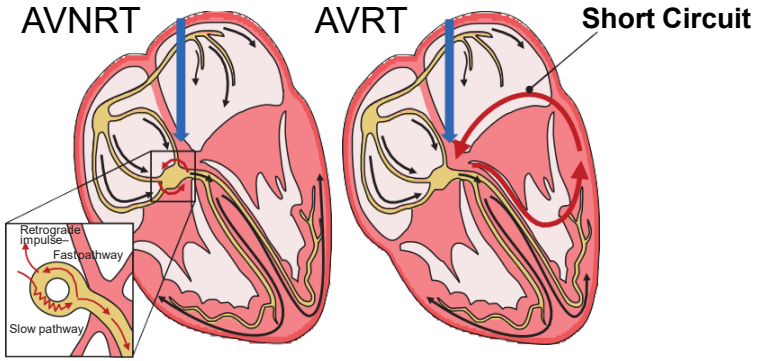
Initial Phase 3 study findings FDA Guidance

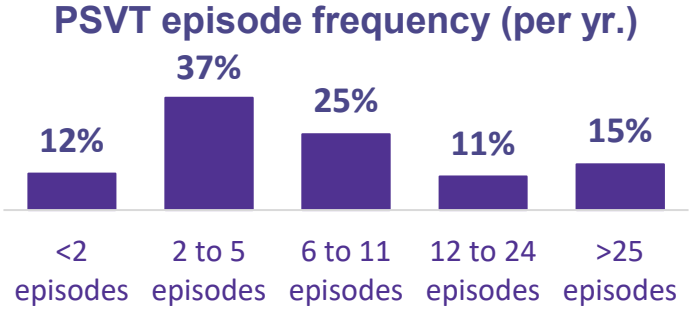
Next Pivotal Phase 3 Efficacy result by early 2022

Financial runway through 2022

PSVT = Paroxysmal Supraventricular Tachycardia; Afib = Atrial Fibrillation; ED = Emergency Department

Paroxysmal Supraventricular Tachycardia (PSVT)





- PSVT is a rapid heart rate condition that starts and stops without warning
- Heart rates >200 bpm are not uncommon
- Symptoms include:
  - ✓ palpitations
  - ✓ sweating
  - ✓ chest pressure or pain, shortness of breath
  - ✓ sudden onset of fatigue
  - ✓ lightheadedness or dizziness
  - ✓ fainting or anxiety

AVNRT = Atrioventricular Nodal Re-entrant Tachycardia AVRT = Atrioventricular Re-entrant Tachycardia bpm = beats per minute

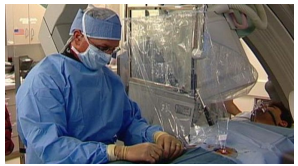
Sources: Internal estimates based on market research

Current Standard of Care for PSVT

Current acute treatment options are invasive, inconvenient, anxiety-provoking and/or costly

Chronic / preventive

- Chronic oral medication with modest efficacy and unpleasant side effects
- 4-7 episodes/year despite preventive medications



- Catheter ablation
- ~80K ablations/year
- Only ~10% of patients opt for ablation

Acute

- IV adenosine or DC cardioversion in the ED
- >150K ED visits/hospital admissions per year
- Many patients endure episodes when they occur

DC = Direct Current

Sources: Internal estimates based on market research and longitudinal analysis of Truven/Marketscan and Medicare claims data; Page RL et al, 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: executive summary: a report of the ACC/AHA Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016;133:e471–e505

A Paradigm-Changing Approach

Opportunity to develop the first approved treatment to be used by patients whenever and wherever an episode of PSVT occurs

Non-invasive → Convenient → Empowering

- Avoidance of ED visits / hospital admissions
- Less need for chronic medications
- Alternative or bridge to ablation procedure

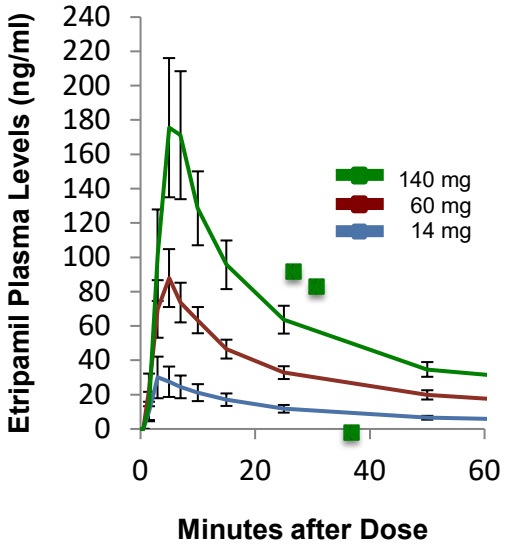
Etripamil Nasal Spray

A paradigm-changing approach for treating PSVT

	Etripamil
Class	Novel CCB
Potency (IC_{50})	11 nM
Metabolism	Rapid: Esterase-mediated

- **Clinically-validated mechanism**
  - Etripamil, Calcium Channel Blockers (CCBs), terminate PSVT through AV node modulation
- **Rapid onset of action**
- **Short duration of action**
- **Convenient patient self-administered nasal spray**

- **Rapid onset (T_{max} < 5 min)**
- **Transient plasma levels**



Error bars indicate standard error of the mean

AV = Atrio-ventricular

Pivotal Phase 3 Study Design

NODE-301
Etripamil Clinical Research in PSVT

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

Randomized
Etr : Pbo (2:1)
(N=419, 97%)

Patient dosed for suspected episode
Safety Dataset
(N=198, Etr=138, Pbo=60)

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

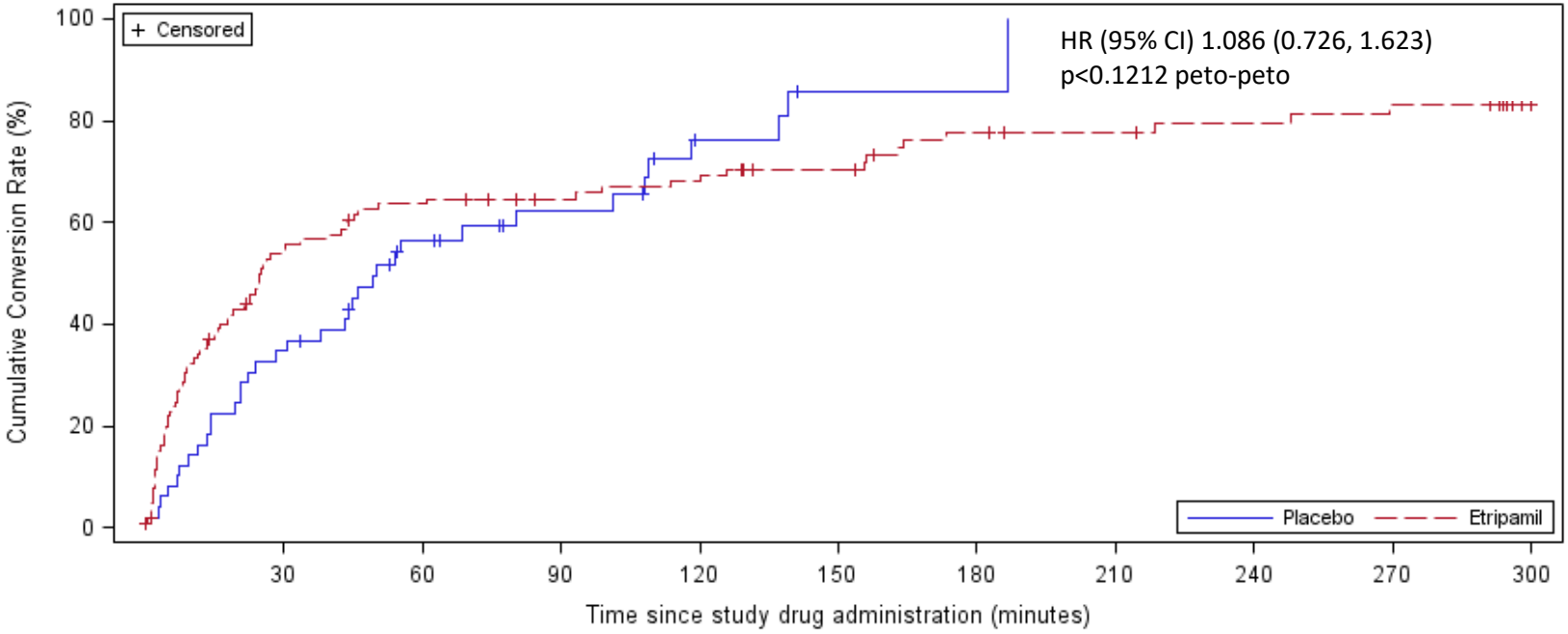
Adjudicated PSVT events
Efficacy Dataset
(N=156, 79%)
Etr=107, Pbo=49)

Documented diagnosis of PSVT
History of longer episodes

SR = Sinus Rhythm; Etr = etripamil; Pbo = placebo

NODE-301 Kaplan-Meier Plot of Conversion up to Hour 5

Pre-specified Primary Endpoint

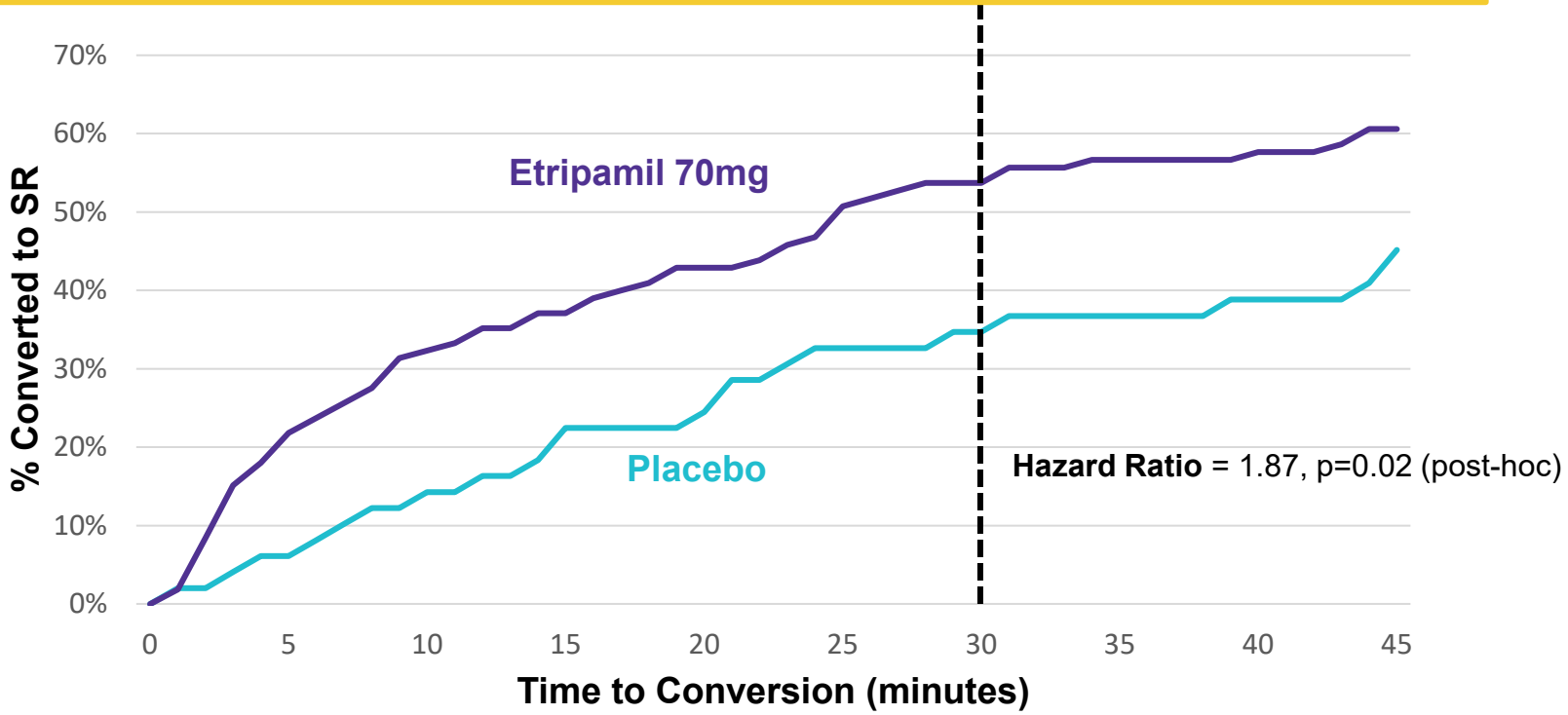


Phase 3 Efficacy Study – Time to Conversion up to 30 min

Post-hoc Analysis

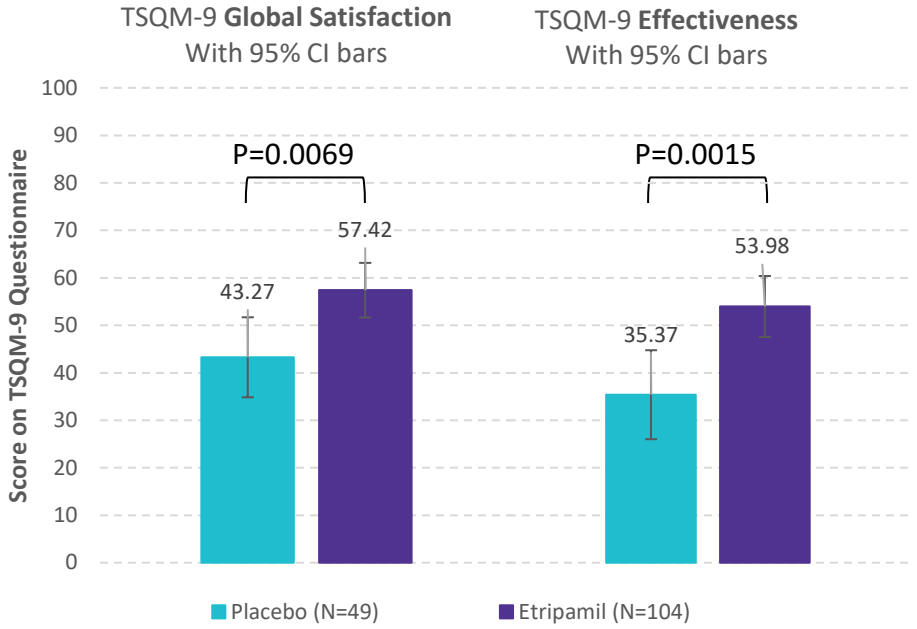
NODE-301
Etripamil Clinical Research in PSVT

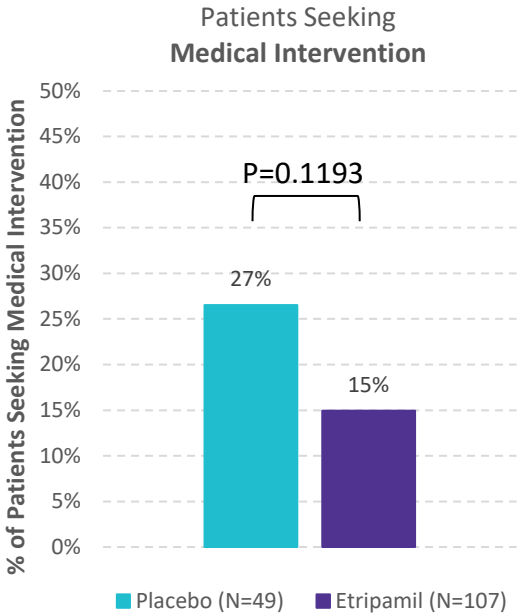
70 mg etripamil dose showed rapid time to conversion (median ~25 min)



NODE-301 Key Secondary Endpoints

Key secondary endpoints from NODE-301 support benefit of etripamil to patients and payers





NODE-301 Safety Analysis

Randomized Treatment Emergent Adverse Events (RTEAE)	Etripamil N=138	Placebo N=60
Subjects with any RTEAE	53 (38.4)	12 (20.0)
Maximum severity of RTEAE		
Mild	45 (32.6)	10 (16.7)
Moderate	8 (5.8)	3 (3.3)
Severe	0 (0.0)	0 (0.0)
Subjects with any Serious Adverse Event (SAE)	0 (0.0)	1 (1.7)
Subjects with any SAE related to study drug	0 (0.0)	0 (0.0)
Subjects with any AE leading to death	0 (0.0)	0 (0.0)
Subjects with AE leading to study drug discontinued	0 (0.0)	0 (0.0)

RTEAE timing – up to 24 hours following double-blind study drug administration

Source: Data on File, Milestone Pharmaceuticals Inc.

NODE-301 Safety Analysis

Randomized 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)
Migraine	1 (0.7)	0 (0.0)

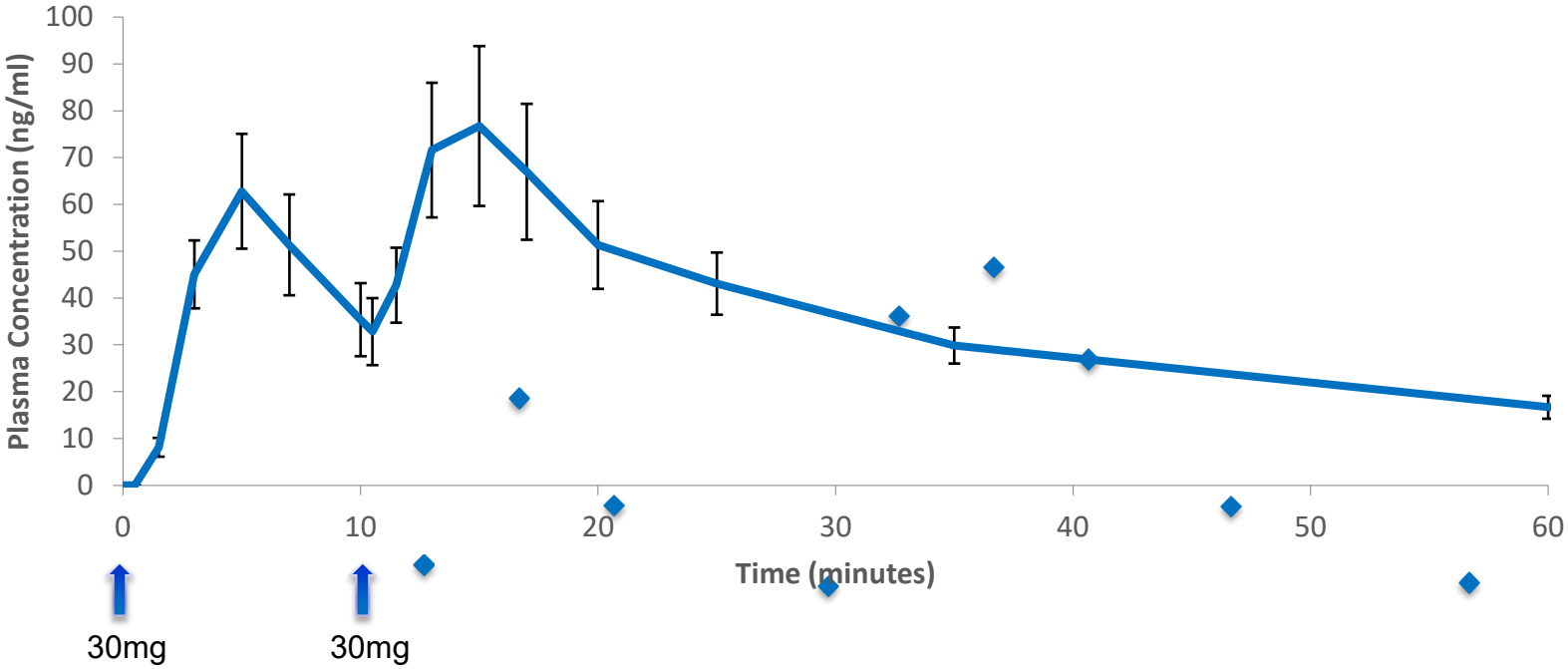
Stambler, BS et al; Etripamil Nasal Spray for Acute Termination of Spontaneous Episodes of PSVT (NODE-301); Heart Rhythm Society Late Breaking Clinical Trails Randomized Trials D-LBCT01; Presented Online May 8, 2020

Overview of Regulatory Updates Based on FDA Feedback

- Agreed that NODE-301 and RAPID studies together can be used to fulfill the efficacy requirement for an NDA filing for etripamil in PSVT
- Agreed to target p-value of $p < 0.05$ for the RAPID Study
- Agreed to primary analysis of 30-minute observation window and proposed statistical methods
  - Wilcoxon – greater weighting for earlier endpoints
  - Rescue medications treated as treatment failure at the end of the treatment window
- Suggested the evaluation of higher exposures to improve efficacy and clinical meaningfulness
  - We agreed the NODE-301 safety and tolerability data support study of higher exposure
- Agreed to tailored dosing regimen as part of a pivotal trial
  - Adding an optional second 70 mg dose for patients who still have symptoms 10 min after their first administration
  - Agreed we can pool doses to maintain power and compare to placebo
  - If approved, the higher exposure results would be expected to be displayed in the label

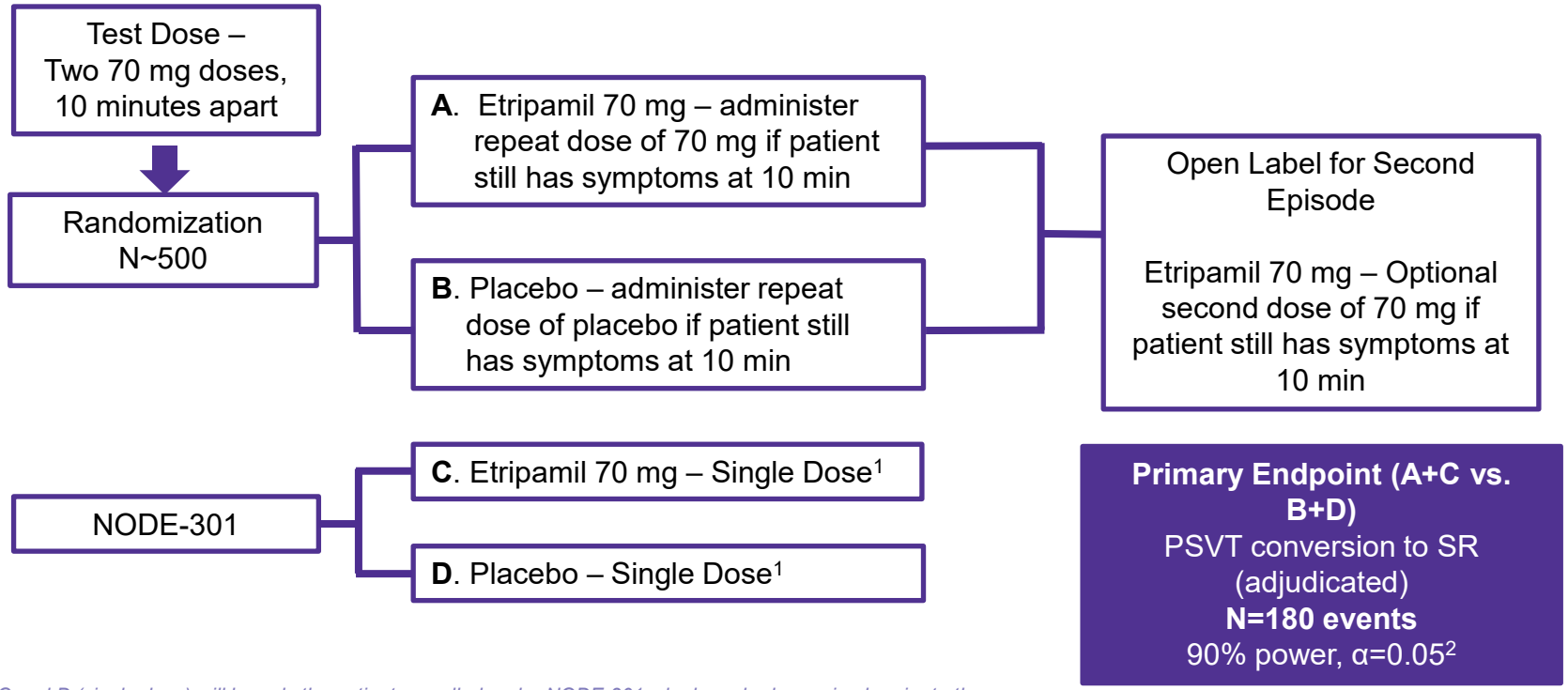
PK of Etripamil 30 mg Repeat Administration at T=10 min
(Study MSP-2017-1096)

Repeat administration increases both C_{max} and AUC



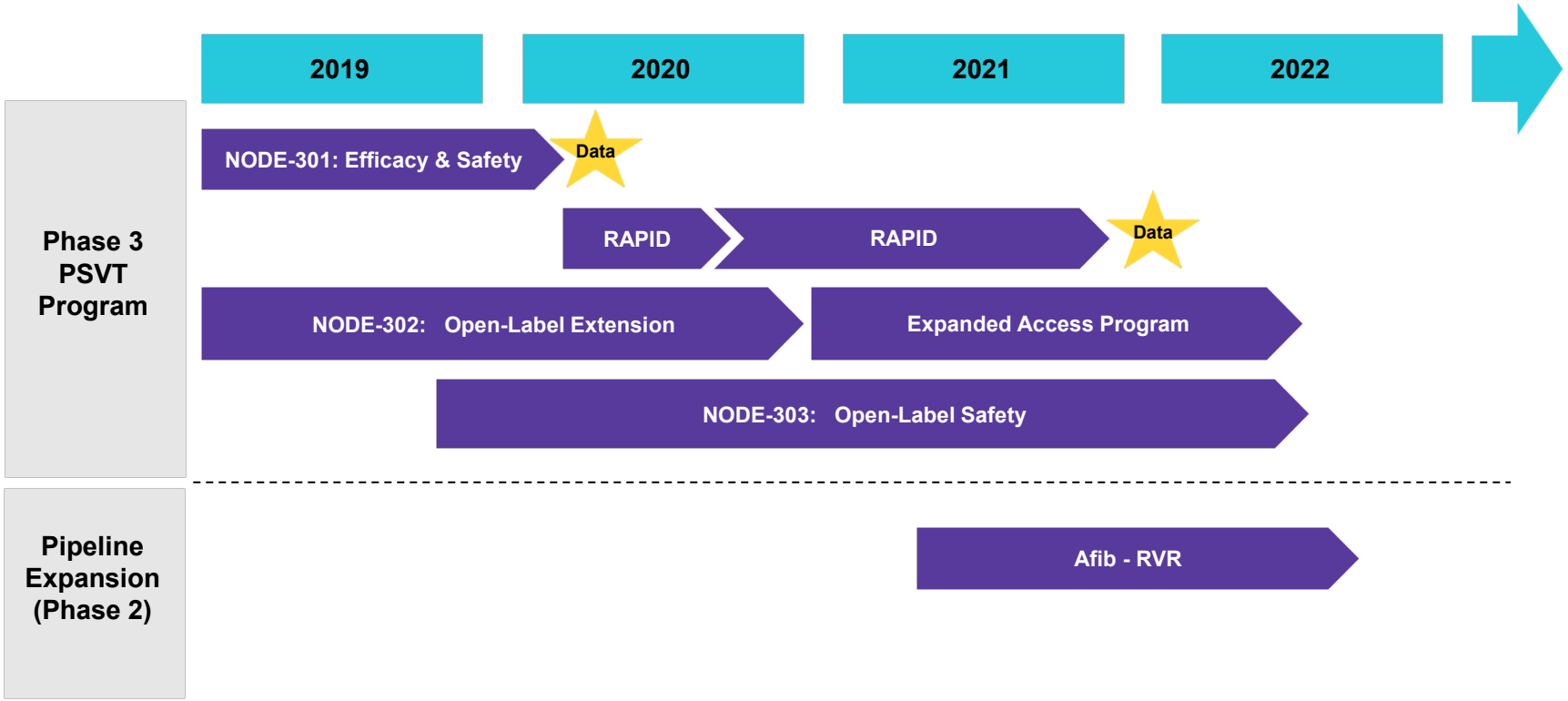
N=7, Error bars are standard error

RAPID Study Design



[1] Arms C and D (single dose) will be only the patients enrolled under NODE-301 who have had an episode prior to the RAPID Study protocol amendment
[2] Wilcoxon analysis modeling from NODE-301 data

Etripamil Development Plan



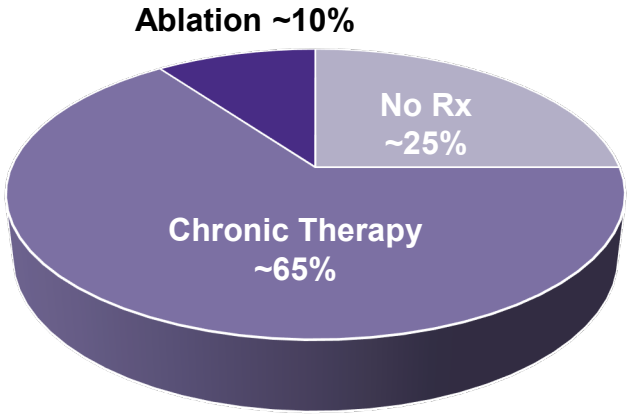
Afib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

Current US PSVT Market

Total annual US healthcare expenditures of ~$3B

- Prevalence ~2M diagnosed PSVT patients
- ~300K newly diagnosed per year
- ~600K patients treated per year
- >150K ED/hospital visits per year
- ~80K ablations per year

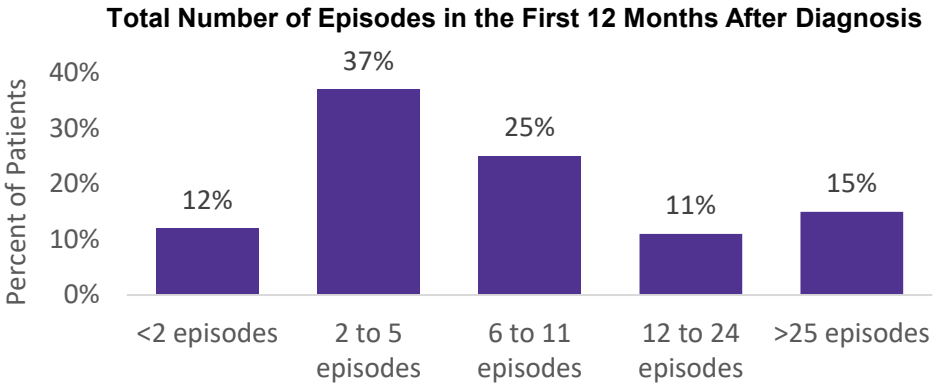
Current Management



Source: Sacks, N.C. et al; Prevalence of Paroxysmal Supraventricular Tachycardia (PSVT) in the US in Patients Under 65 Years of Age; Abstract and Oral Presentation at the International Academy of Cardiology Annual Scientific Sessions 2018, 23rd World Congress on Heart Disease; Precision Xtract, Boston, MA, USA; and data-on-file from IBM Marketscan® Commercial Research Database (<65y) and the Medicare Limited Dataset (≥65y), with demographic, enrollment and claims data for commercially insured (Truven) and Medicare covered patients using PSVT code 427.0 or I47.1 for up to a 9-year interval between 2008 and 2016 inclusive.

Projected US Market for Etripamil in PSVT

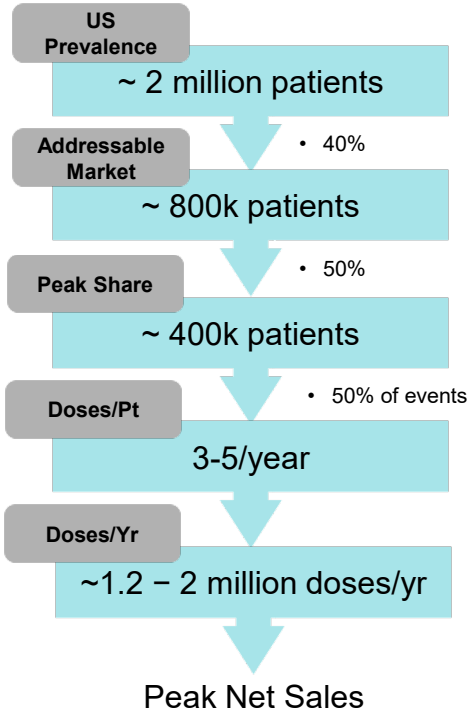
Market research suggests utilization of 1-2 million doses of etripamil in peak year



40% patients with multiple episodes >10min/yr*

65% patients on chronic medications for PSVT

40% patients with ≥1 ED visits for PSVT/yr*



TAM – Target Addressable Market

**Estimates are for patients in year after initial diagnosis; rates drop by 13-29% in years following their initial diagnosis*

Sources: Internal estimates based on market research, Milestone Pharmaceuticals Inc.

Finances – as of December 31, 2020

- $142M in cash, cash equivalents and short-term investments
- Expected to fund planned operations through 2022

- Equity - 41.2M in shares and pre-funded warrants outstanding
  - 29.8M common shares
  - 11.4M pre-funded warrants

Milestone (Nasdaq: MIST) - Corporate Highlights

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Milestone
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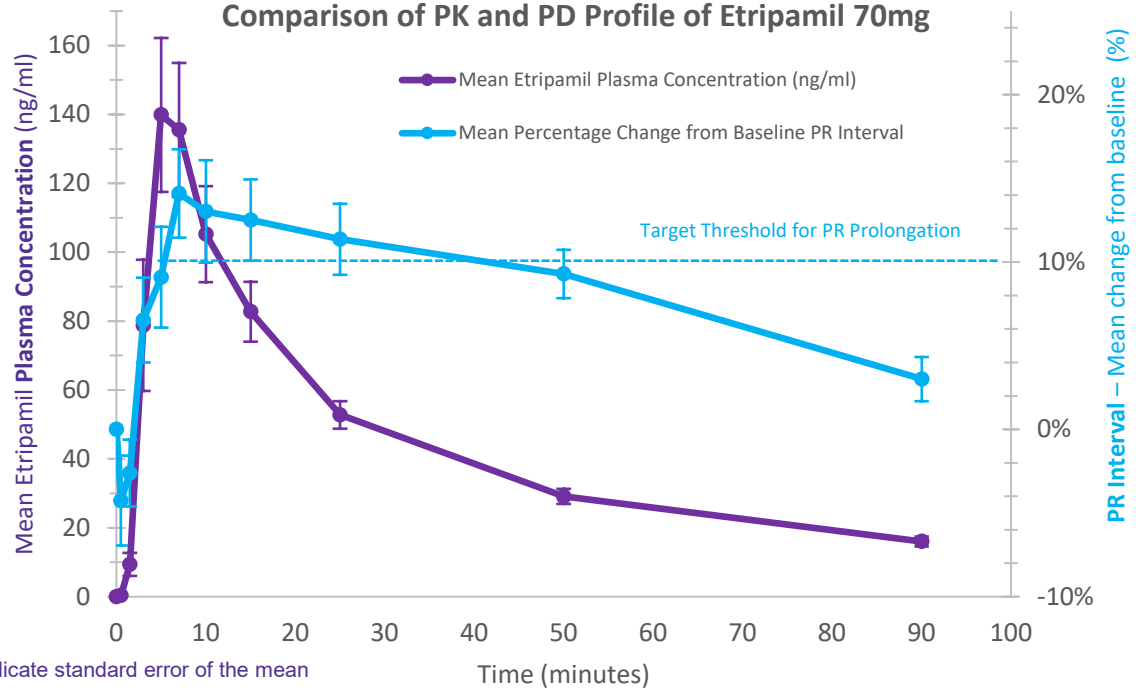
Thank you

Etripamil Nasal Spray Pharmacological Results (NODE-102)

Anticipated therapeutic effect within 45 minutes; peak within 10 minutes



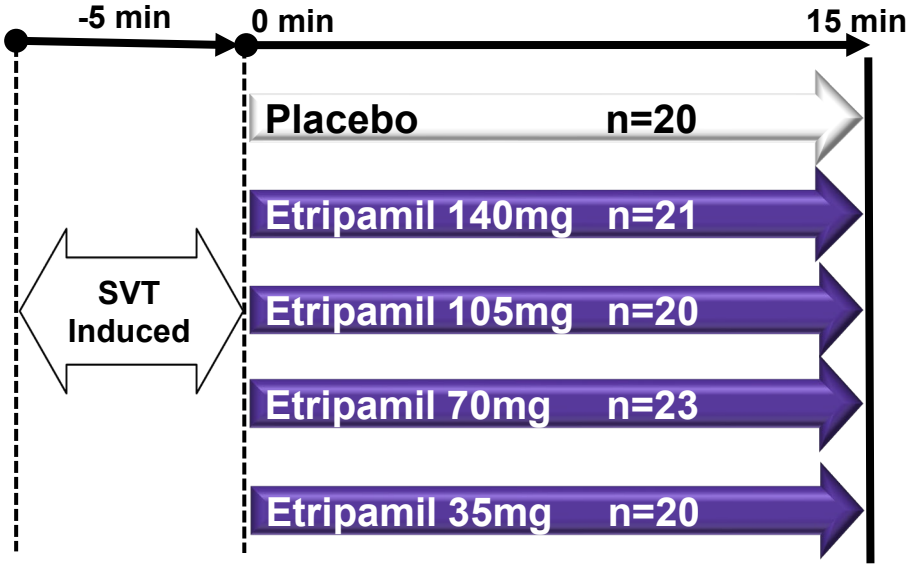
N=24; Error bars indicate standard error of the mean

Phase 2a/b Study Design

node-1
Etripamil Clinical Research in PSVT

Objectives: Demonstrate superiority of etripamil over placebo in terminating SVT and dose ranging trend analysis

PSVT patients with scheduled cardiac ablation (EP lab)

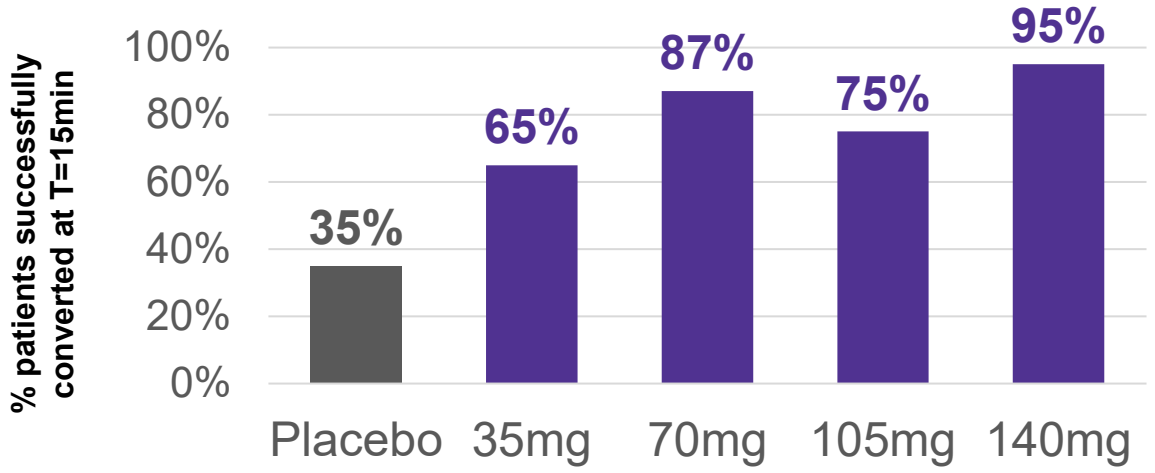


Endpoint: conversion to sinus rhythm within 15 minutes

EP = electrophysiology, SVT = supraventricular tachycardia, PSVT = Paroxysmal Supraventricular Tachycardia

Phase 2 Primary Endpoint

Etripamil three highest doses demonstrated 75-95% conversion rates which are statistically significant compared to placebo



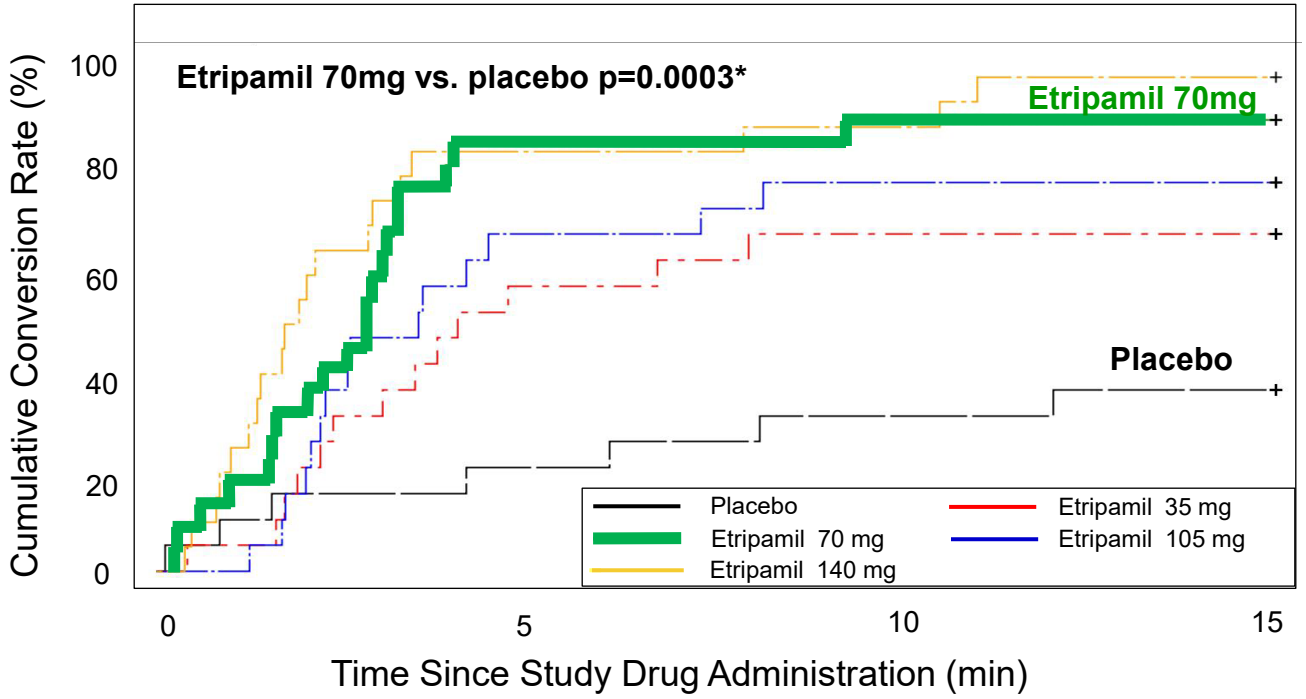
# patients converted at 15 min	7/20	13/20	20/23	15/20	20/21
p-value		0.1128	0.0006	0.0248	<.0001

Source: Stambler, B.S. et al.; Etripamil Nasal Spray for Rapid Conversion of Supraventricular Tachycardia to Sinus Rhythm; J Am Coll Cardiol. 2018;72(5):489–97

Phase 2 Efficacy Study - Time to Conversion

Electrophysiology Lab Setting

70mg etripamil dose showed rapid time to conversion (median < 3 min)

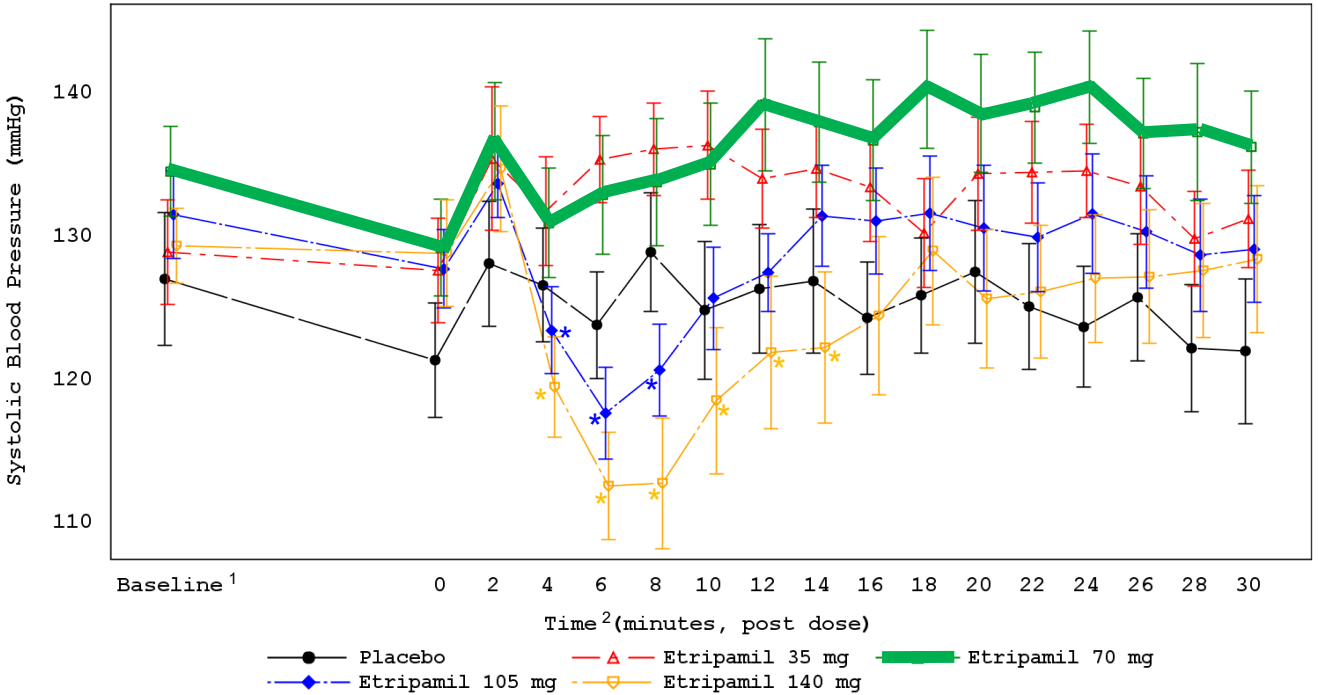


*Hazard Ratio and 95% Confidence Intervals etripamil 70mg vs. placebo; 4.99 (2.09, 11.93)

Source: Stambler, B.S. et al.; Etripamil Nasal Spray for Rapid Conversion of Supraventricular Tachycardia to Sinus Rhythm; J Am Coll Cardiol. 2018;72(5):489–97

Phase 2 Mean Systolic Blood Pressure Effects

Etripamil 70 mg showed no drop in blood pressure



[1] Baseline is defined as the average of the 20-min and 10-min pre-dose measurements. [2] Time 0 is defined as the average of the measurements during supraventricular tachycardia between 5 and 0 min before study drug administration. *p < 0.05 versus baseline.

Source: Stambler, B.S. et al.; Etripamil Nasal Spray for Rapid Conversion of Supraventricular Tachycardia to Sinus Rhythm; J Am Coll Cardiol. 2018;72(5):489–97

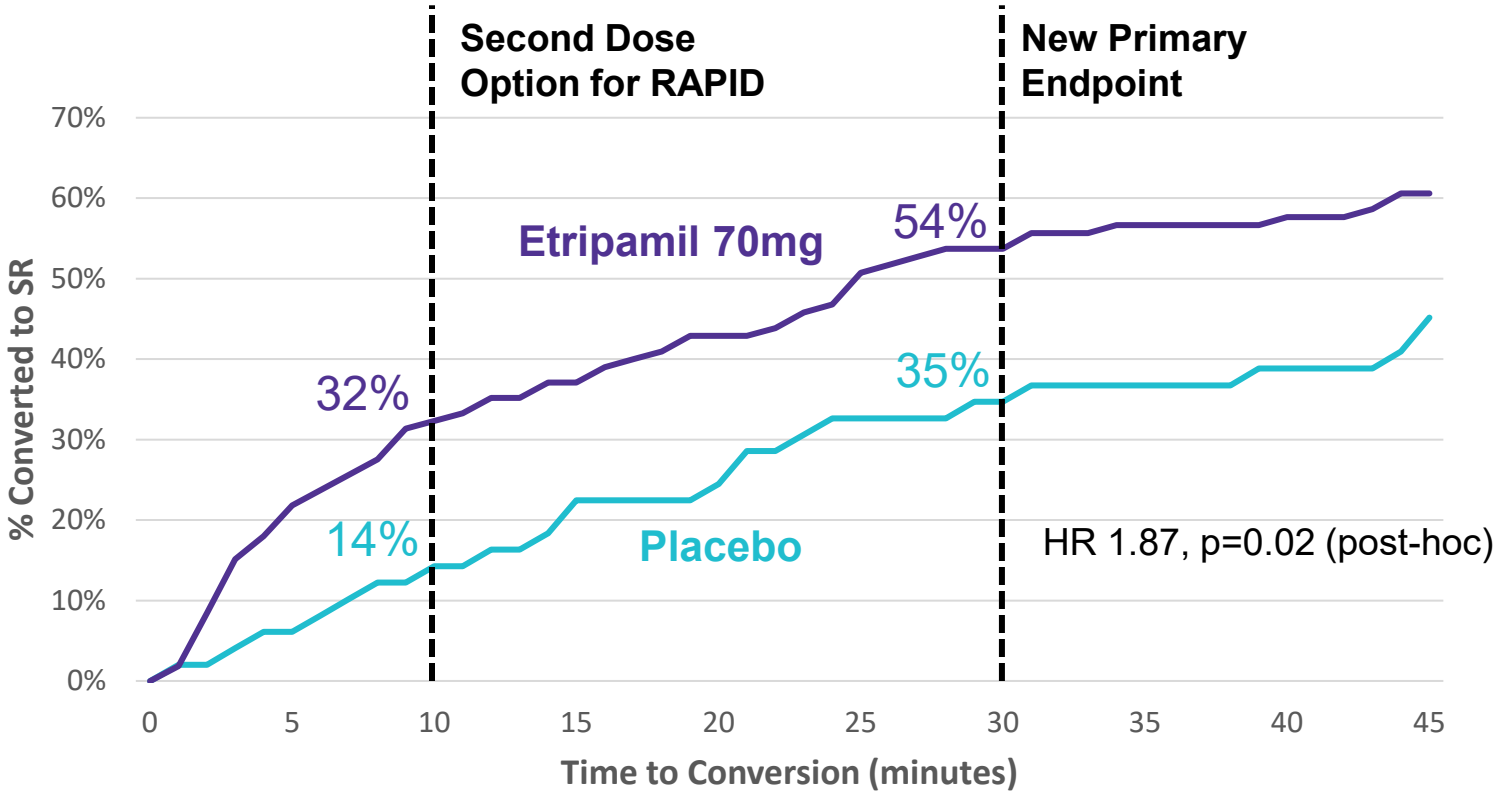
Overview of NODE-301 Findings

- Missed its primary endpoint over 5 hours
- Showed clinically meaningful efficacy during the first 45 minutes consistent with the known pharmacology of etripamil
- Secondary efficacy endpoints encouraging
  - Patient reported outcomes of satisfaction and effectiveness
  - Rescue medication and emergency department use
- Demonstrated a positive safety profile showing etripamil was well tolerated in the at-home setting
- Study execution - human factors had little impact on study execution or results

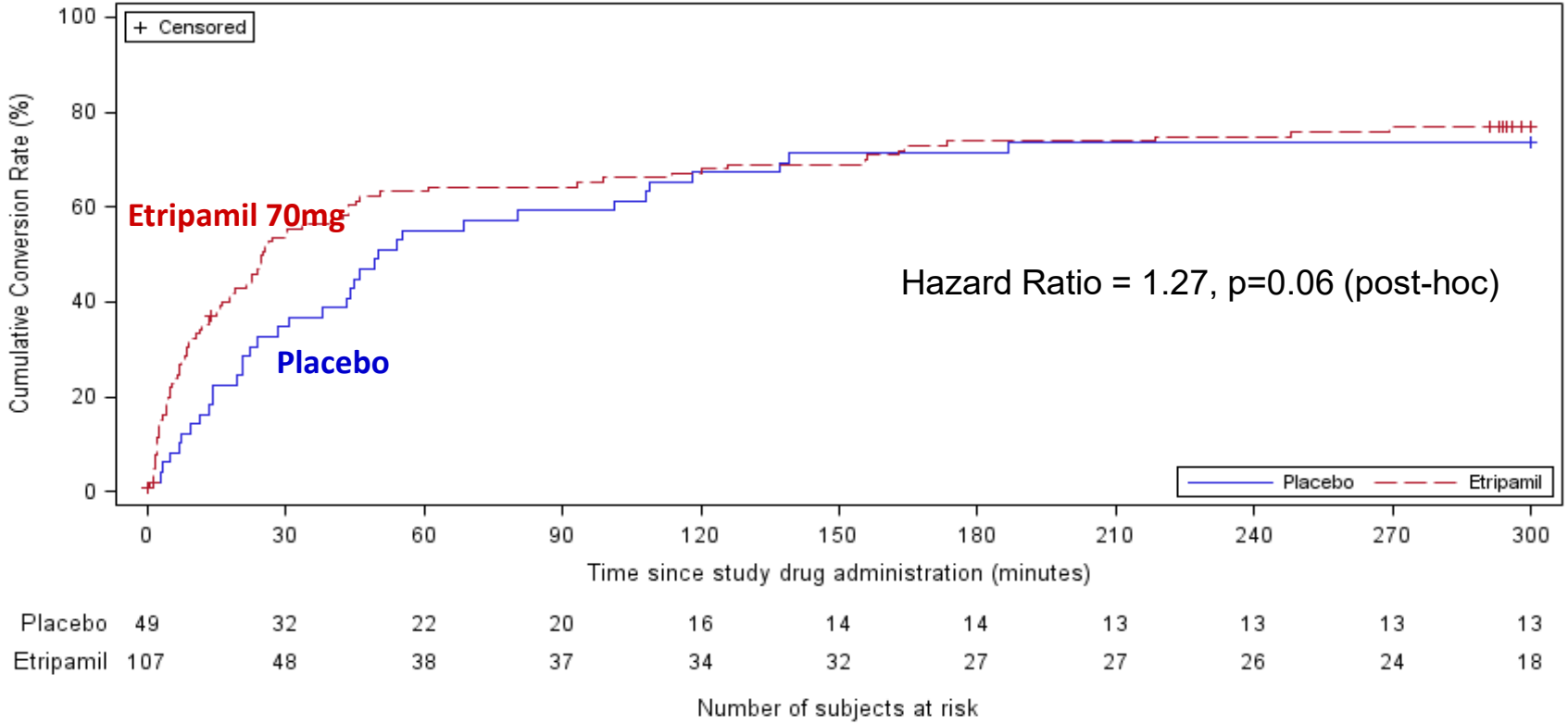
Etripamil Tailored Dosing Regimen Rationale

- A second 70 mg dose ~10 minutes after the initial designed to increase drug exposure
  - Data from early PK work on 30 mg indicates two doses, 10 minutes apart, increases exposure
  - Allows time for nasal cavity to drain, or patient to blow their nose prior to additional administration
- From a safety and tolerability standpoint, the 2nd dose regimen is preferable vs. starting out at a higher dose
  - Patients are not exposed to an additional 70 mg if symptoms resolve following the first dose
  - Reductions in average systolic BP seen at the higher doses in the Phase 2 study mainly resolved within 10 minutes
- Current practice accustomed to second “shot on goal” approach
  - Potential value with a second chance to impact the AV node and break the tachycardia

NODE-301 Efficacy– Time to Conversion over 45 Minutes



NODE-301 Conversion up to Hour 5 with Medical Intervention Patients Analyzed as Treatment Failures at 5 hours (post-hoc)



Subjects who convert following medical assistance are censored at 5 hours. Subjects who present missing data from time t to the end are censored at the time of last available data. Subjects who do not convert or are not censored before 5 hours are censored at 5 hours

Etripamil – Addressing Market Needs

Potential for high receptivity to the profile of etripamil across stakeholders

Patients	Physicians (Cards, EPs, PCPs)	Payors
		
Future with Etripamil– a Better Treatment Option		
• Self-management of acute episodes • Less need for chronic medications • Avoidance of 50-75% of ED visits/hospital admissions	• Better risk/reward profile • Expected to have significant adoption in unablated patients • Alternative to ablation • Bridge to ablation	• Reduction in ED/hospital admissions • Deferral of ablation • Improvement in patient satisfaction

Cards = Cardiologists, EPs = Electrophysiologists, PCPs = Primary Care Physicians

Sources: Internal market research, Milestone Pharmaceuticals Inc.

PSVT Patient Management and Call Point Targeting

Majority of PSVT patients managed by CV specialists, leading to commercial efficiencies

		Clinical Cardiologists	Primary Care Physicians	Electro-physiologists
% of PSVT patients managed		**~60%**	**~30%**	**~10%**
Long-term Use	*Add to or Replace Chronic Medications*	**Primary Target**		
Medium-term Use	*Defer Ablation*			**Secondary Target**
Short-term Use	*Bridge to Ablation*			

- Targeted sales force to reach majority of available opportunity
- Significant overlap with most common CV portfolio call points

Source: Internal market research