Milestone PHARMACEUTICALS

# Company Overview

August 10, 2023

# Forward Looking Statement

The Presentation contains forward-looking statements within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Words such as ‘‘aim,’’ ‘‘anticipate,’’ ‘‘assume,’’ ‘‘believe,’’ ‘‘contemplate,’’ ‘‘continue,’’ ‘‘could,’’ ‘‘design,’’ ‘‘due,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘goal,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘objective,’’ ‘‘plan,’’ ‘‘predict,’’ ‘‘positioned,’’ ‘‘potential,’’ ‘‘project,’’ ‘‘seek,’’ ‘‘should,’’ ‘‘target,’’ ‘‘will,’’ ‘‘would’’ (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward- looking statements are based on Milestone's expectations and assumptions as of the date of this Presentation. Each of these forward-looking statements involves risks and uncertainties. Actual results may differ materially from these forward-looking statements. Forward-looking statements contained in this Presentation include statements regarding (i) the design, progress, timing, scope and results of the etripamil clinical trials in PSVT and AFib-RVR, (ii) the potential efficacy, safety and tolerability of etripamil, (iii) the potential of etripamil to deliver a clinically meaningful benefit to patients with PSVT in the home-setting environment and to empower patients to take control of their condition as well as provide value to the healthcare system, (iv) the possibility that data could fulfill the efficacy requirement for an NDA submission with the FDA for etripamil, (v) plans relating to commercializing etripamil, if approved, including the geographic areas of focus and sales strategy and (vi) the potential market size and the rate and degree of market acceptance of etripamil and any future product candidates and the implementation of Milestone's business model and strategic plans for its business, etripamil and any future product candidates. Important factors that could cause actual results to differ materially from those in the forward-looking statements include, but are not limited to, the risks inherent in biopharmaceutical product development and clinical trials, including the lengthy and uncertain regulatory approval process, uncertainties related to the timing of initiation, enrollment, completion and evaluation of clinical trials, including the RAPID and ReVeRA trials, and whether the clinical trials will validate the safety and efficacy of etripamil for PSVT, AFib-RVR, or other indications, among others, as well as risks related to pandemics and public health emergencies, including those related to COVID-19, and risks related the sufficiency of our capital resources and our ability to raise additional capital. These and other risks are set forth in Milestone's filings with the U.S. Securities and Exchange Commission, including in its annual report on Form 10-K for the year ended December 31, 2021, under the caption "Risk Factors”, as such discussion may be updated in future filings we make with the SEC. Except as required by law, Milestone assumes no obligation to update any forward- looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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Etripamil is an investigational new drug, which is not approved for commercial distribution in the United States.

# Milestone Pharma - Targeting Vast Unmet Need for Patient Management of Common Heart Conditions

## **Targeting** Common Arrhythmias

- PSVT
- AFib-RVR
- High burden on patients *and* on the healthcare system

## **Empowering** Patients to Treat Themselves

- Etripamil: novel calcium channel blocker
- Fast-acting, well-tolerated, portable, on-demand
- Shift from Emergency Department to patient self-management

## Positioned for **Success**

- Positive Phase 3 results in PSVT
- NDA submission Oct 2023
- AFib-RVR program expands market
  - ➢ Phase 2 data Q4 2023
- Experienced leadership driving commercialization

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; NDA = New Drug Application

# PSVT and AFib-RVR Cause Markedly Symptomatic Attacks That Disrupt Patients' Lives

## Symptoms include…

- Heart palpitations
- Chest pressure or pain
- Shortness of breath
- Fatigue
- Light-headedness
- Anxiety

**Many patients feel anxious and powerless**

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

# Current Treatment of Acute Attacks in the Emergency Department are Burdensome and Costly

## For many patients, physicians and payers:

- Time-consuming, disruptive
- Often results in a hospital admission
- Expensive use of healthcare system resources

**Need for simple, fast-acting treatment, reduce trips to ED and calls to physicians**

ED = Emergency Department

# PSVT & Atrial Fibrillation with Rapid Ventricular Rate are Sizable and Underserved Markets in the US

| | PSVT | Atrial Fibrillation |
|---|---|---|
| **Total Patients** (2030) | 2.6 Million[3] | 10 Million[1] |
| **Discharged ED Visits & Hospital Admissions** (2016)[2] | 145 Thousand | 785 Thousand |
| **Target Addressable Market (2030) Patient Population** | **1.0-1.6 Million[5]** | **AFib-RVR ~3-4 Million[4]** |

ED = Emergency Department

Source(s): **1.** Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Miyasaka et al., Circulation, 2006, 114, 119-125. American Heart Association **2**. HCUP ED & Admissions Data (2016), accessed January 2021. **3.** Rehorn et al. Journal of Cardiovascular Electrophysiology. 2021 Aug; 32(8): 2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. 2018 prevalence of 2M anticipated to grow at a CAGR of ~2% **4.** Quantitative Survey conducted by Triangle Insights, May 2021, N=250 Clinical Cardiologists, Interventional Cardiologists, and Electrophysiologists **5.** Estimate of TAM (~40%-60% of prevalence) based on internal PSVT patient market research (BluePrint Research Group, n=247) and longitudinal analysis of claims data.

# Etripamil Nasal Spray is a Novel L-type Investigational Calcium Channel Blocker Designed to Treat Quickly

**Fast onset** of action
($T_{max}$ ≤ 7 min)

Patient
**self-administered**

Small enough to
**fit in your pocket**

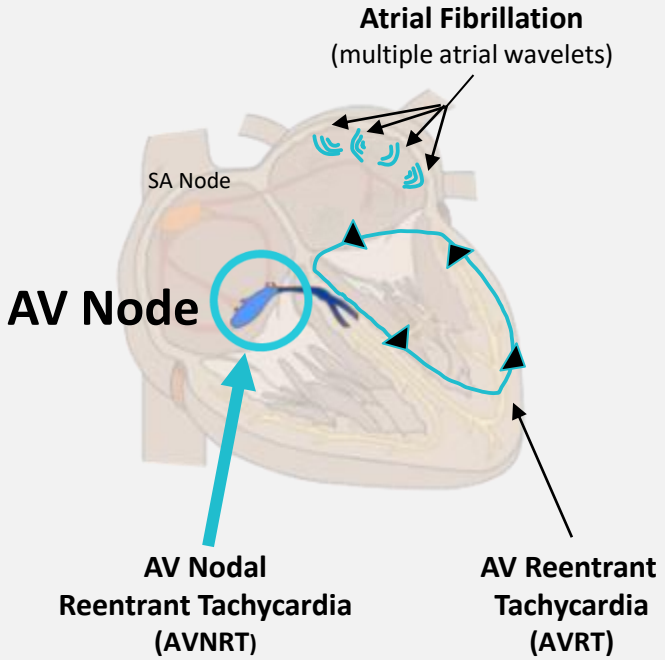
**Empowering patients to treat symptomatic attacks**

# Intravenous Calcium Channel Blockers Are Proven Effective for PSVT and AFib-RVR

## Intravenous Calcium Channel Blockers (CCB)

- Slows conduction signal from the atria to the ventricles over the AV Node
- PSVT: breaks the circuit, returning heart to normal rhythm
- AFib-RVR: slows heart rate and reduces symptoms while remaining in Atrial Fibrillation

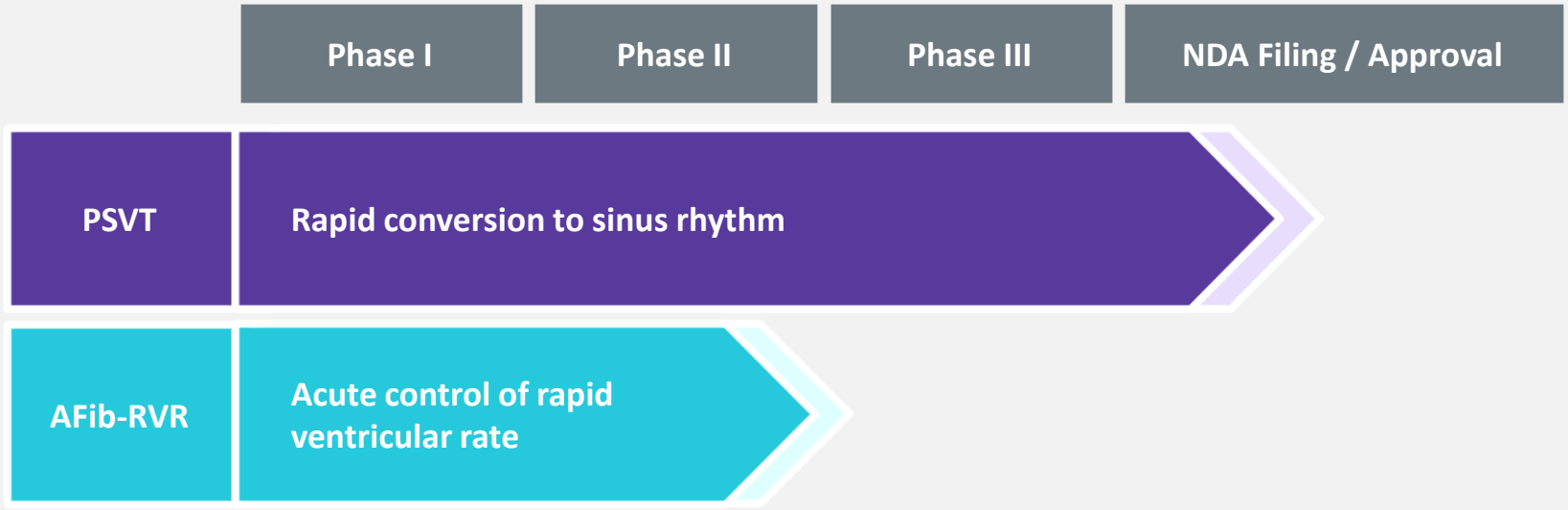
**Etripamil Nasal Spray is an investigational novel CCB**




PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate
Sources: adapted from https://en.ecgpedia.org/index.php?title=Supraventricular_Rhythms, accessed 2/2021

# Clinical Pipeline Advancement for Etripamil

## Pharmacology of L-type calcium channel blockers drives broad clinical utility




PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; NDA = New Drug Application

# Comprehensive Data Supports FDA New Drug Application for Rapid Conversion of SVT Episodes to Sinus Rhythm in Adults

| NODE-1 | NODE-301 | NODE-302 (Ext. of NODE-301) | RAPID | NODE-303 |
|---|---|---|---|---|
| **Phase 2** | **Phase 3** | **Phase 3** | **Phase 3** | **Phase 3** |
| Efficacy (dose finding) | Efficacy | Safety & Efficacy (Repeat Episodes) | Efficacy | Safety (Repeat Episodes) |
| N = 64 | N = 431 | N = 169 | N=706 | N ~450 |

- >1,600 Patient Exposures to Etripamil ≥ 70 mg
- Positive Phase 3 pivotal RAPID trial anchors NDA submission (2023)

NDA = New Drug Application; SVT = Supraventricular Tachycardia
NB: NODE-301 and RAPID studies also collected Safety information
Source: Milestone Pharmaceuticals Data on File

# Positive Phase 3 RAPID Trial in Patients with PSVT

**Randomized, double-blind, placebo-controlled trial enrolled 706 patients to self-administer Etripamil 70 mg regimen or placebo during a PSVT event outside the medical setting**

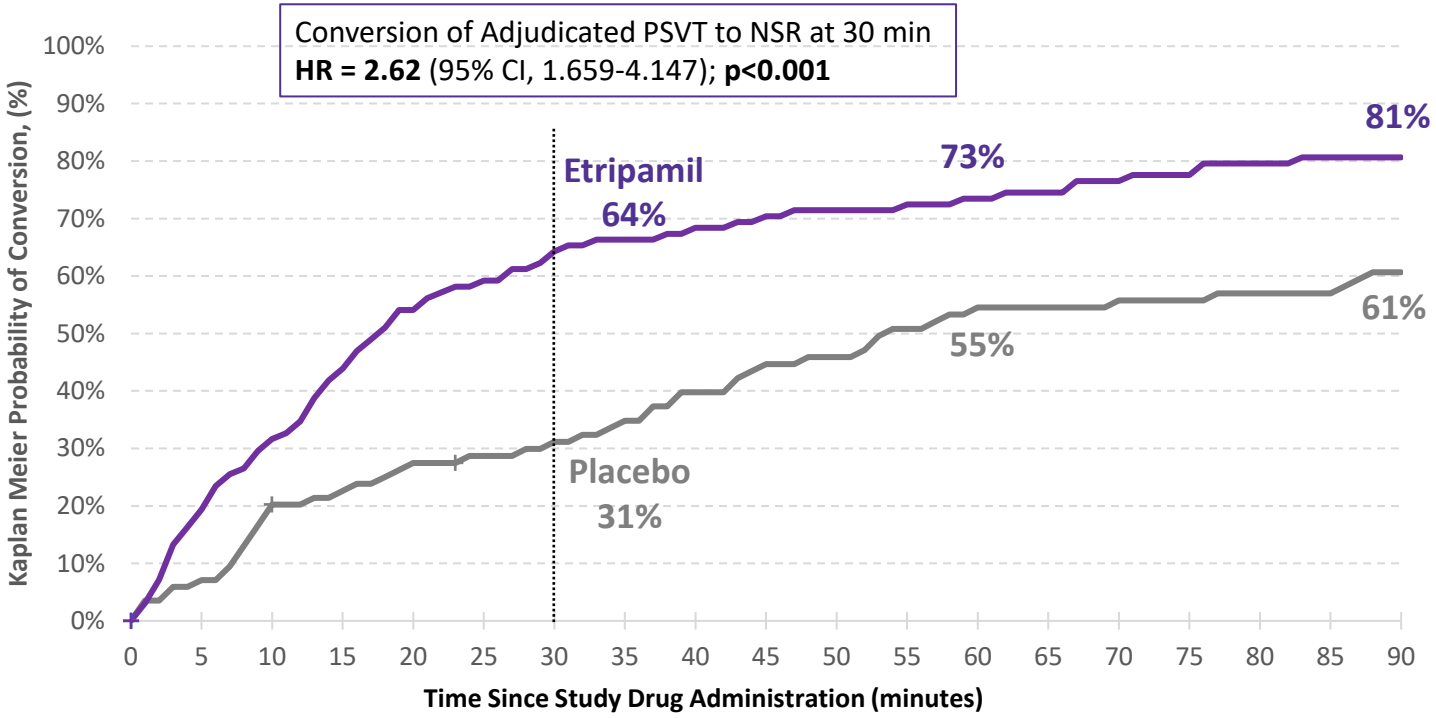
**Repeat-dose regimen – if symptoms not resolved in 10 minutes, second dose administered**

- Achieved primary endpoint - statistical significance (HR = 2.62;  95% CI 1.66, 4.15; p<0.001)
- Need for additional medical interventions or emergency department care ~40% lower for etripamil patients compared to placebo
- Favorable safety and tolerability consistent with prior studies – the most common AEs localized to nasal administration site

**Primary: Conversion of Adjudicated PSVT to Normal Sinus Rhythm (NSR) at 30 min**

HR = Hazard Ratio; CI = Confidence Interval
Source: Milestone Pharmaceuticals Data on File

# Data Indicates Fast Conversion to Normal Sinus Rhythm (NSR)
## RAPID Study

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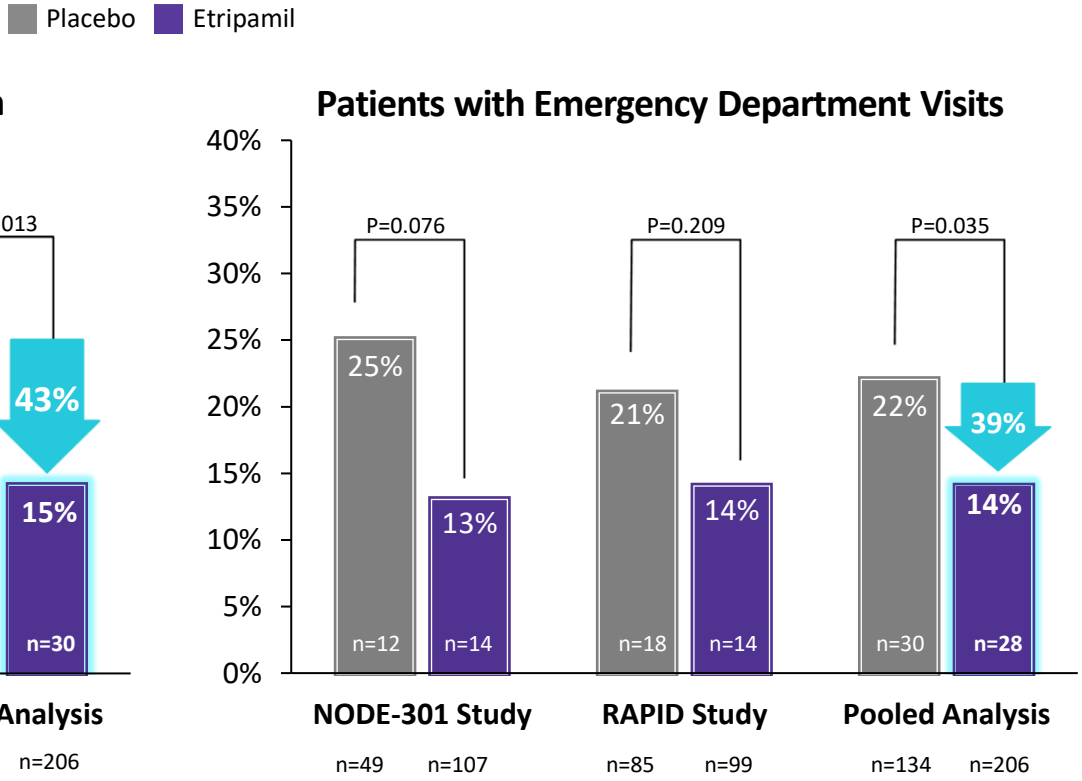
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Subjects at Risk** | Placebo | 85 | 78 | 67 | 64 | 60 | 58 | 56 | 53 | 49 | 45 | 44 | 40 | 37 | 37 | 36 | 36 | 35 | 35 | 32 |
| | Etripamil | 99 | 79 | 67 | 55 | 45 | 40 | 35 | 33 | 31 | 29 | 28 | 27 |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

Source: Milestone Pharmaceuticals Data on File

HR = Hazard Ratio; CI = Confidence Interval

# Fewer Medical Interventions and Emergency Department Visits
## RAPID Study




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.

# Etripamil Well-Tolerated with a Favorable Safety Profile
## RAPID Study – Safety Events

| Subject-reported AEs,[1] n (%) | Placebo[2] N=120 | Etripamil[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] |
| 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] |
| **Subjects with Events from Independent ECG Reading,[5] n (%)** | **Placebo[6] N=116** | **Etripamil[6] N=128** |
| 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 |

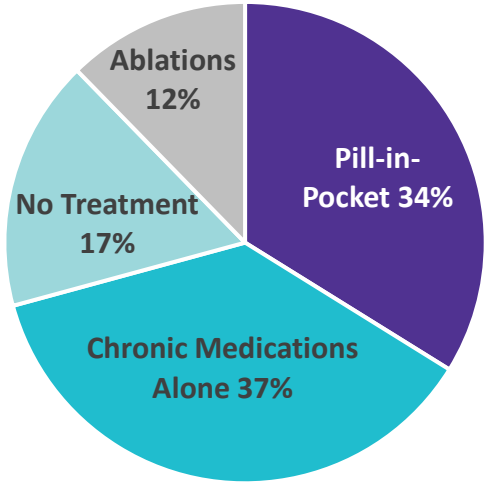
[1] Randomized-period treatment-emergent adverse events, those >5% or those specifically tracked as potentially representing lowered blood pressure. [2] Safety Population. [3] Six of 8 rated as mild, 2 of 8 rated as moderate, 0 needing intervention. [4] Rated as mild. [5]Expert cardiac electrophysiologist adjudication committee. [6]Safety population with evaluable 5-hr. ambulatory ECG data. AE timing – up to 24 hours following drug administration. Source: Milestone Pharmaceuticals Data on File.

# Current US PSVT Market

Total annual US healthcare expenditures of ~$3B

- Prevalence ~2M patients diagnosed with PSVT
- ~650K patients treated per year
  - ~300K newly diagnosed per year
  - >150K ED/hospital visits per year
  - ~80K ablations per year

Current Management



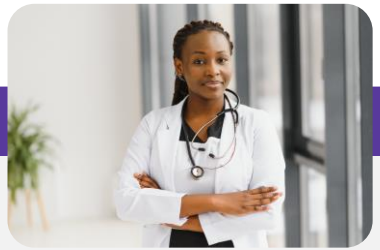

ED = Emergency Department

Source: (1) 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; (2) Quantitative market research conducted by Triangle Insights Group (n=250 cardiologists), June-September 2020

# Etripamil Has Substantial Potential Value for Stakeholder Groups If Approved

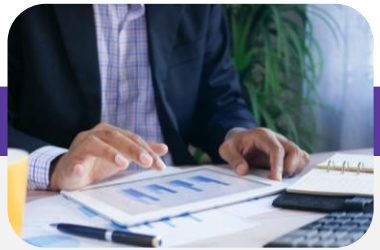
## Patients - Empowerment

- Fast, reliable self-administration
- Less disruption, reliance on the Emergency Department
- Less fear over when the next event will occur



## Physicians – Dependable Tool

- Designed for patient self-management
- Frees up physician time and office resources
- Trusted CCB mechanism



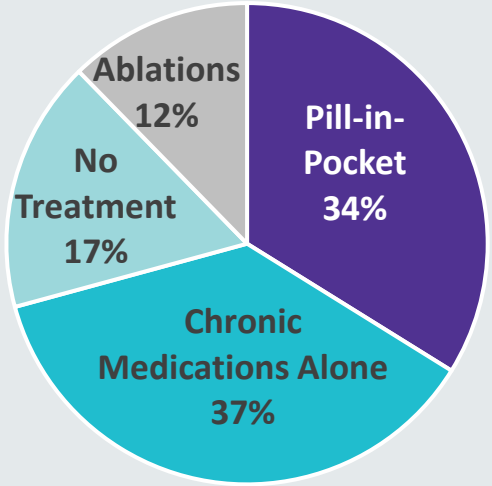
## Payers – More Efficient Use of Resources

- Novel and cost-effective treatment
- Reduction in ED/hospital admissions

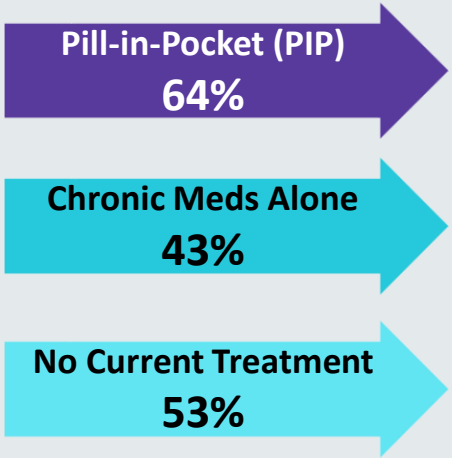
Sources: Internal market research, PSVT = Paroxysmal Supraventricular Tachycardia, ED = Emergency Department

# Cardiologists Expect to Prescribe Etripamil to the Majority of Unablated Patients with PSVT

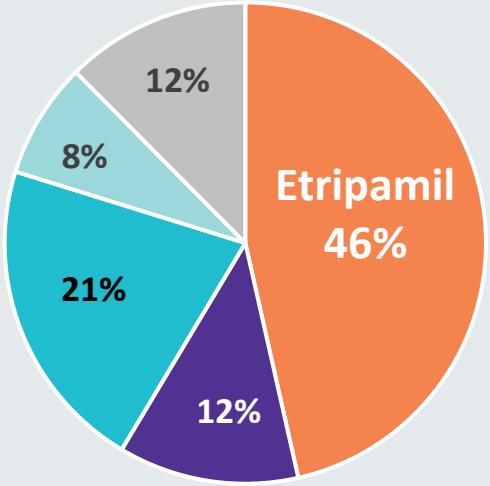
## Current PSVT Management




## Cardiologists' Stated Adoption of Etripamil per Segment

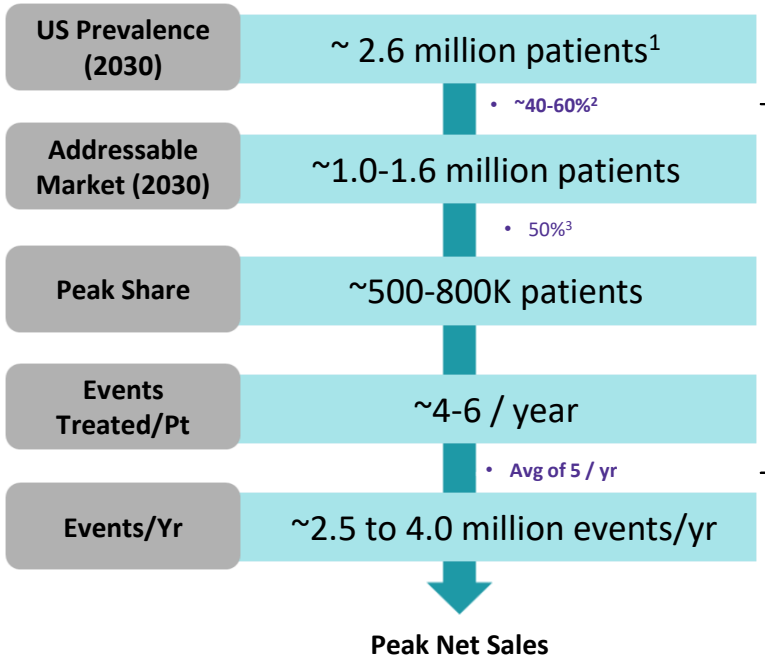



## Impact of Cardiologist Adoption of Etripamil




Source: Quantitative market research conducted by Triangle Insights Group (n=250 cardiologists), June-September 2020; Estimated number of unique patients with annual claims for PSVT from Truven MarketScan data, 2008-2016 analyzed by Precision Xtract, 2019

# Peak US Market Opportunity for Etripamil in PSVT




**~40-60% of patients**
experience multiple longer and/or moderate/severe* events per year

**12-15** annual events (median)

**60%** events longer than 10 minutes

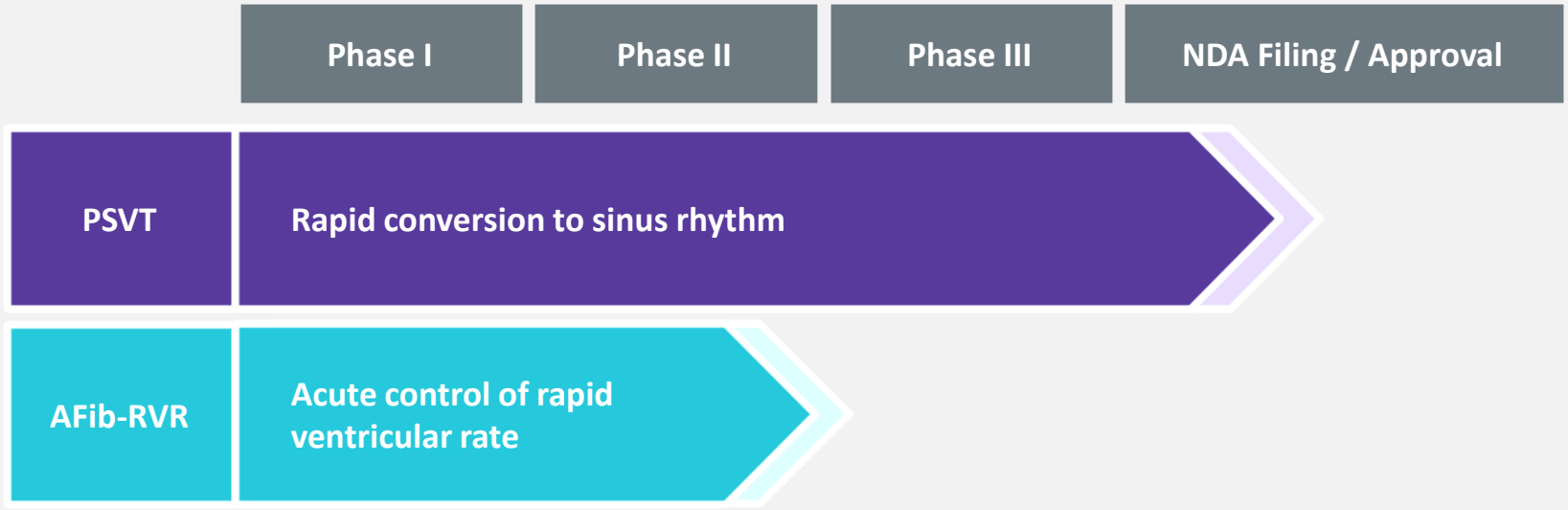
**35%** events longer than 30 minutes

*Patient stated severity of SVT episode (mild, moderate, or severe)

Sources: Internal estimates based on market and outcomes research, Milestone Pharmaceuticals. **1.** Rehorn et al. Journal of Cardiovascular Electrophysiology. 2021 Aug; 32(8): 2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. **2.** 2019 market research with patients conducted by BluePrint Research Group (n=247) . **3.** 2020 market research with HCPs conducted by Triangle Insights Group, 2020 (n=250).

# Clinical Pipeline Advancement for Etripamil

## Pharmacology of L-type calcium channel blockers drives broad clinical utility

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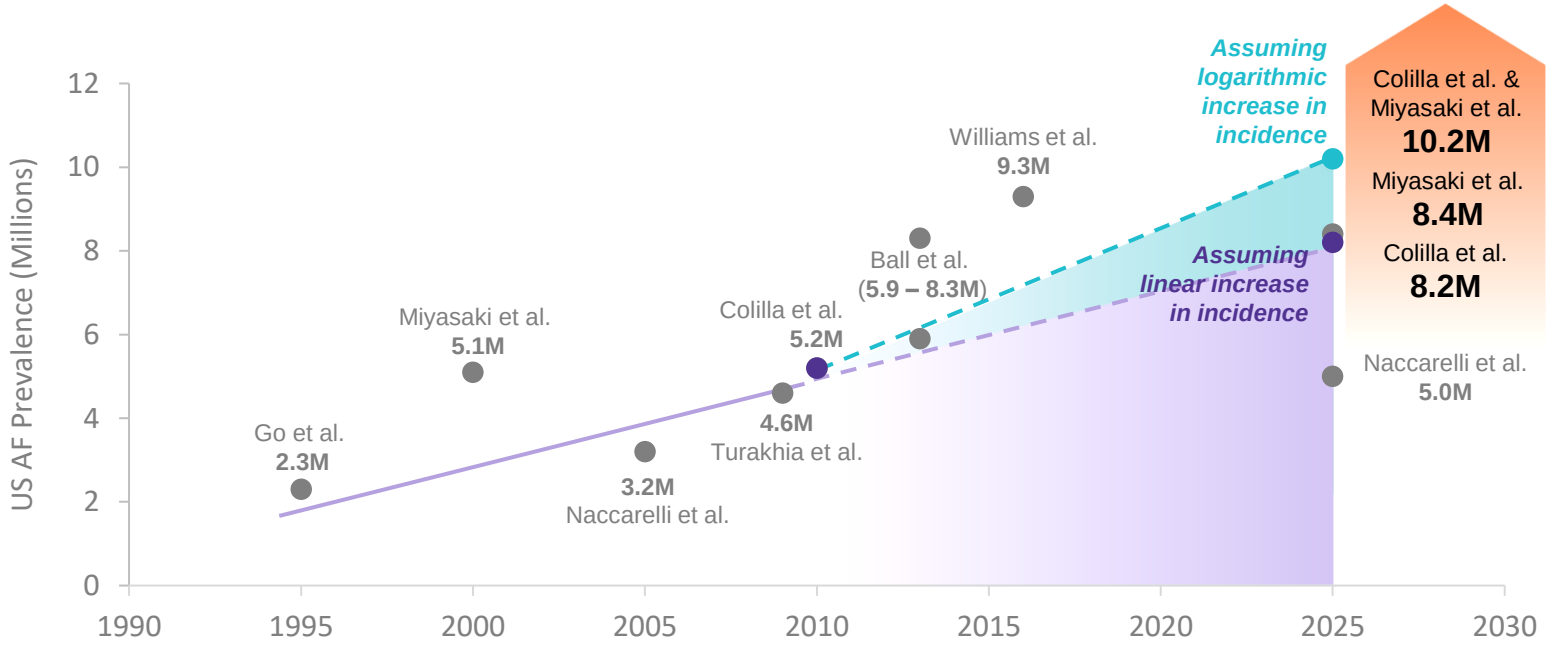
# US Prevalence of Atrial Fibrillation Projected to be 8.2 – 10.2 million by 2025




***Projections include US prevalence of 12M by 2030.***

***Adapted from AHA Heart Disease and Stroke Statistics 2019 Update***

Sources: Benjamin et al., Circulation, 2019, 139, e56-e528; Go et al., JAMA, 2001, 285(18), 2370-2375; Turakhia et al., PLOS ONE, 2018, 13(4), e0195088; Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Kornej et al. Circ. Res., 2020, 127, 4-20; Miyasaka et al., Circulation, 2006, 114, 119-125; Naccarelli et al., Am. J. Cardiol., 2009, 104(11), 1534-1539; Williams et al., Am. J. Cardiol., 2017, 120(11), 1961-1965; Ball et al., Int. J. Cardiol., 2013, 5(1), 1807-1824

# PSVT & AFib-RVR Populations in the US

| | PSVT | Atrial Fibrillation |
|---|---|---|
| **Total Patients** (2030) | 2.6 Million[3] | **10 Million[1]** |
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# Initial Clinical Experience with Etripamil in AFib-RVR

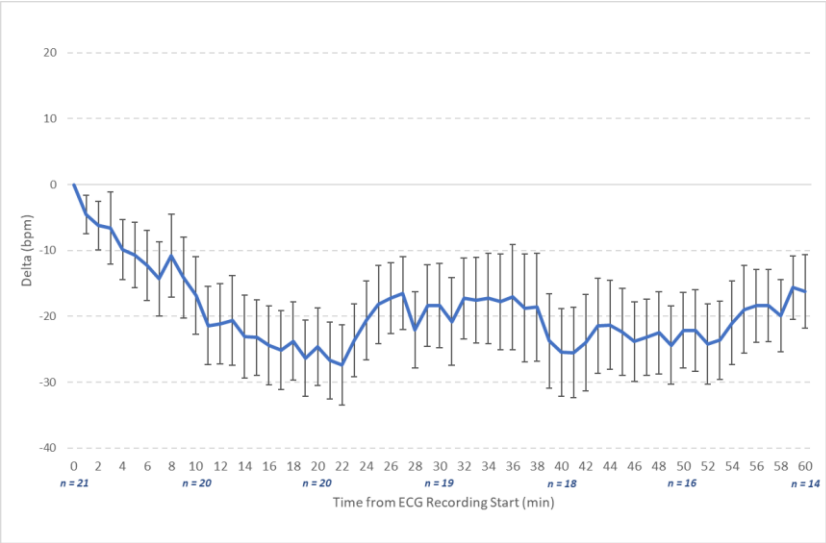
## NODE-303: Phase 3, Open Label Safety Study of Etripamil in patients with PSVT

- A total of **21 AFib-RVR events were treated** by a subset of 18 patients
  - Patients were treating perceived SVT events
  - The ECG recordings of the events were adjudicated to be Atrial Fibrillation
- Mean Ventricular Rate (VR) at baseline equal to 130 bpm
  - 17 of 21 Atrial Fibrillation episodes had VR ≥110 bpm at baseline; mean VR = 138 bpm
- Six of 21 episodes converted to sinus rhythm over 60 minutes following etripamil administration; data was censored at the time of conversion

VR = Ventricular Rate; bpm = Beats per Minute; PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; ECG = Electrocardiogram

Source: Dorian, et. al. Heart Rhythm Society 2023 Annual Meeting

# NODE-303 AFib-RVR Events
# Change in Ventricular Rate from Baseline




## Ventricular Rate Reduction in Afib-RVR

**20 bpm** at 10 minutes

**27 bpm** at 22 minutes

**16 bpm** at 60 minutes

Average difference ± standard error from baseline in ventricular rate. The start of the ECG recording was used as an estimated dosing time for all episodes

Source: Dorian, et. al. Heart Rhythm Society 2023 Annual Meeting

# ReVeRA - Phase II Proof of Concept Trial of Etripamil in AFib-RVR in the Emergency Department Setting

**1** Patient presents to ED with episode of AFib-RVR

**2** Dosing & Assessment

**3** Efficacy Analysis

**Inclusion:**
- Atrial Fibrillation ≥ 1 hour
- Ventricular Rate (VR) ≥ 110 bpm

**Select Exclusions:**
- Treated with antiarrhythmic drugs
- Hemodynamically unstable
- Heart failure

1. Baseline ECG for ≥ 10 min
2. Administer double blind study drug 70 mg etripamil : Placebo (1:1)
3. Monitor in-patient for 1 hour
4. Six-hour remote cardiac monitor
5. Complete safety 24 hours post dose

**Primary: Maximum reduction** in VR within 60 min

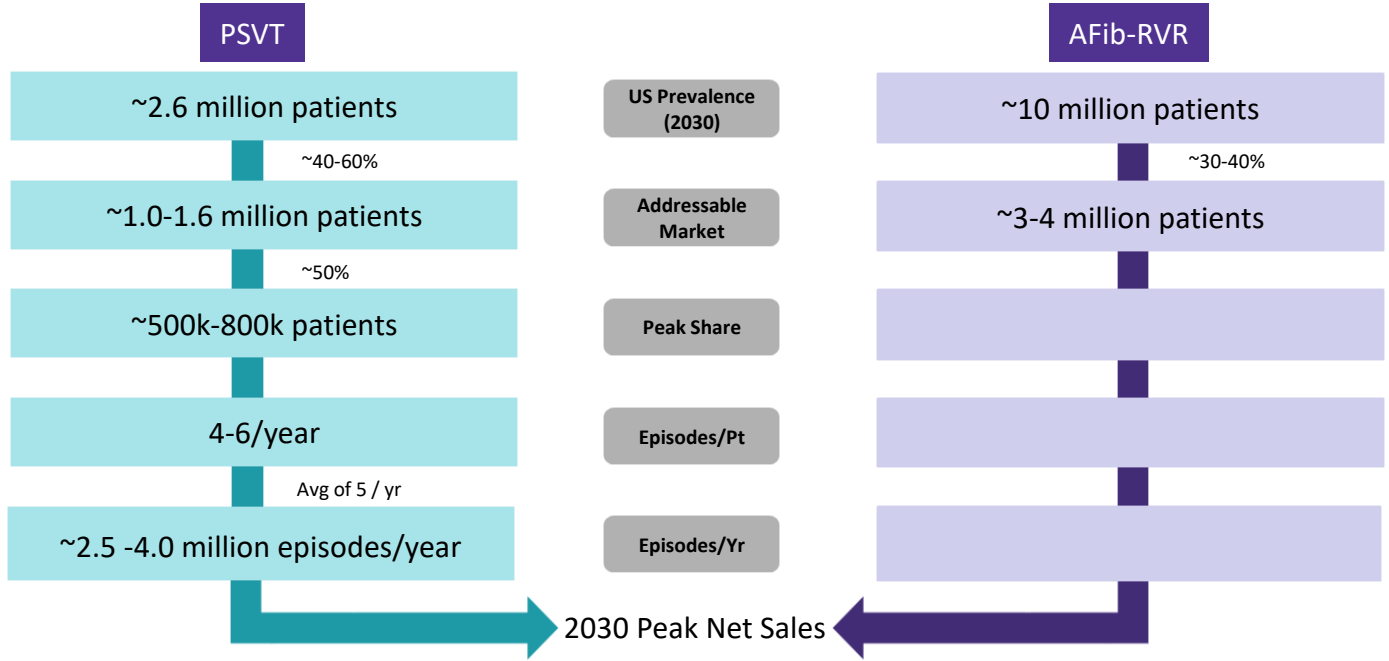
N=50: 90% powered to detect 20 bpm difference in max reduction, α=0.05;

- **Time to** VR reduction
- **Duration** of VR reductions
  - <100 bpm, ≥ 10% reduction, ≥ 20% reduction
- Patient satisfaction with treatment (TSQM-9)

AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; TSQM-9, Treatment Satisfaction Questionnaire for Medication; ED = Emergency Department

**Assessing Etripamil Ventricular Rate Reduction – How Much; How Fast; How Long**

# Peak US Market Opportunity for Etripamil in PSVT and AFib-RVR




**Market Research Suggests a TAM of 4+ Million Patients across both PSVT and AFib-RVR Indications**

Sources: Internal estimates based on market research, Milestone Pharmaceuticals Inc.
AF – RVR = Atrial Fibrillation with Rapid Ventricular Rate; TAM = Target Addressable Market; Internal estimates based on market and outcomes research, Milestone Pharmaceuticals

# Finances – as of June 30, 2023

- Cash and short-term investments of $87.6M
- Synthetic Royalty Financing of $75M available upon approval(1)
- Cash as of June 30, 2023 together with strategic financing expected to fund operations into mid-2025
- Equity - 42.9M in shares and pre-funded warrants outstanding
  - 33.4M common shares
  - 9.6M pre-funded warrants(2)

(1) In March 2023, Milestone announced a $125.0M strategic with RTW Investments. The financings consists of $50.0M in convertible notes issued in March 2023, and a commitment $75.0M in non-dilutive royalty funding if etripamil is approved by the FDA.
(2) Common shares as of August 10, 2023. Pre-funded warrants as of June 30, 2023.

# Recent Progress and Key Upcoming Events

1. **Positive FDA feedback Pre-NDA meeting for PSVT** – Q1, 2023
2. **Completed last two Phase 3 PSVT trials** – Q1, 2023
3. **Expected NDA filing for PSVT** – October 2023
4. **Initial data in AFib-RVR (NODE-303 study)** – May 2023
5. **AFib-RVR Phase 2 (ReVeRA study) topline data** – Q4, 2023
6. **Operating runway to mid-2025 via RTW financing**

# Milestone Pharma - Targeting Vast Unmet Need for Patient Management of Common Heart Conditions

## **Targeting** Common Arrhythmias

- PSVT
- AFib-RVR
- High burden on patients *and* on the healthcare system

## **Empowering** Patients to Treat Themselves

- Etripamil: novel calcium channel blocker
- Fast-acting, well-tolerated, portable, on-demand
- Shift from Emergency Department to patient self-management

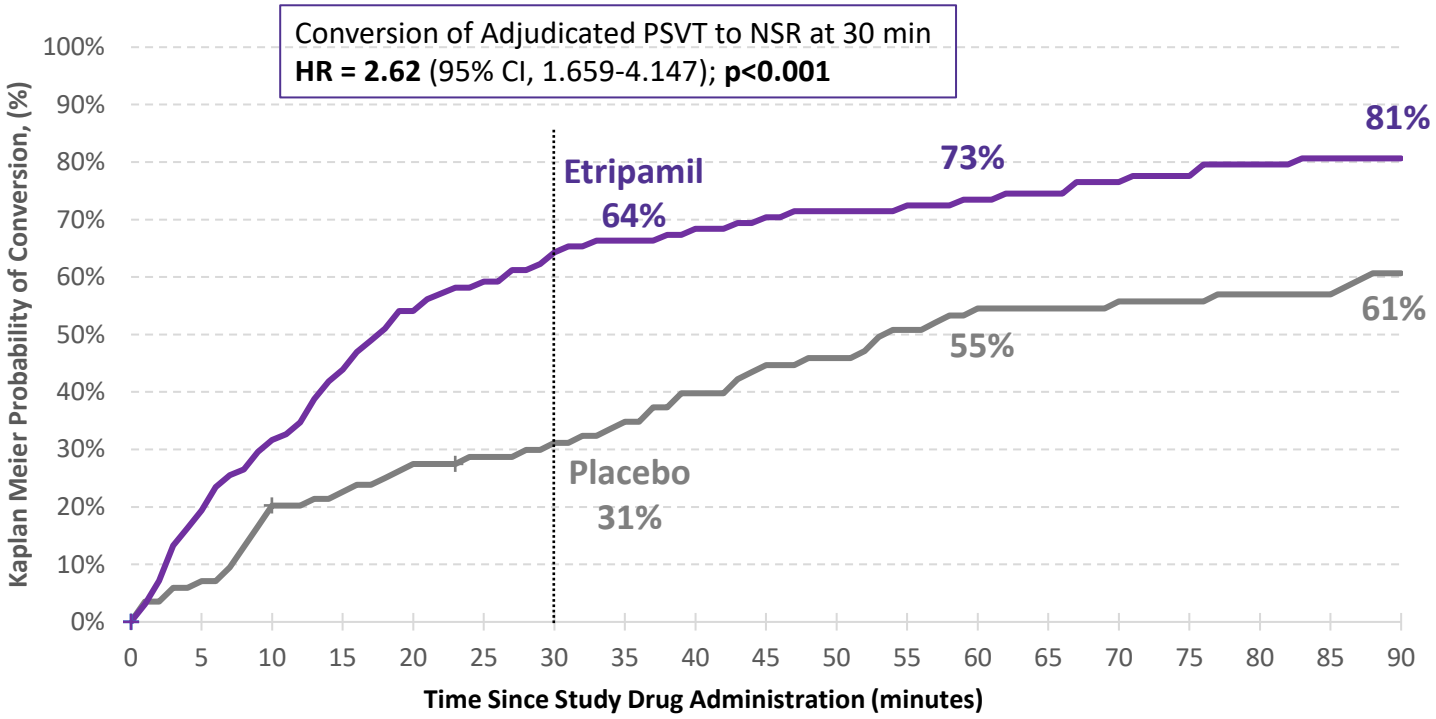
## Positioned for **Success**

- Positive Phase 3 results in PSVT
- NDA submission Oct 2023
- AFib-RVR program expands market
  - ➢ Phase 2 data Q4 2023
- Experienced leadership driving commercialization

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; NDA = New Drug Application

# Appendix

# Data Indicates Fast Conversion to Normal Sinus Rhythm (NSR)
## RAPID Study

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Subjects 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 |

Source: Milestone Pharmaceuticals Data on File

HR = Hazard Ratio; CI = Confidence Interval

# Strategic Financing with RTW Extends Runway to Mid-2025
## Helps fund launch and commercialization of Etripamil in PSVT

**$50M**
**Convertible Notes**

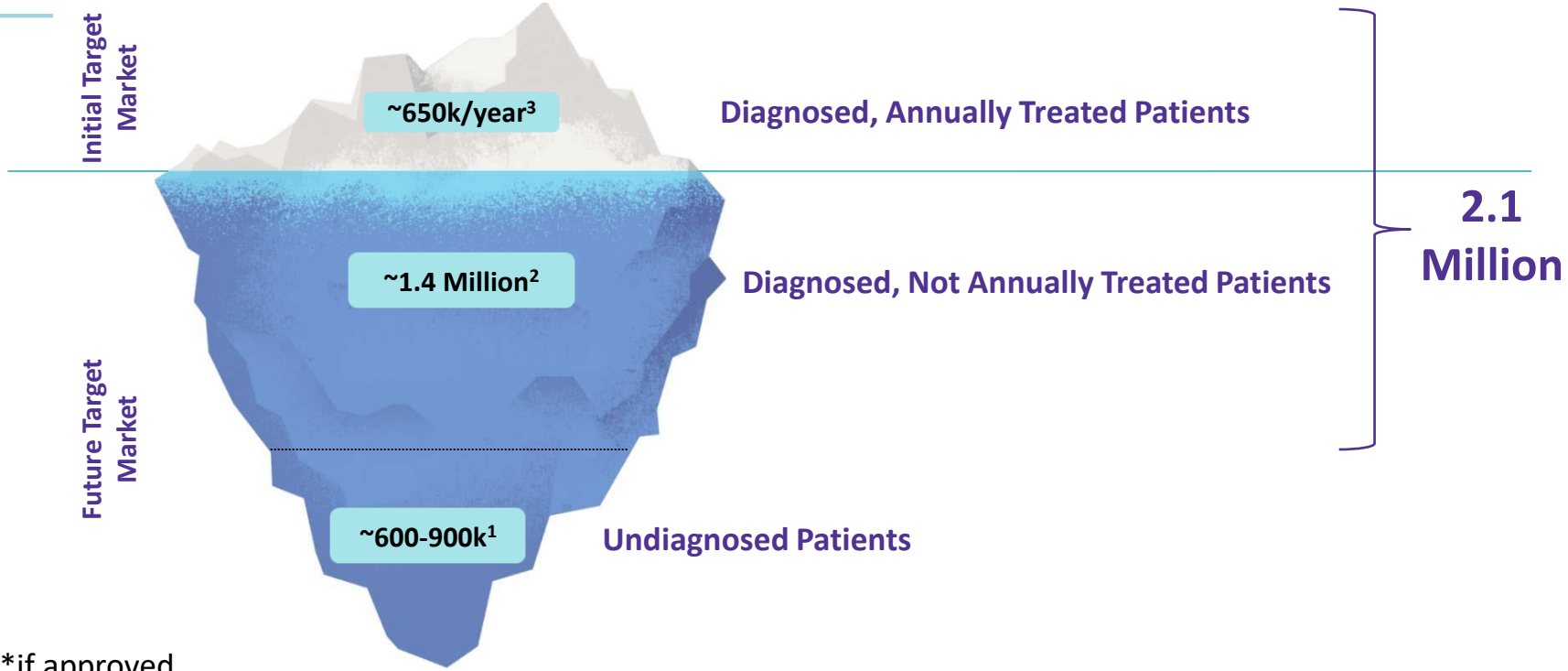
- 6-year term
- Initial Conversion Price $5.23/share
  - 50% premium to 30-day VWAP[1]
- 6% coupon
  - Payable quarterly, or at our option payable in kind (PIK) for first 3 years

**$75M**
**Synthetic Royalty**

- Funded upon FDA approval of etripamil in PSVT
- Non-dilutive synthetic royalty
- 7% Royalty[2] <$500M[3]
- 4% Royalty $500-$800M
- 1% Royalty >$800M

[1] VWAP – Volume Weighted Average Price as of 3/27/23 [2] Rate can increase by 2.5% if certain annual net sales thresholds are not met [3] Annual net product sales of etripmail in the United States

# Core PSVT Market is Addressable *Now**, with Large Potential for Expansion




*if approved

Sources: 1) assumes annual incidence rate for PSVT of ~300k from longitudinal claims analysis and the average time to diagnosis (currently 2-3 years) can be reduced to <6 months 2) Calculated as the difference between PSVT prevalence of 2.1M and annual treatment rate of ~650k from Truven MarketScan data, 2008-2016 analyzed by Precision Xtract, 2019 3) Estimated number of unique patients with annual claims for PSVT from Truven MarketScan data, 2008-2016 analyzed by Precision Xtract, 2019.

# Standard of Care is Inadequate – Most Patients Experience Events Despite Preventive Options

| | Chronic / Preventive | Acute |
|---|---|---|
| **PSVT** | • Oral Beta Blockers and Calcium Channel Blockers (CCB) to reduce episodes<br>• Catheter ablation | • Vagal maneuver & "Pill in Pocket" (oral CCB or BB, off-label) have poor efficacy<br>• **IV adenosine, IV CCB or DC cardioversion - requires ED or hospital visits** |
| **AFib-RVR** | • Oral Therapies for rate or rhythm control<br>• Catheter ablation | • Oral drugs for rate or rhythm control – however do not prevent breakthrough AFib<br>• **IV CCB or DC cardioversion - requires ED or hospital visits** |

BB = Beta blocker; IV = Intravenous; DC = Direct Current; ED = Emergency Department

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

# Understanding Epidemiology of PSVT Using Longitudinal Claims Data

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total |
|---|---|---|---|---|---|---|
| Unique Patients | 648,518 | 417,249 | 379,346 | 344,891 | 311,771 | 2,101,775 |

**Annually Treated Patients**

**5-year Incidence Patients**

**5-year Prevalence Patients**

Analyzed commercial and Medicare claims data over a 9-year period, where patients were required to have five years of continuous enrollment

- ✓ **1+ PSVT code** required in the **Emergency Department or inpatient setting** (unique patients managed acutely) or,
- ✓ **2+ PSVT codes** required in the **outpatient setting** (additional unique patients managed chronically)

Source: 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.

# New Publication Addresses Under-reporting of Prevalence of PSVT

Received: 10 December 2020 | Revised: 4 May 2021 | Accepted: 10 May 2021

DOI: 10.1111/jce.15109

ORIGINAL ARTICLES

WILEY

## Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States


Michael Rehorn MD, MS[1] | Naomi C. Sacks PhD[2,3] | Maia R. Emden BA[2] | Bridget Healey MPH[2] | Madison T. Preib MPH[2] | Philip L. Cyr MPH[2,4] | Sean D. Pokorney MD, MBA[1]

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**Disclosure** : Michael Rehorn receives research support from Pfizer and Boston Scientific. Naomi Sacks, Maia Emden, Bridget Healey, Madison Preib, and Philip Cyr are employees of Precision Health Economics, which received research support from Milestone Pharmaceuticals. Sean Pokorney reports research support from Bristol-Myers Squibb, Pfizer, Janssen Pharmaceuticals, Food and Drug Administration, Gilead, and Boston Scientific; consulting/advisory board support from Medtronic, Boston Scientific, Philips, Janssen Pharmaceuticals, Bristol-Myers Squibb, Pfizer, and Portola; DSMB support from Medpace.



**Abstract**

**Background:** Paroxysmal supraventricular tachycardia (PSVT) encompasses a range of heart rhythm disorders leading to rapid heart rates. By virtue of its episodic nature, diagnosing PSVT is difficult and estimating incidence and prevalence on a population level is challenging. The objective of this study was to estimate the incidence and prevalence of PSVT in the United States (US) in contemporary practice.

**Methods and Results:** An observational retrospective longitudinal study using claims, enrollment, and demographic data from the IBM MarketScan® Commercial Research database (age < 65) and the Medicare Limited Data Set (age ≥ 65) from 2008 to 2016. Patients with a PSVT diagnosis code (ICD-9: 427.0, ICD-10: I47.1) on ≥ 2 outpatient, ≥ 1 emergency room, or ≥ 1 inpatient visit were considered as having PSVT. Patients with atrial fibrillation/atrial flutter (AF/AFL) were excluded from the initial analysis given the potential for misclassification. Incidence was estimated by assessing diagnoses made during year 5 of continuous enrollment. Finally, a sensitivity analysis was performed by including patients with both PSVT and AF/AFL diagnoses. Period prevalence and incidence rate were estimated to be 332.9 (323.2–342.9) and 57.8 (52.8–63.3) per 100 000 individuals, respectively, when excluding patients with AF/AFL. Projected to the 2018 US Census, prevalence and incidence are 1.26 million (1.21–1.30 million) and 188,981 (172,891–206,943), respectively. Including patients with AF/AFL, the prevalence may increase to 479.7 (467.9–491.8) with an incidence of 93.4 (86.9–100.5) per 100 000 individuals or a prevalence of 2.06 million (2.01–2.12 million).

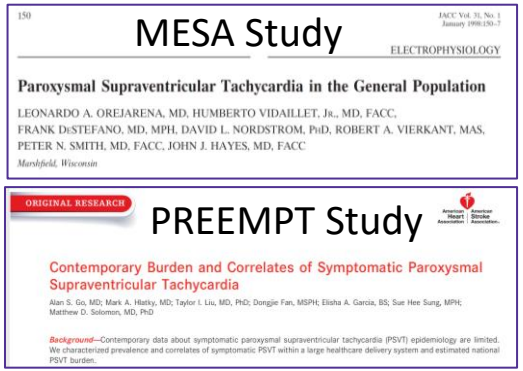
**Conclusions:** Approximately 1 in 300 people in the US had PSVT with the highest rates in older and female patients.



KEYWORDS

atrial fibrillation, atrial flutter, incidence, paroxysmal supraventricular tachycardia, prevalence



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JACC Vol. 31, No. 1
January 1998:150–7

ELECTROPHYSIOLOGY

MESA Study

**Paroxysmal Supraventricular Tachycardia in the General Population**

LEONARDO A. OREJARENA, MD, HUMBERTO VIDAILLET, Jr., MD, FACC, FRANK DeSTEFANO, MD, MPH, DAVID L. NORDSTROM, PhD, ROBERT A. VIERKANT, MAS, PETER N. SMITH, MD, FACC, JOHN J. HAYES, MD, FACC

*Marshfield, Wisconsin*



ORIGINAL RESEARCH

PREEMPT Study

American Heart Association | American Stroke Association

**Contemporary Burden and Correlates of Symptomatic Paroxysmal Supraventricular Tachycardia**

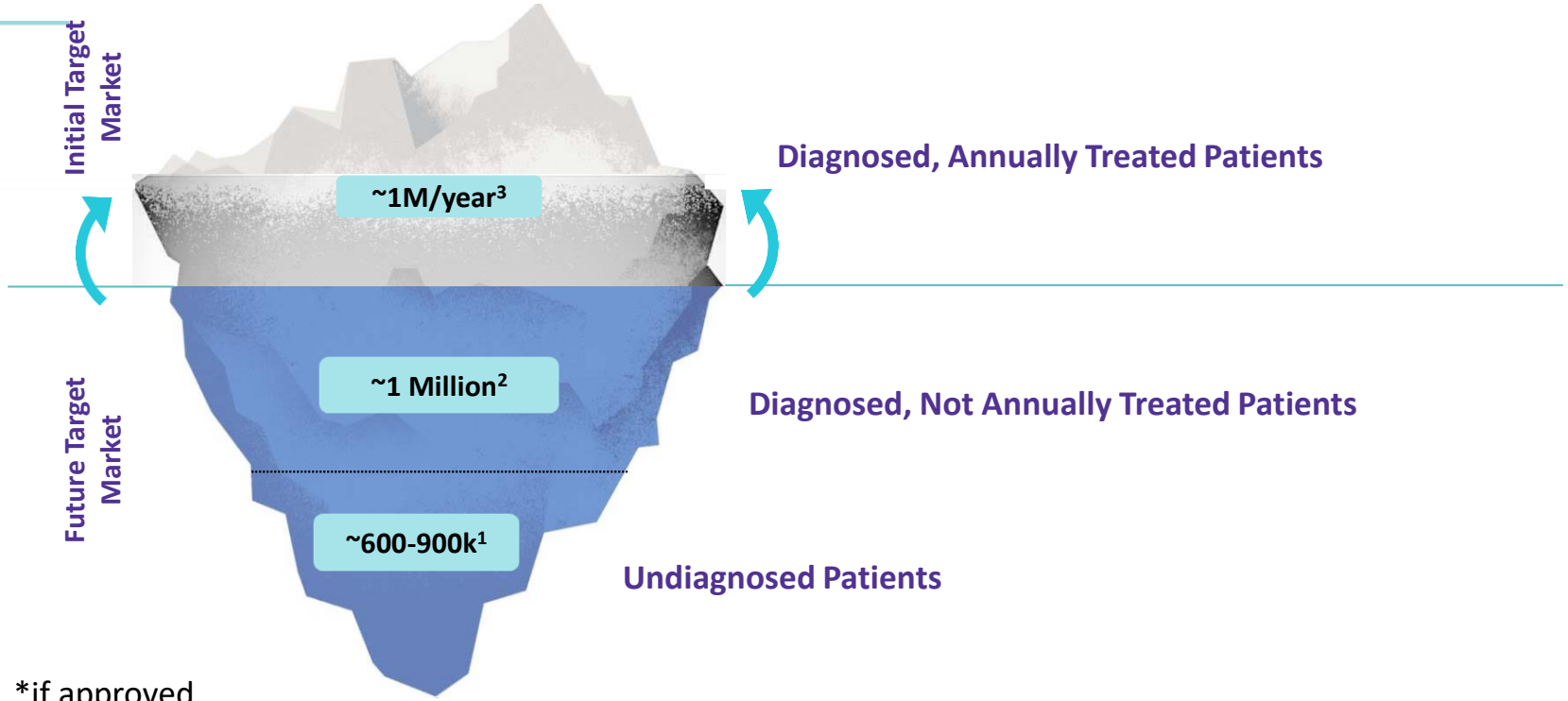
Alan S. Go, MD; Mark A. Hlatky, MD; Taylor I. Liu, MD, PhD; Dongjie Fan, MSPH; Elisha A. Garcia, BS; Sue Hee Sung, MPH; Matthew D. Solomon, MD, PhD

*Background*—Contemporary data about symptomatic paroxysmal supraventricular tachycardia (PSVT) epidemiology are limited. We characterized prevalence and correlates of symptomatic PSVT within a large healthcare delivery system and estimated national PSVT burden.

- 1.3-2.1M diagnosed patients with PSVT
- MESA/PREEMPT identify only patients presenting to healthcare settings acutely, with the episode confirmed on ECG during the encounter
- Less than 25% of patients in RAPID on placebo sought medical intervention
- Less than 40% of incident cases in MESA would have been detected by PSVT ICD-9 Code 427.0
- Potential 2.5X under-reporting of diagnosed patients with PSVT

Source: Orejarena LA, Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith, PN, Hayes JJ. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol. 1998;31:150–157. Alan S. Go, MD; Mark A. Hlatky, MD; Taylor I. Liu, MD, PhD; Dongjie Fan, MSPH; Elisha A. Garcia, BS; Sue Hee Sung, MPH; Matthew D. Solomon, MD, PhD. Contemporary Burden and Correlates of Symptomatic Paroxysmal Supraventricular Tachycardia. J Am Heart Assoc. 2018;7:e008759. DOI: 10.1161/JAHA.118.008759.

# Core PSVT Market is Addressable *Now**, with Large Potential for Expansion




*if approved

Sources: 1) assumes annual incidence rate for PSVT of ~300k from longitudinal claims analysis and the average time to diagnosis (currently 2-3 years) can be reduced to <6 months 2) Calculated as the difference between PSVT prevalence of 2.1M and annual treatment rate of ~650k from Truven MarketScan data, 2008-2016 analyzed by Precision Xtract, 2019 3) Estimated number of unique patients with annual claims for PSVT from Truven MarketScan data, 2008-2016 analyzed by Precision Xtract, 2019.

# Management of Patients with PSVT and Call Point Targeting

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

| | | Clinical Cardiologists | Primary Care Physicians | Electro-physiologists |
|---|---|---|---|---|
| **% of 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

# Published Disease Data Likely Under-Reports Burden of PSVT


## Strengths

- Provides important demographic and clinical characteristic data on patients with PSVT
- Positive Predictive Values from PREEMPT useful
- Less than 40% of incident cases in MESA would have been detected by PSVT ICD-9 Code 427.0

## Weaknesses

- Data only from patients presenting to healthcare settings acutely, with the episode confirmed on ECG during the encounter
- PSVT episodes were only adjudicated during the first healthcare encounter with a PSVT or PSVT-related code in PREEMPT
- Non-representative, small, and non-contemporary population (MESA)

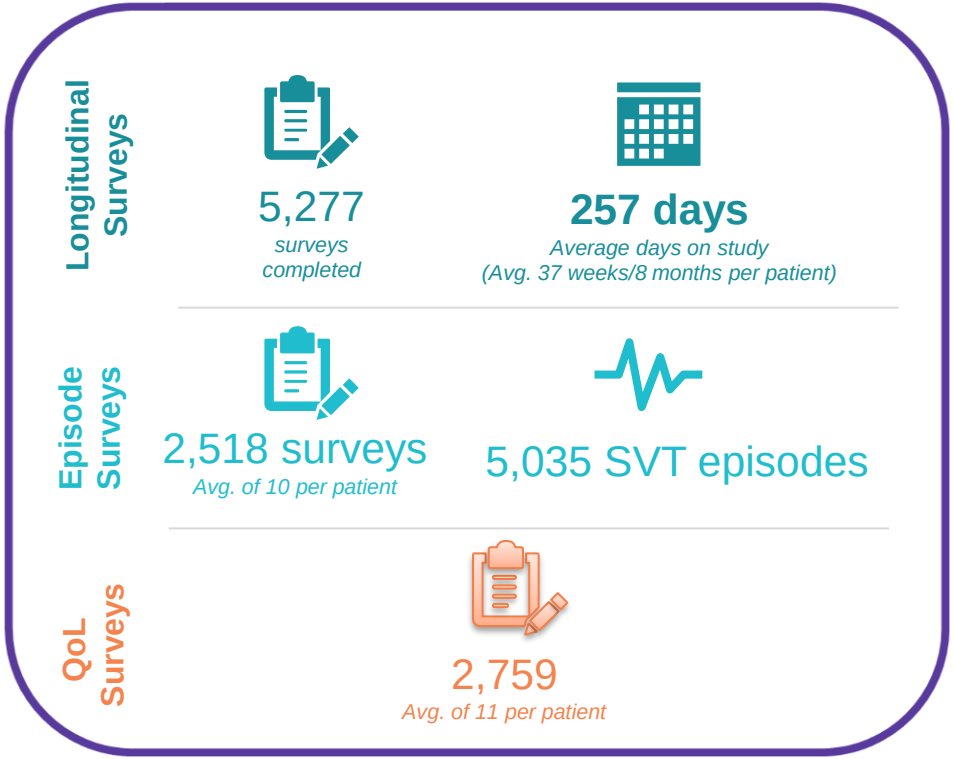
Source: Orejarena LA, Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith, PN, Hayes JJ. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol. 1998;31:150–157. Alan S. Go, MD; Mark A. Hlatky, MD; Taylor I. Liu, MD, PhD; Dongjie Fan, MSPH; Elisha A. Garcia, BS; Sue Hee Sung, MPH; Matthew D. Solomon, MD, PhD. Contemporary Burden and Correlates of Symptomatic Paroxysmal Supraventricular Tachycardia. J Am Heart Assoc. 2018;7:e008759. DOI: 10.1161/JAHA.118.008759.

# New Data Enhances Understanding of Burden of PSVT

**Analysis of Prospective Patient Reported Outcomes Longitudinal Data**

**247 US & UK patients**

- **Phase 1: Baseline Survey** *(medical and SVT episode history)*
- **Phase 2: Longitudinal Weekly Surveys** *(episode survey if experienced an episode, QoL survey if not)*




Source(s): PSVT patient market research, 2019 (BluePrint Research Group, n=247, n=198 US & n=49 UK)

# PRO Analyses Provide A Clearer Picture of Burden of PSVT than Market Research Alone

Unablated patients experience 5-6 episodes per year relevant for etripamil use

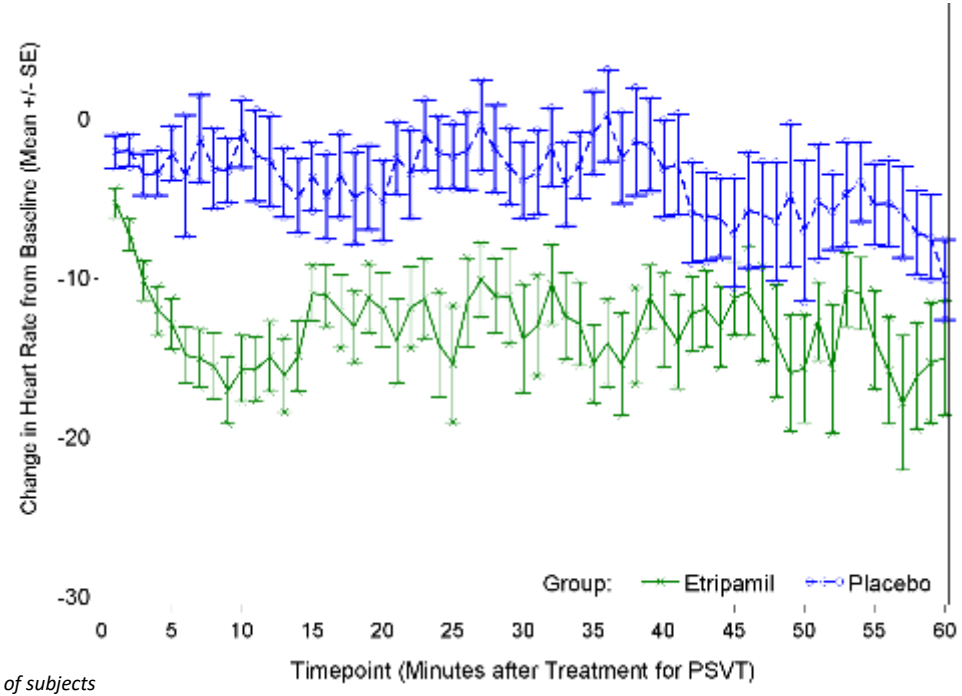
| **Episode Freq. for Patients <u>not</u> Receiving Catheter Ablation** | **Market Research[1]** *(annual recall, n=250)* | **PRO Longitudinal Data[2]** *(weekly tracking, n=247)* |
|---|---|---|
| Annual Episode Freq | 4-7 episodes / year | 15 episodes/year* |
| % of patients with multiple 10+ min episodes / year | 40% | 68% |
| Annual Freq of Moderate-Severe 5+ min episodes | *N/A* | 5-6 episodes / year* |

Weekly tracking shows that patients are experiencing more episodes than previously thought – but that they tend to recall the moderate/severe episodes of longer duration (e.g., 5+ minutes)

*Patients on study at least 6 months were used to project annual episode frequency. Sample projections were weighted by stated episode frequency from an intake survey

Sources: Internal estimates based on market and outcomes research, Milestone Pharmaceuticals. 1. PSVT patient market research conducted by Triangle Insights Group, 2018 (n=250). 2. PSVT patient market research conducted by BluePrint Research Group, 2019 (n=247).

# Effect of Etripamil on Heart Rate (HR) while in SVT (NODE-301 Study)




*Number of subjects*

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 48 | 41 | 41 | 28 | 20 | 17 |
| Etripamil | 102 | 69 | 60 | 41 | 31 | 30 |

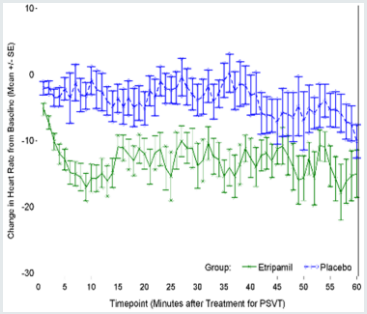
- Improvement in HR observed within first minute, with maximum difference at 10 minutes
- Differences were statistically significant through 40 minutes
- Reduction in heart rate in etripamil group sustained for 1 hour
- Some patients reported symptom relief even though they had not converted to sinus rhythm

Source: Ip, JE et al; "Etripamil Nasal Spray Reduces Heart Rate in Patients With Paroxysmal Supraventricular Tachycardia Prior to Conversion to Sinus Rhythm"; Poster presentation at AHA Scientific Sessions, November 14, 2021.

# Potential Effect of Etripamil on Ventricular Rate in Patients with AFib-RVR; documented impact of drug on AV-Node

### THR Reduction during AVN-Dependent SVT (NODE-301, Phase 3, event-driven, pbo-controlled trial)

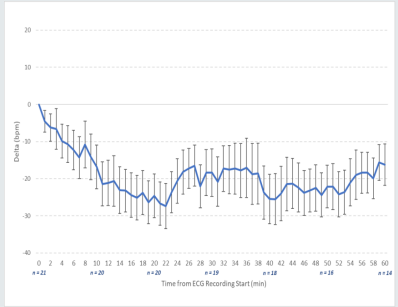
- Tachycardia Heart Rate reduction with drug, shows AV-nodal impact during SVT pre-termination.
- On-set consistent with drug's PK, and rate reduction is sustained for at least 60 min.




**American Heart Association, 2021**

### Patients with AFib-RVR enrolled into SVT Program (NODE-303, Phase 3, open-label trial)

- Ventricular rate reduction shown in AFib-RVR after etripamil self-administration.
- Timing on-set is consistent with drug's PK, and rate reduction is sustained for at least 60 min.




**Heart Rhythm Society, May 2023**

### Patients with AFib-RVR administered etripamil in emergency department presentation

ReVeRA, NODE-202, Phase 2 randomized, double-blinded, placebo-controlled trial. Efficacy and Safety of Intranasal Etripamil to Control Ventricular Rates in AFib/RVR

**Top Line Results, Q4, 2023**

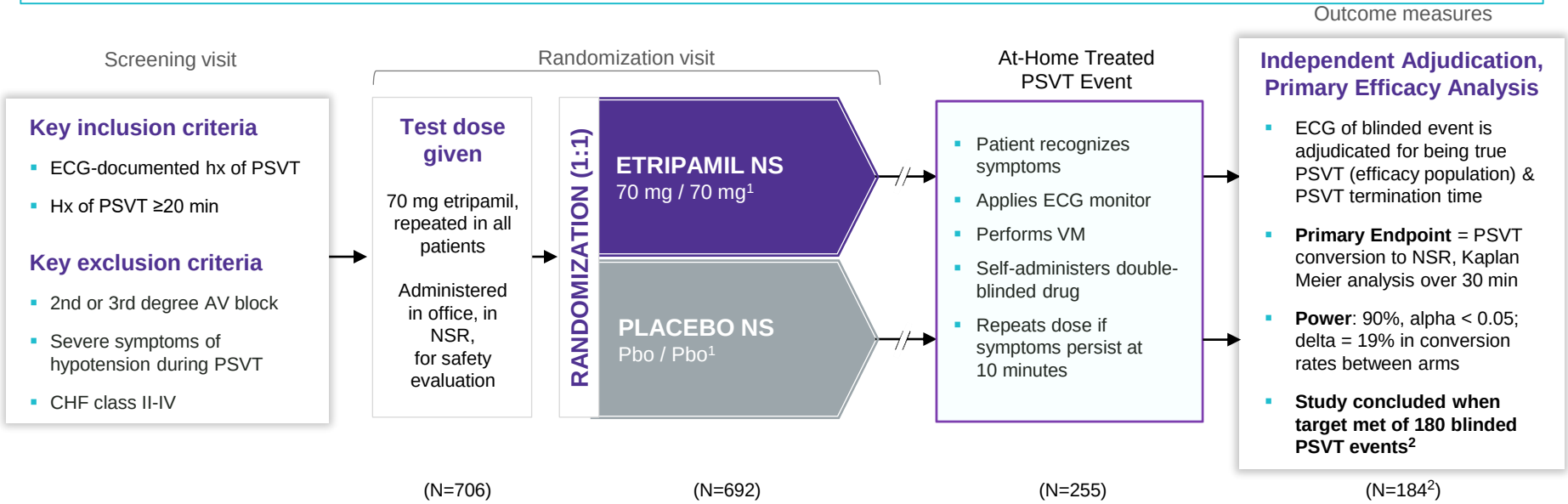
**Utilizing Proof of Concept Data to Design Pivotal AFib-RVR Study**

# Phase 3 PSVT Program – Additional detail

- RAPID – additional details
- NODE-301
- NODE-302

# Phase 3 RAPID Clinical Study Design & Enrollment

**Objective:** Evaluate the efficacy & safety of self-administered etripamil nasal spray in patients experiencing a PSVT episode in the at-home setting




[1] Repeat dose of study drug self-administered if PSVT episode does not resolve within 10 minutes after first dose. Of the patients in the RAPID Study who had the repeat dose regimen available to them, 66% of etripamil arm and 79% of placebo arm took a repeat dose of study drug. [2] Includes 29 events treated with one dose of double-blind study drug administration in NODE-301 Part 1, patients with events after that study met its target event goal & had database lock; all blinds maintained. Hx = history; CHF = congestive heart failure; NSR = normal sinus rhythm; VM = vagal maneuver; NS = nasal spray

Ref.: Stambler, BS et al. Rationale for & design of a multicenter placebo-control, phase 3 study to assess efficacy and safety of intranasal etripamil for the conversion of PSVT. *Amer Heart J* (2022).

# RAPID Safety – Direct ECG Reading[1]

| | Placebo Randomized Dose[2] N=120 | Etripamil Randomized Dose[2] N=135 |
|---|---|---|
| Non-sustained ventricular tachycardia[3] | 19 (16.4) | 18 (14.1) |
| Sustained ventricular tachycardia (≥ 30 seconds) | 1 (0.9)[4] | 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) |
| 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] Independent cardiac-electrophysiologist adjudication committee evaluated all ECG recordings in the Safety Population. All adjudication performed blinded to treatment assignment.

[2] Safety Population, based on 5-hour ECG recordings beginning prior to double-blind drug dosing. [3] No dizziness reported in these patients. [4] 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.

# 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 of any RTEAE, n' (%) of subjects with any RTEAE | | |
| 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: Frequent PVCs and couplets after PSVT termination; non-sustained VT after PSVT termination; allergic reaction, treated with oral Benadryl.

TEAE timing – up to 24 hours following drug administration. TEAE = treatment-emergent adverse event; RTEAE = randomized-period TEAE; SAE = serious adverse event; AE = adverse event; PVC = premature ventricular complex; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia.

Source: Milestone Pharmaceuticals Data on File

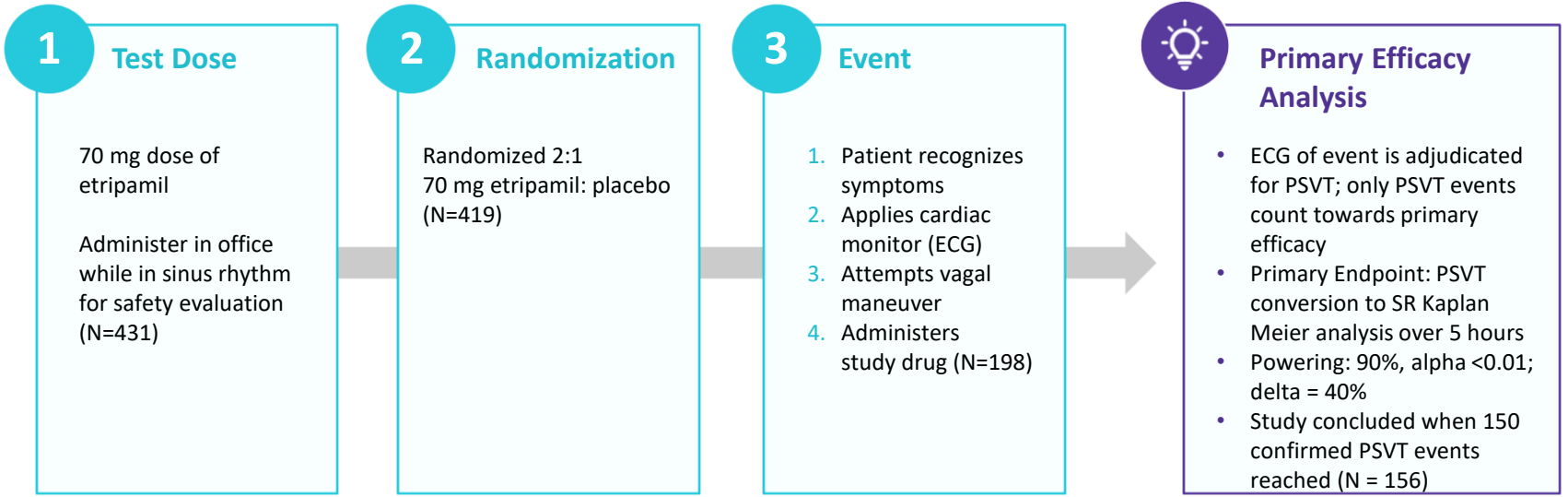
# RAPID Safety – Adverse Events

| 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 = treatment-emergent adverse event. TEAE timing – up to 24 hours following drug administration.

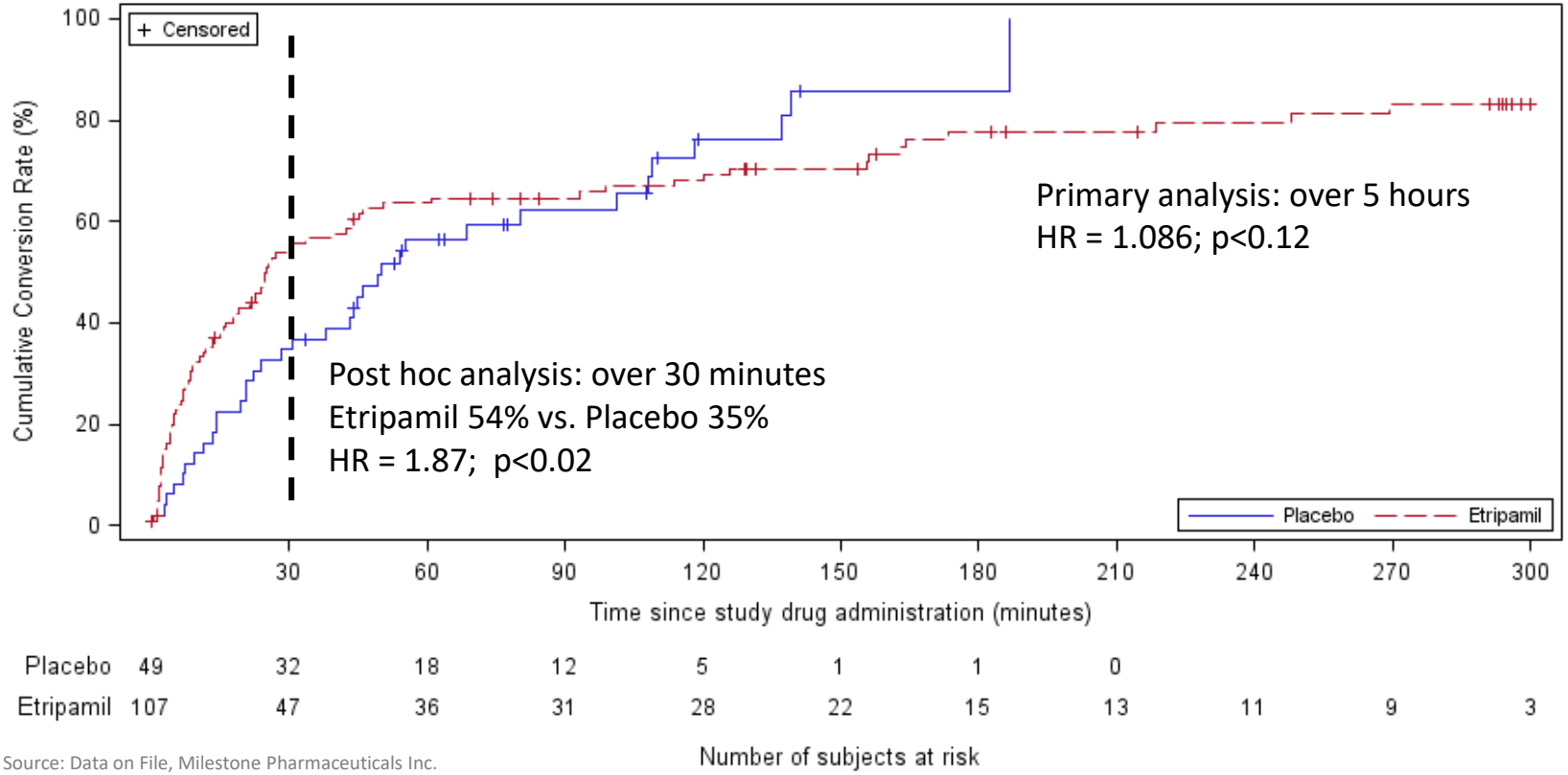
*Source: Milestone Pharmaceuticals Data on File0*

# NODE-301 Study Design



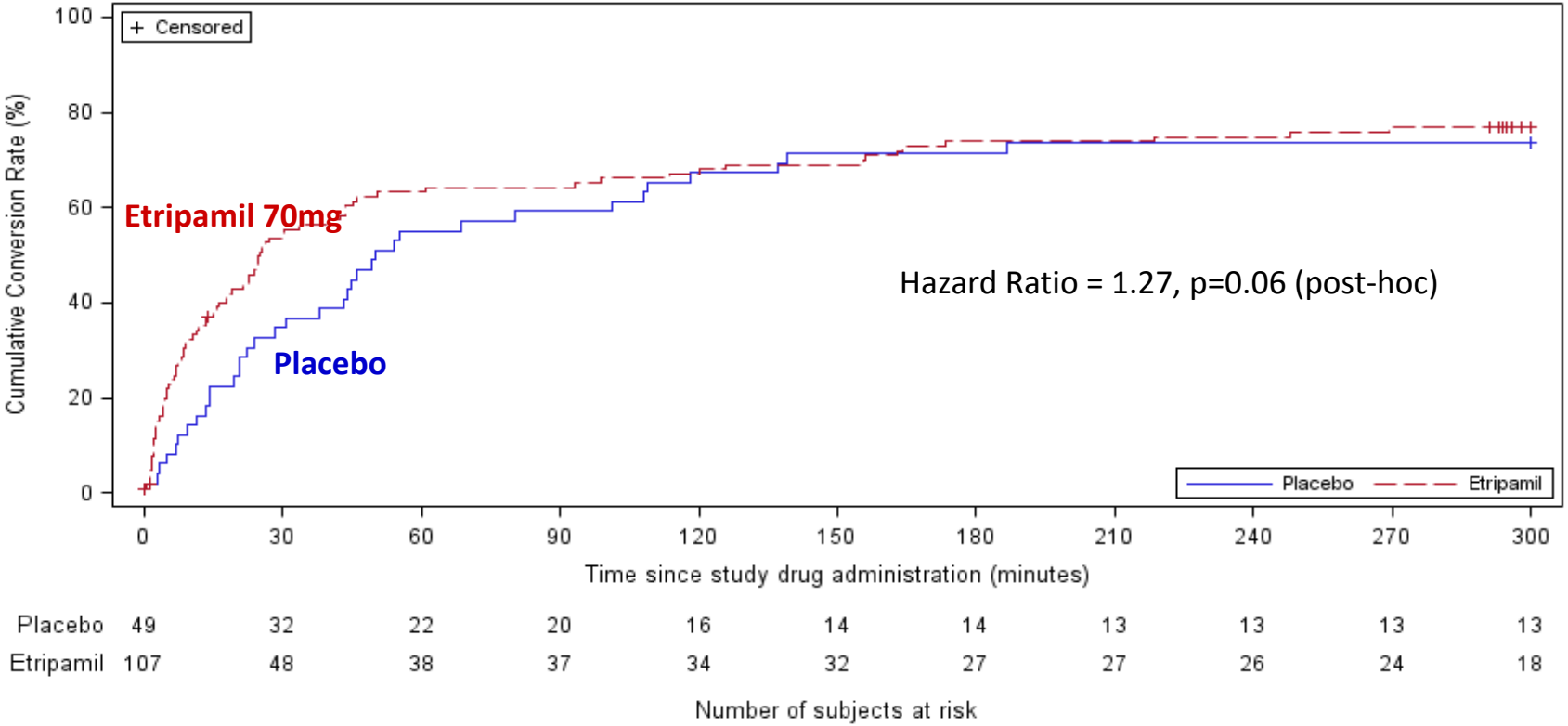

SR = Sinus Rhythm; ECG = Electrocardiogram; PSVT = paroxysmal supraventricular tachycardia

# NODE-301 Kaplan-Meier Plot of Conversion to Sinus Rhythm



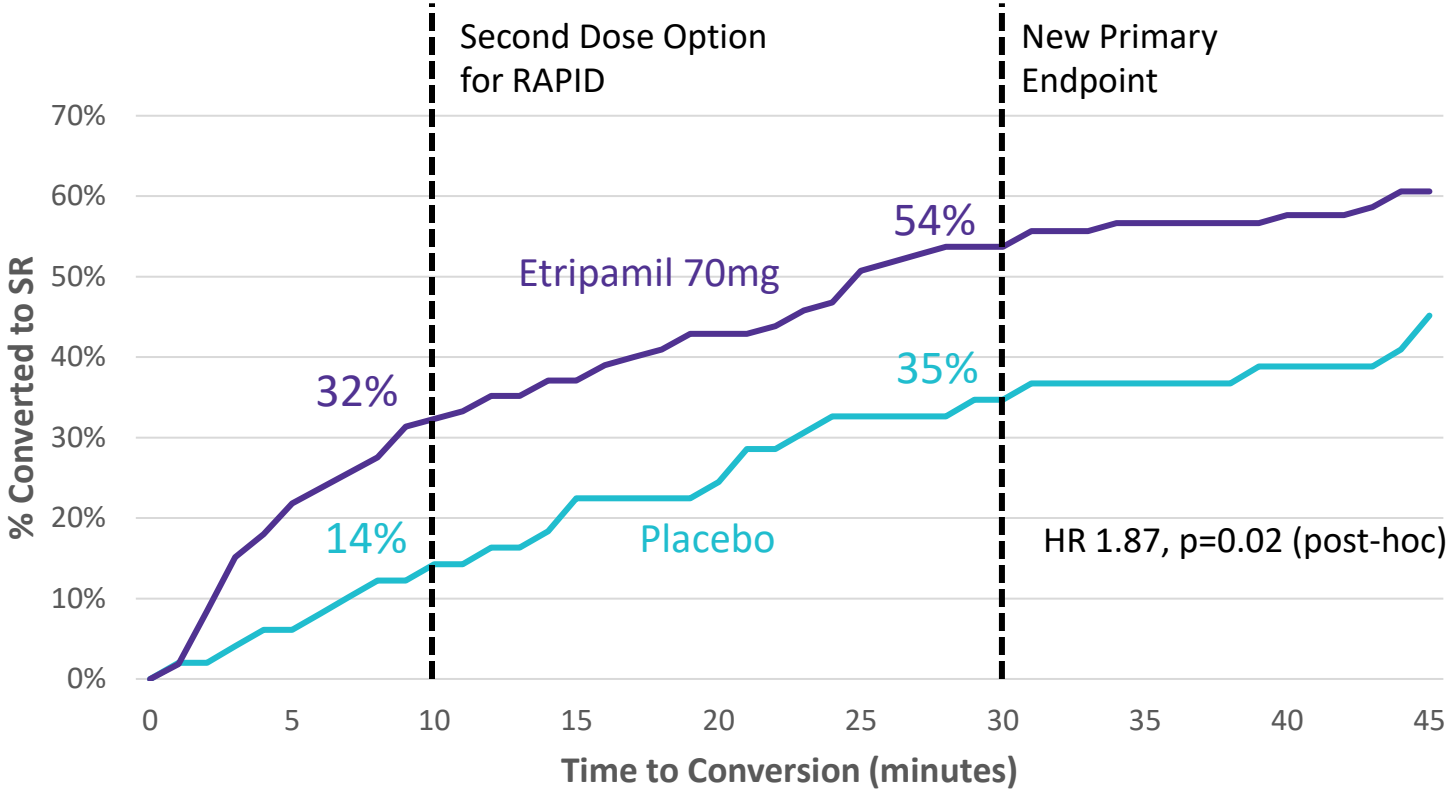

Source: Data on File, Milestone Pharmaceuticals Inc.

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



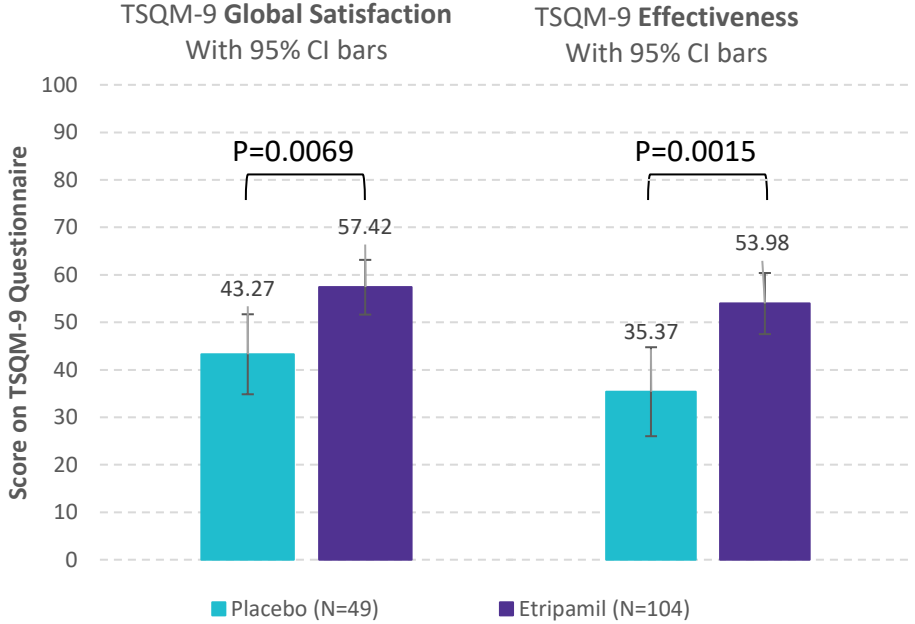

Subjects who convert following medical assistance are censored at 5 hours. Subjects who present missing data from time t to the end are censored at the time of last available data. Subjects who do not convert or are not censored before 5 hours are censored at 5 hours

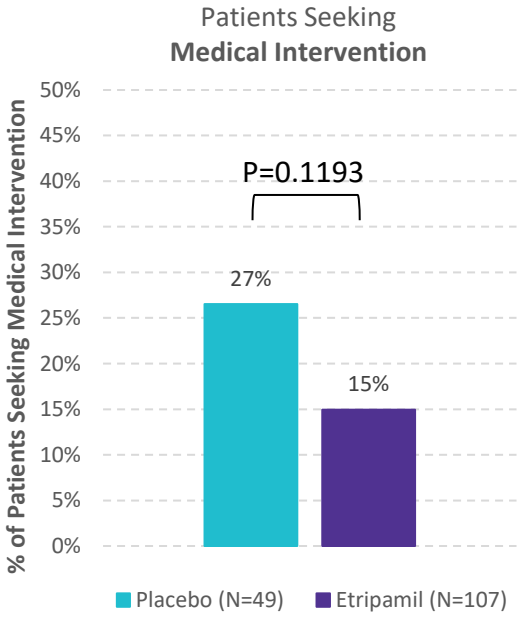
# NODE-301 Efficacy – Time to Conversion over 45 Minutes



# 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) |
| **Most Common Adverse Events (>5%)** | | |
| **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) |

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 (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) |

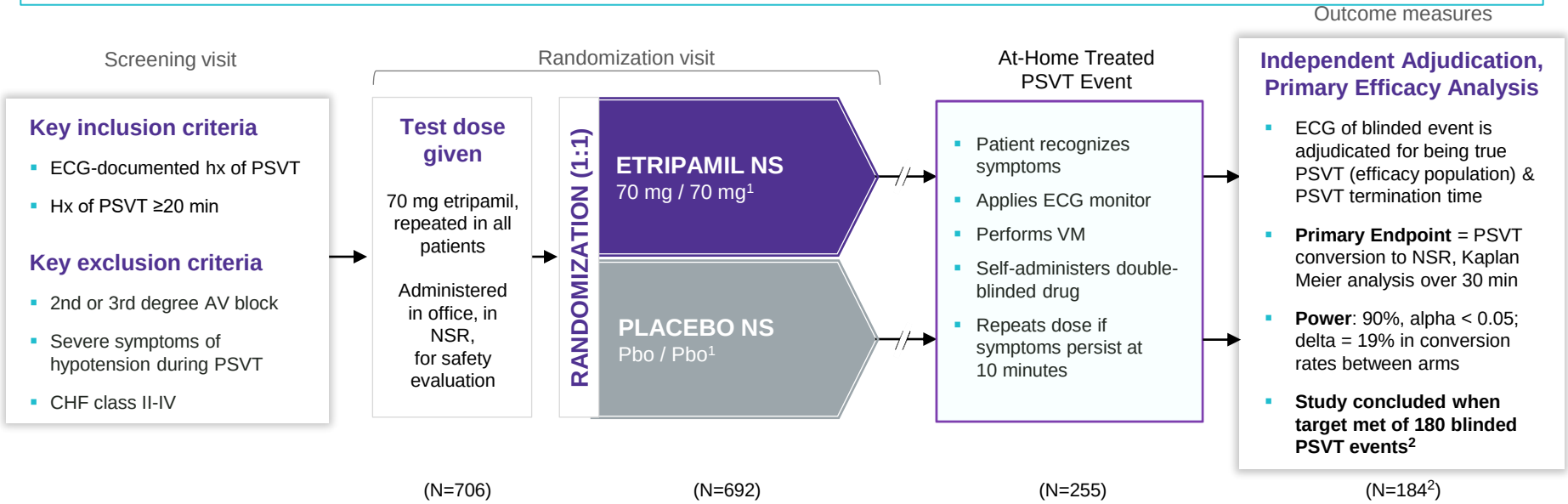
Stambler, BS et al; Etripamil Nasal Spray for Acute Termination of Spontaneous Episodes of PSVT (NODE-301); Heart Rhythm Society Late Breaking Clinical Trails Randomized Trials D-LBCT01; Presented Online May 8, 2020

Milestone PHARMACEUTICALS

# RAPID Detailed Slides

# Phase 3 RAPID Clinical Study Design & Enrollment

**Objective:** Evaluate the efficacy & safety of self-administered etripamil nasal spray in patients experiencing a PSVT episode in the at-home setting



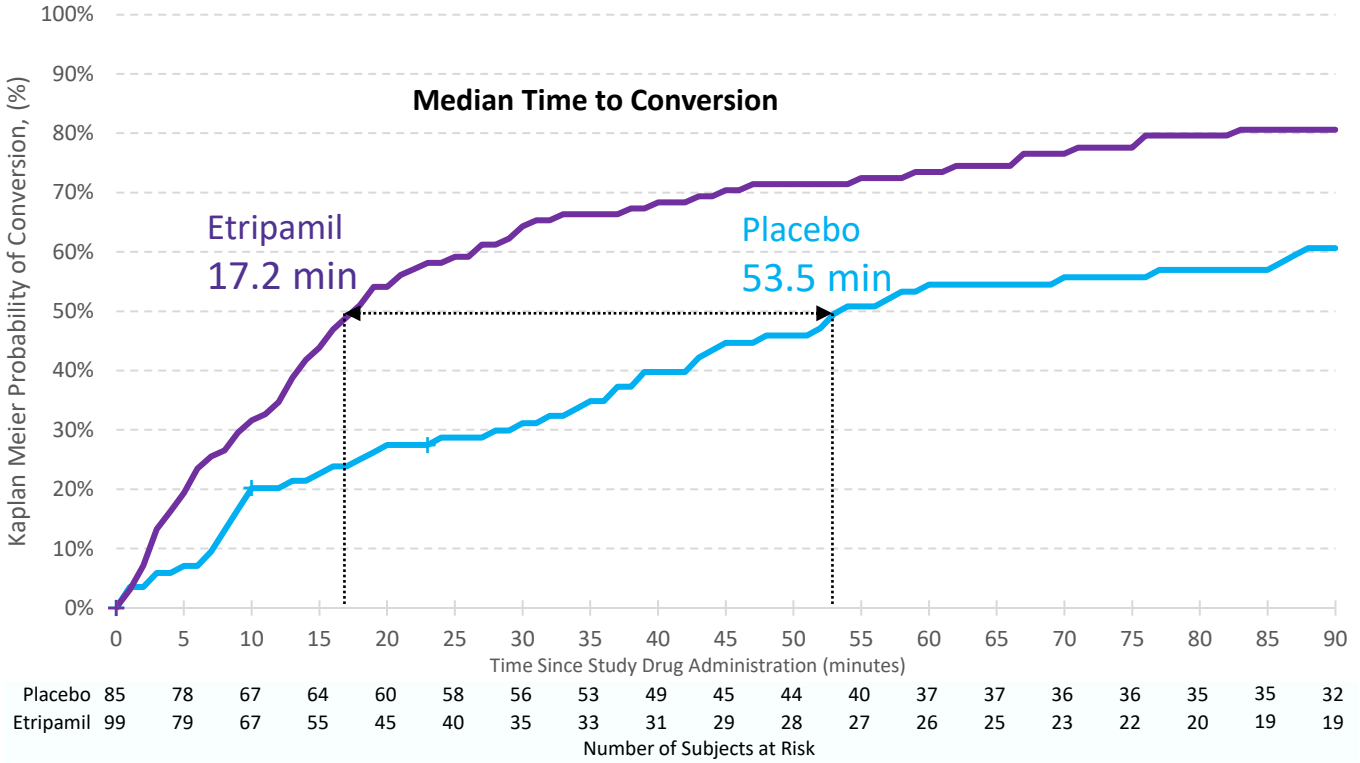

[1] Repeat dose of study drug self-administered if PSVT episode does not resolve within 10 minutes after first dose. Of the patients in the RAPID Study who had the repeat dose regimen available to them, 66% of etripamil arm and 79% of placebo arm took a repeat dose of study drug. [2] Includes 29 events treated with one dose of double-blind study drug administration in NODE-301 Part 1, patients with events after that study met its target event goal & had database lock; all blinds maintained. Hx = history; CHF = congestive heart failure; NSR = normal sinus rhythm; VM = vagal maneuver; NS = nasal spray

Ref.: Stambler, BS et al. Rationale for & design of a multicenter placebo-control, phase 3 study to assess efficacy and safety of intranasal etripamil for the conversion of PSVT. *Amer Heart J* (2022).

# RAPID 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) |

# RAPID Efficacy




"+" symbol on graph indicates censoring for signal loss (n=4 over 90 minutes)

Source: Milestone Pharmaceuticals Data on File

# 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 of any RTEAE, n' (%) of subjects with any RTEAE | | |
| 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: Frequent PVCs and couplets after PSVT termination; non-sustained VT after PSVT termination; allergic reaction, treated with oral Benadryl.

TEAE timing – up to 24 hours following drug administration. TEAE = treatment-emergent adverse event; RTEAE = randomized-period TEAE; SAE = serious adverse event; AE = adverse event; PVC = premature ventricular complex; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia.

Source: Milestone Pharmaceuticals Data on File

# 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 = treatment-emergent adverse event. TEAE timing – up to 24 hours following drug administration.

Source: Milestone Pharmaceuticals Data on File

# Conversion Rates from PSVT to Normal Rhythm (all studies)

| R&D Phase, Study | Etripamil, 70 mg (% Conversion) | Placebo (% Conversion) | Hazard Ratio | p value | Statistical Analysis Notes |
|---|---|---|---|---|---|
| Phase 3 RAPID | 64 | 31 | 2.62 | <0.001 | Kaplan Meier analysis through 30 min |
| Phase 3 NODE-301 | 54 | 35 | 1.87 | <0.02 | Kaplan Meier analysis through 30 min, post-hoc |
| Phase 3 NODE-302 | 60 | – | – | – | Kaplan Meier analysis through 30 min |
| Phase 2 NODE-1 | 87 | 35 | – | 0.0006 | Landmark analysis at 15 min |

Source: Milestone Pharmaceuticals Data on File