Milestone PHARMACEUTICALS

Virtual Key Opinion Leader Event

Etripamil for the Treatment of PSVT

April 21, 2022

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Participants on Today's Call

Joseph Oliveto
President and Chief Executive Officer

Amit Hasija
Chief Financial Officer and Executive Vice President of Corporate Development

Lorenz Muller
Chief Commercial Officer

David Bharucha, MD, PhD, FACC
Chief Medical Officer

Francis Plat, MD
Chief Scientific Officer

Bruce Stambler, MD, FHRS
Director of Cardiac Arrhythmia Research and Education, Piedmont Heart Institute, Atlanta, GA

Sean Pokorney, MD, MBA
Director of the Arrhythmia Core Laboratory, Duke Clinical Research Institute, Assistant Professor of Medicine, Duke University School of Medicine, Durham, NC

Today's Agenda

Brief Introduction and Patient Video	Amit Hasija	CFO & EVP of Corporate Development
PSVT - Overview and Etripamil Characterization and Data	Bruce Stambler, MD, FHRS	Director of Cardiac Arrhythmia Research and Education, Piedmont Heart Institute, Atlanta, GA
Etripamil - Development Plans Moving Forward	Joseph Oliveto	President & CEO
PSVT – Burden of Disease	Sean Pokorney, MD, MBA	Director of the Arrhythmia Core Laboratory, Duke Clinical Research Institute, Assistant Professor of Medicine, Duke University School of Medicine, Durham, NC
Etripamil - Commercial Opportunity	Lorenz Muller	Chief Commercial Officer
Q&A		

Milestone (Nasdaq: MIST) - Corporate Highlights

Phase 3 Cardiovascular Company

Targeting Large Areas of Unmet Need

- PSVT
- AFib-RVR
- Additional pipeline opportunities

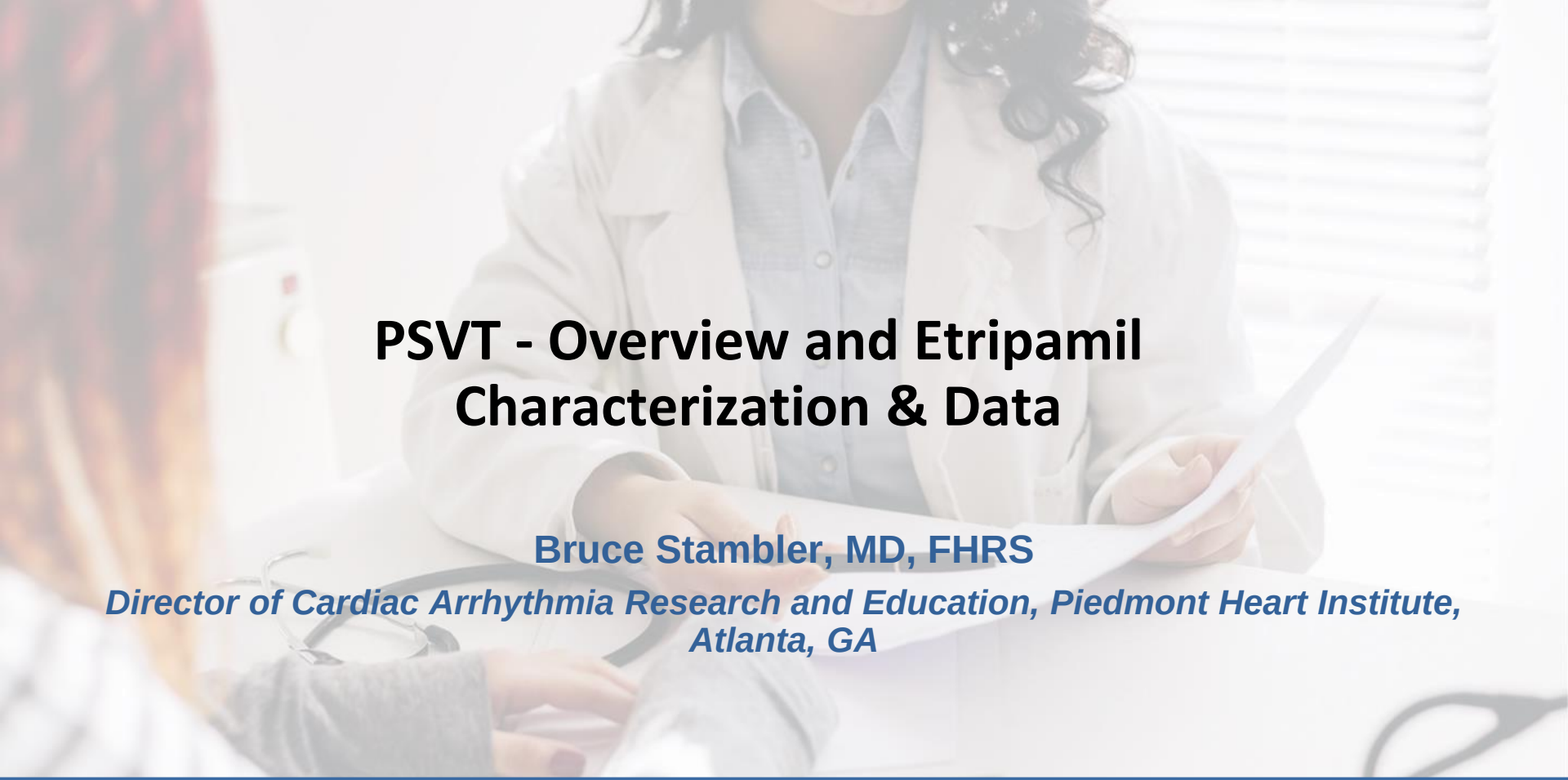
Paradigm-Changing Approach

- Etripamil: novel calcium channel blocker (IP protection until 2036)
- Shift from the ED to patient self-management

Recent Events Position for Future Success

- First Phase 3 study findings and FDA guidance in PSVT
- Next Pivotal Phase 3 efficacy result in PSVT expected by 2H 2022
- Financial runway expected into 2H 2023

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



PSVT - Overview and Etripamil Characterization & Data

Bruce Stambler, MD, FHRS

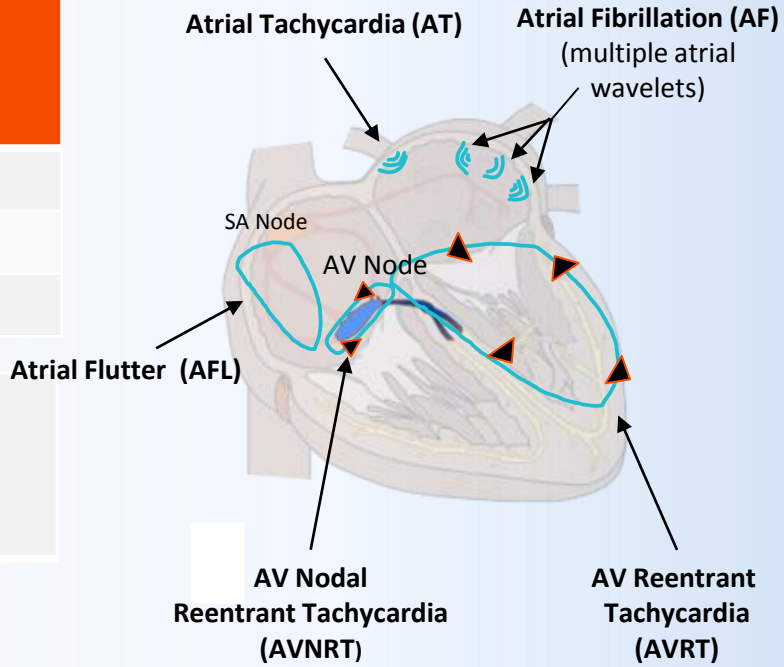
Director of Cardiac Arrhythmia Research and Education, Piedmont Heart Institute, Atlanta, GA

Supraventricular Tachycardia (SVT)

Patients with SVT report impaired quality of life and feeling a loss of control of their health

Paroxysmal Supraventricular Tachycardia (PSVT)	Atrial Fibrillation (AF)
Regular rapid heart rate	Irregular rapid heart rate
Commonly 150 - 250 bpm	Commonly 100 - 175 bpm (RVR)
Episode frequency and duration are highly variable	

Common Symptoms Include		
	Palpitations	Chest pain
	Shortness of breath	Fatigue
	Light-headedness	Anxiety



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

Current Treatment Paradigm for PSVT

How do we typically manage these patients and unmet needs?

Long-term Management Strategies:

- No treatment: "watch and wait" for recurrent episodes, as per patient acceptance
- Chronic oral medications to prevent an episodic condition
  - Calcium channel blockers
  - Beta blockers
  - Antiarrhythmic drugs
- Catheter ablation

Acute PSVT Therapy for Episodes:

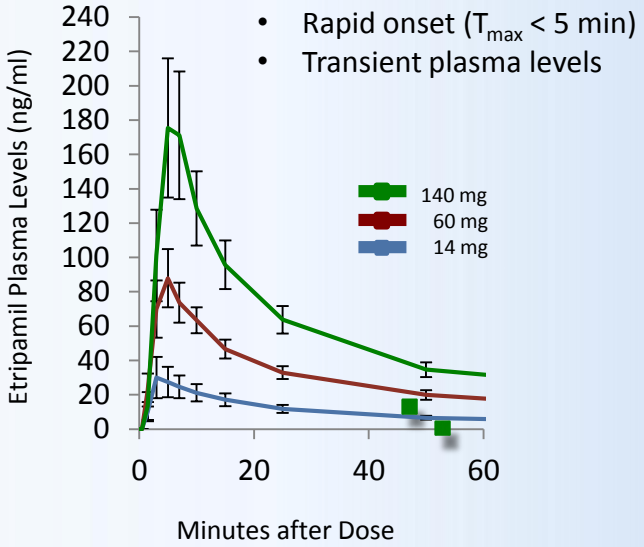
- Vagal maneuver
- Pill in pocket therapy:
  - Try an oral beta blocker or calcium channel blocker medication and wait
- Go to emergency room or urgent care for intravenous therapy (eg, intravenous adenosine, other Rx, or procedure)

Etripamil Nasal Spray is Designed to be Fast, Convenient, and Empowering

Prospectively designed to treat common rapid abnormal heart rhythms outside Emergency Room

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

- Clinically-validated mechanism
  - Calcium channel blockers (CCBs) prolong refractoriness and slow conduction over the AV node
- Rapid onset of action
- Short duration of action
- Convenient on-demand, self-administered nasal spray

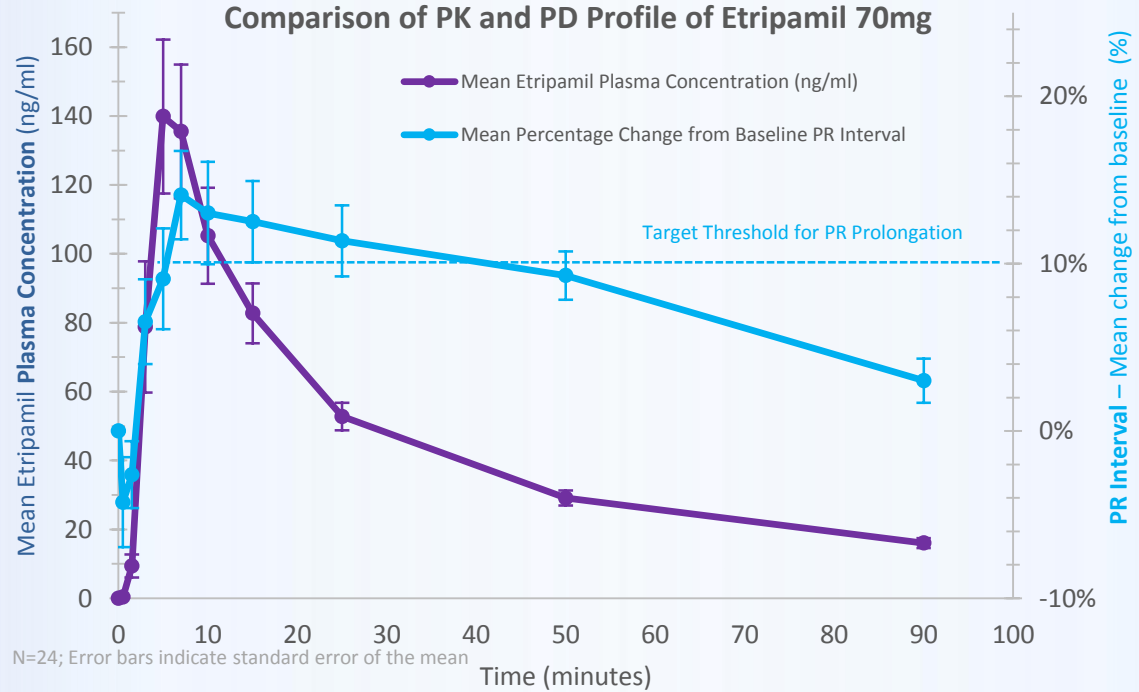


AV = Atrio-ventricular; nM = nanomolar

Error bars indicate standard error of the mean

Phase 1 (NODE-102): Etripamil Nasal Spray Pharmacology

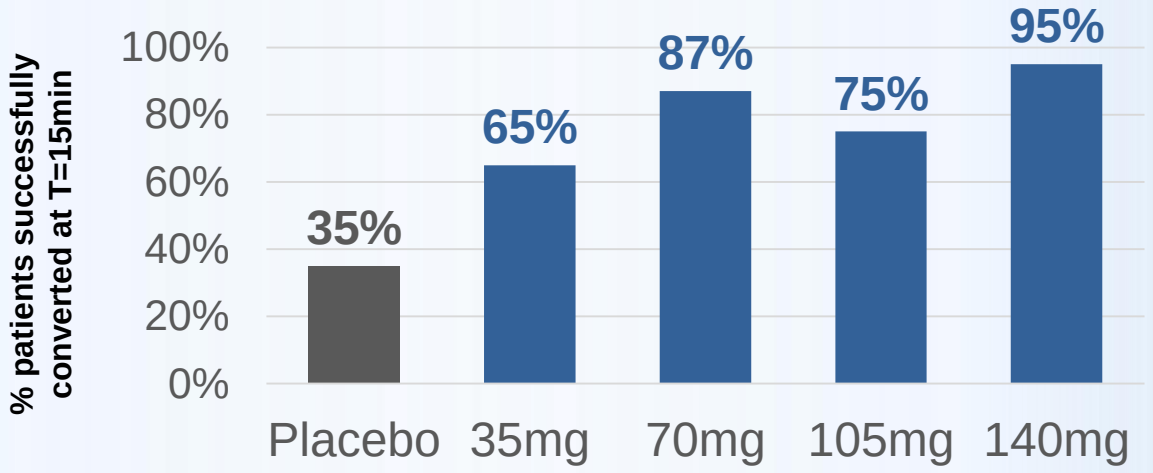
Anticipated therapeutic effect within 45 minutes; peak within 10 minutes



Source: Data on File, Milestone Pharmaceuticals Inc; Berk, et al. Comparison of the pharmacokinetics and electrocardiographic effects of sublingual and intravenous verapamil. Pharmacotherapy. 1992.

Phase 2 Primary Endpoint: Conversion of PSVT Induced in EP lab

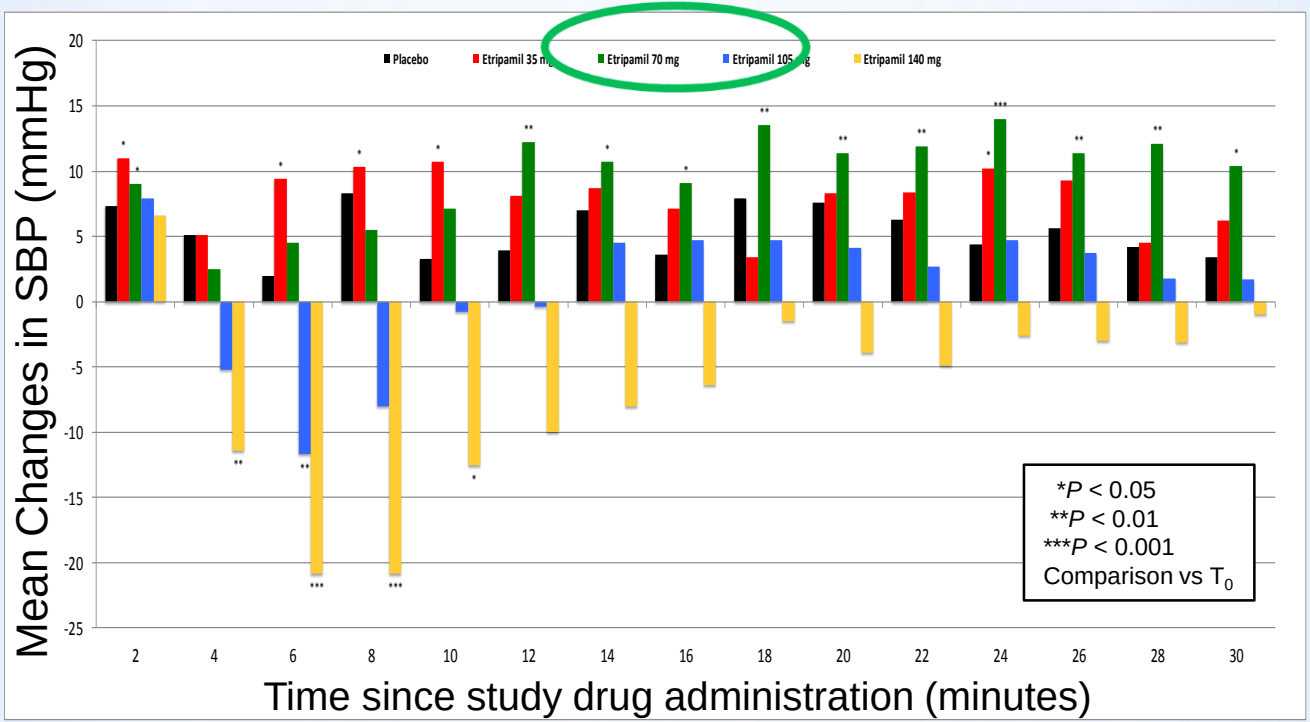
Etripamil three highest doses demonstrated 75-95% conversion rates which were statistically significant compared to placebo



# 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

Systolic Blood Pressure Responses



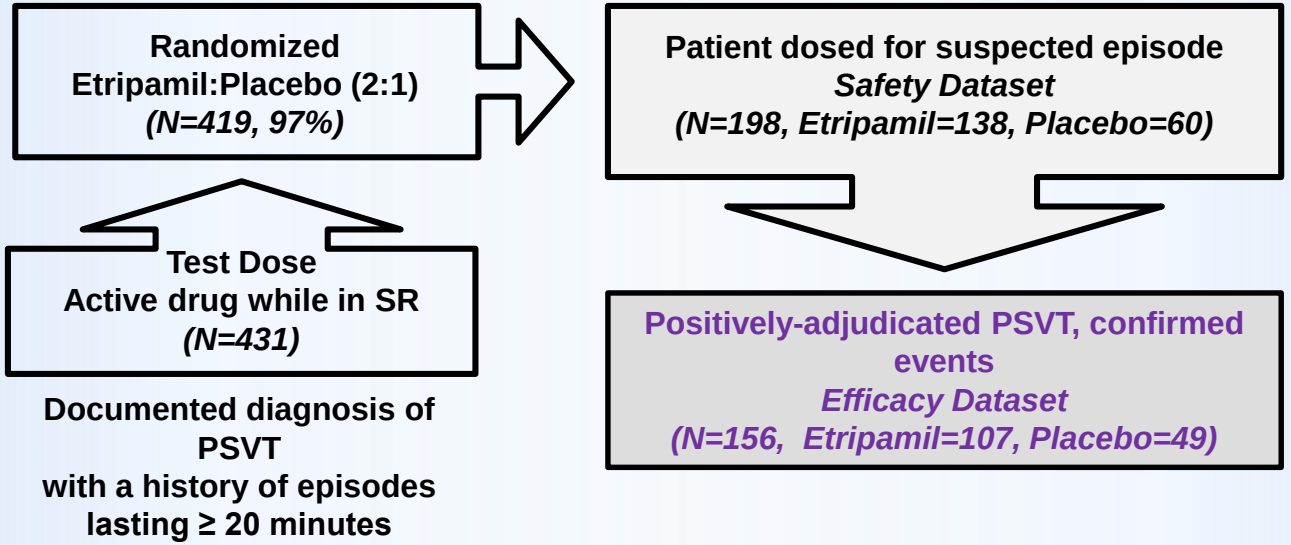
T_0 = subject in SVT

Source: Stambler BS, et al. J Am Coll Cardiol. 2018;72(5):489–497.

Phase 3: Study Design

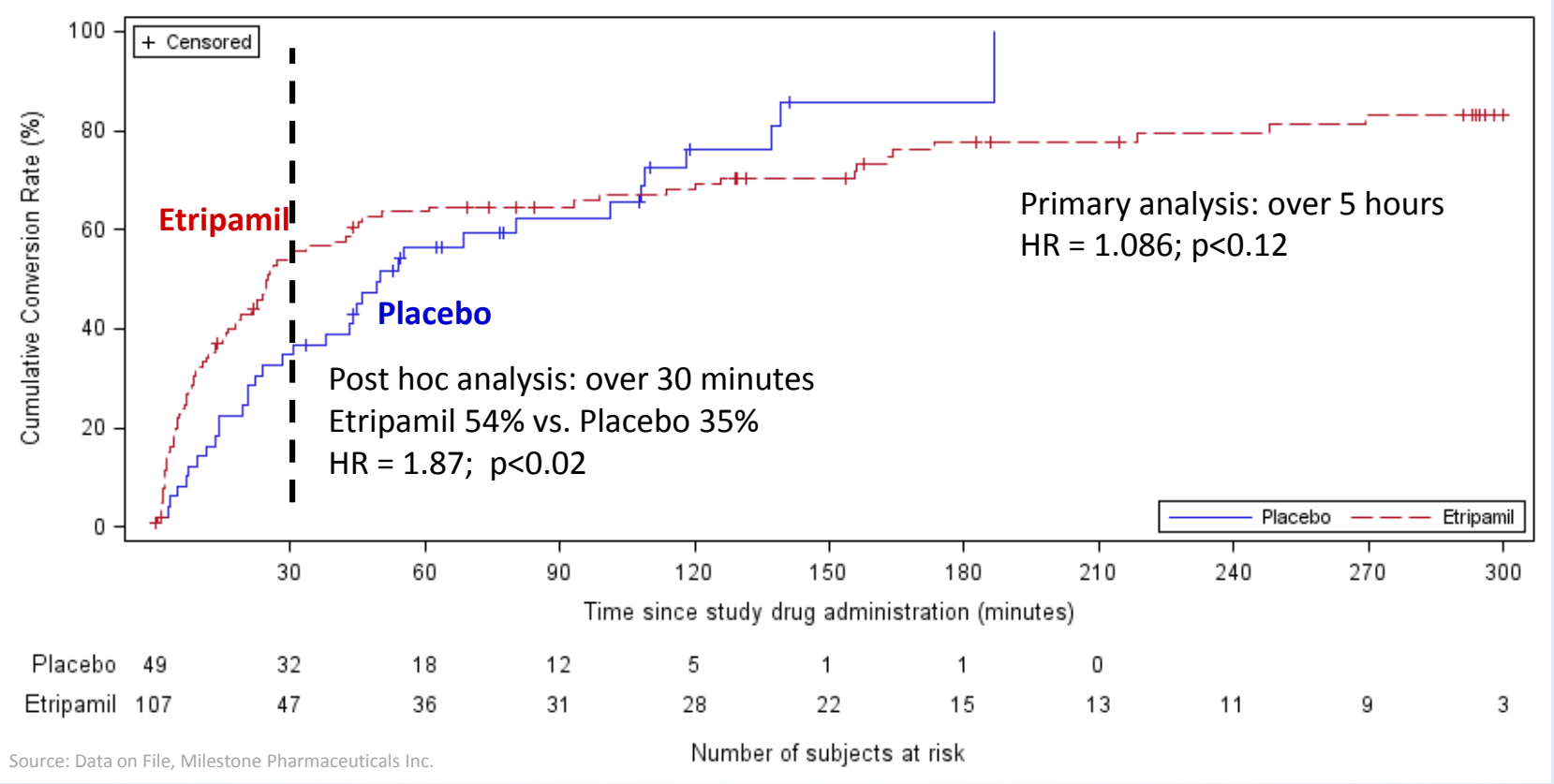
NODE-301
Etripamil Clinical Research in PSVT

Objective: Superiority of self-administered etripamil 70 mg over placebo in terminating PSVT events in a non-medical setting



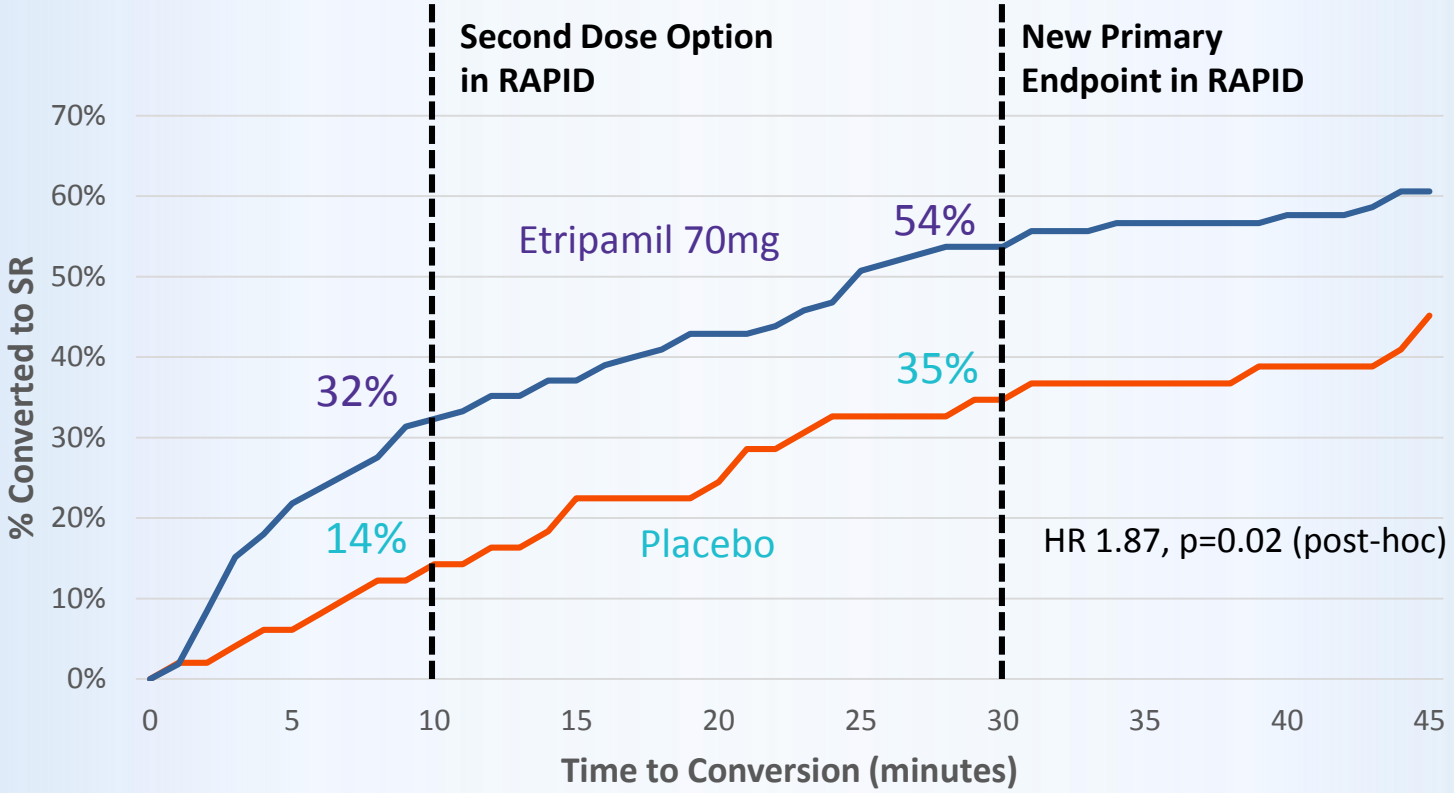
PSVT = Paroxysmal Supraventricular Tachycardia; SR = Sinus Rhythm

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



Source: Data on File, Milestone Pharmaceuticals Inc.

NODE-301 Efficacy – Time to Conversion over 45 Minutes



Source: Data on File, Milestone Pharmaceuticals Inc.

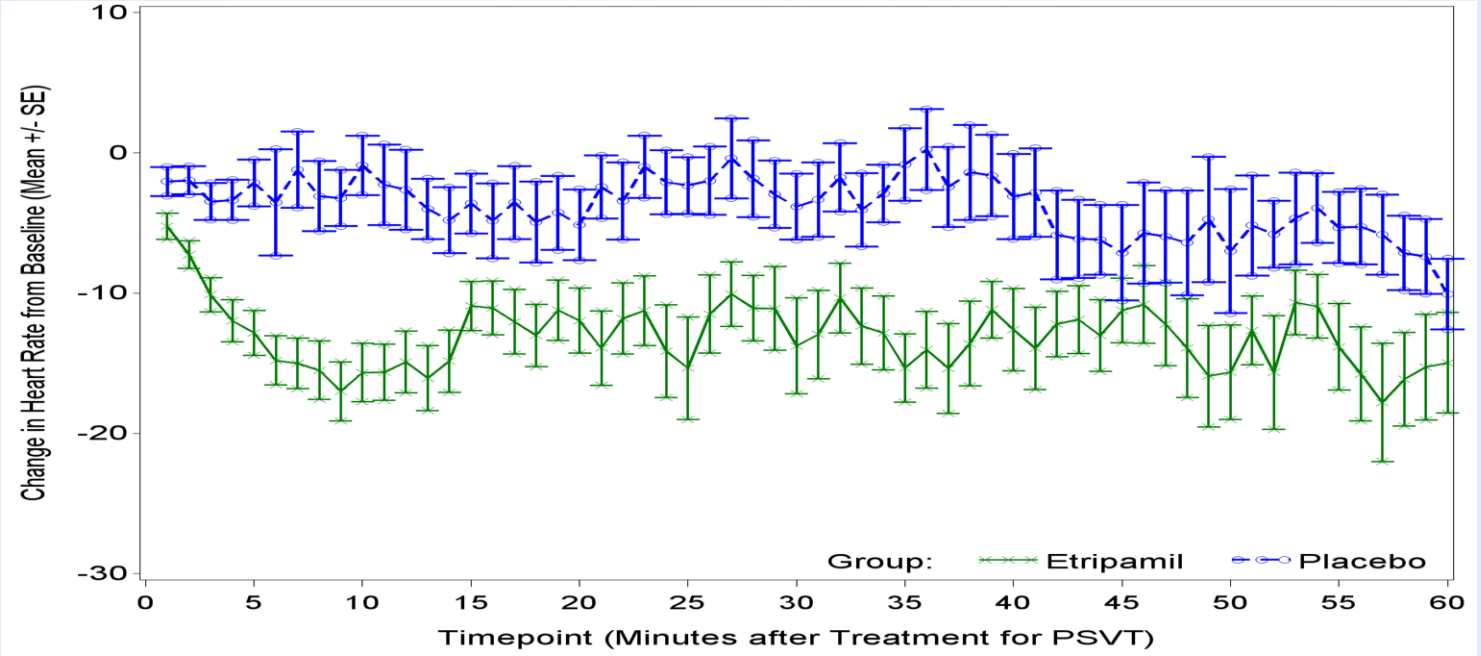
NODE-301: Safety Data Show Etripamil is Well-Tolerated & Safe

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: Effect of Etripamil on Heart Rate (HR) during SVT

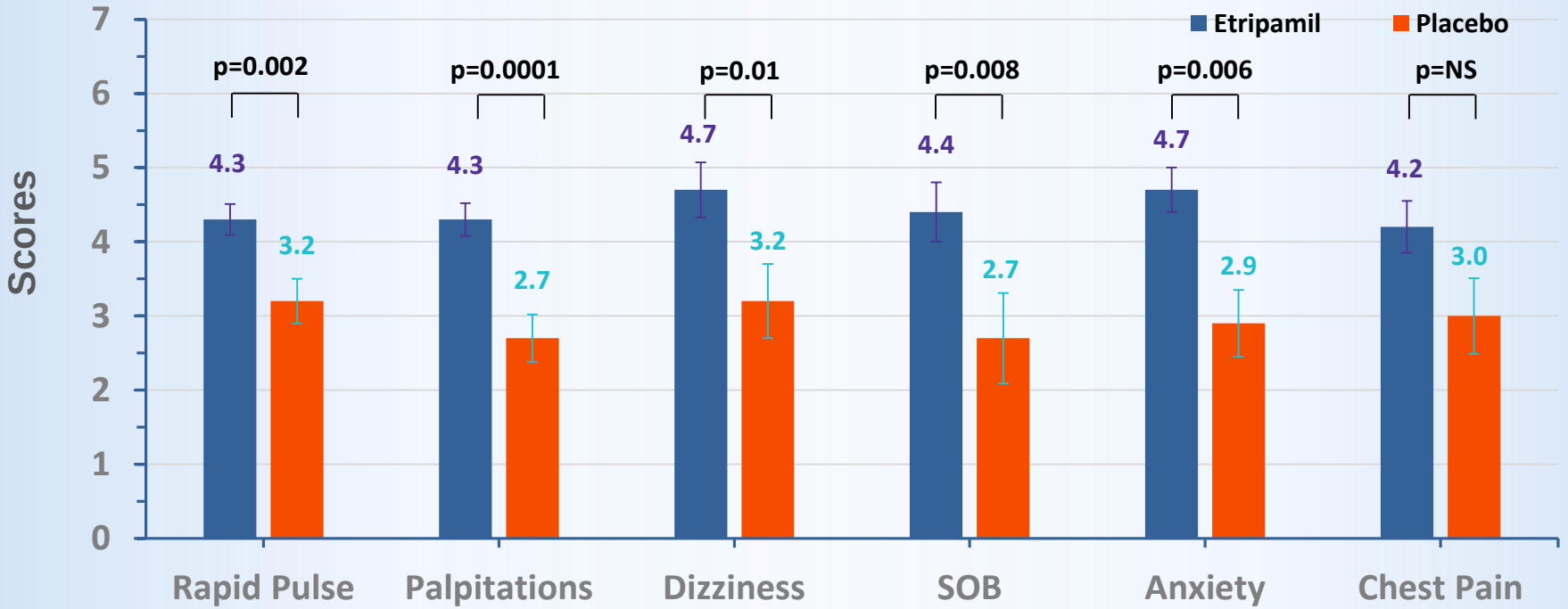


Number of subjects

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

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.

NODE-301: Relief of PSVT Symptoms



Scores: 1 = extremely dissatisfied; 2 = very dissatisfied; 3 = dissatisfied; 4 = somewhat satisfied; 5 = satisfied; 6 = very satisfied; 7 = extremely satisfied

Stambler, B. et al, Etripamil Nasal Spray Relieves Symptoms and Reduces Emergency Room Interventions in Patients with Paroxysmal Supraventricular Tachycardia (PSVT), late-breaking clinical trials presentation, ACC, 2021

Key Take-aways for Etripamil Nasal Spray Development Program

- AV nodal dependent-PSVT occurs frequently and in all age groups
- PSVT negatively impacts patients' QoL and leads to increased emergency department visits & health-care utilization
- Etripamil Nasal Spray would be a novel addition to the PSVT Rx armamentarium
  - Satisfying an unmet need for a safe, effective and rapidly-acting Rx that can be conveniently self-administered by patients on-demand during PSVT at home
- Etripamil Nasal Spray (Phase 1-3) data demonstrate:
  - Mechanism of action and effects on AVN: targeted PR prolongation and PSVT heart rate reduction
  - Tolerability & safety during at-home, self-administration
  - Rates of PSVT termination in placebo-controlled trials that are clinically meaningful
  - PSVT symptom relief and reduced need for other medical interventions including ED visits
- A current Phase 3 RAPID trial should yield even more definitive data on safety, efficacy, & clinical impact including potential utility of sequential dosing

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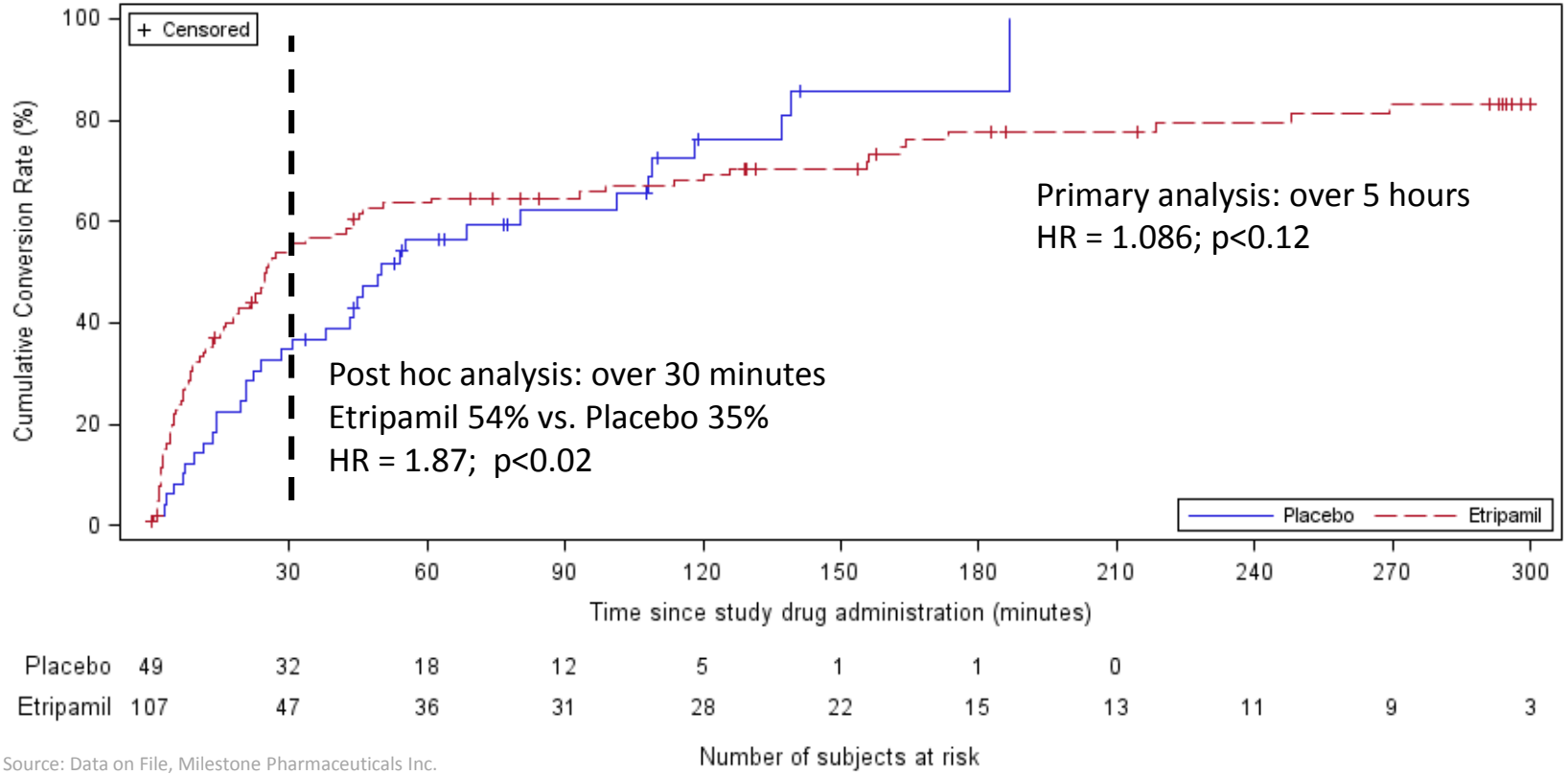
Etripamil – Development Plans Moving Forward

Joseph Oliveto

President & CEO

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



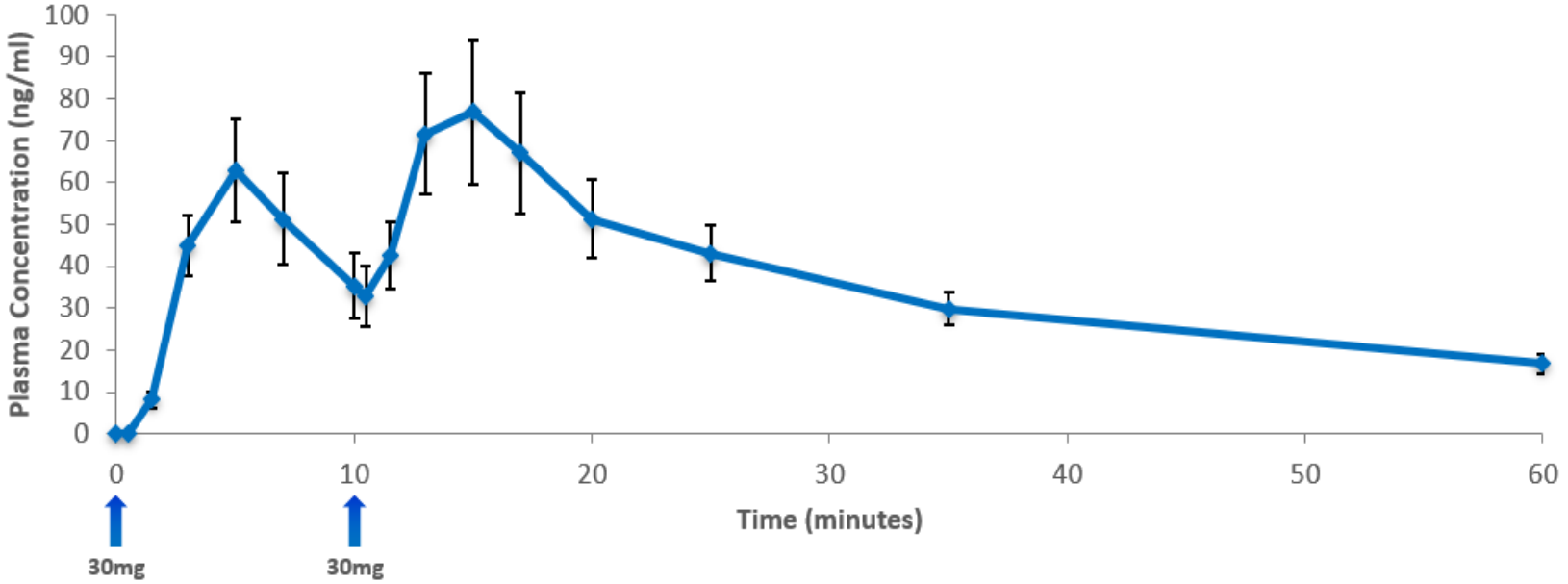
Source: Data on File, Milestone Pharmaceuticals Inc.

FDA Guidance Following NODE-301 Data

- NODE-301 post hoc analysis plus one additional study (RAPID) together can be used to potentially fulfill the efficacy requirement for an NDA filing for etripamil in PSVT
  - Primary analysis of 30-minute observation window
  - RAPID Study target p-value of $p < 0.05$
- Evaluation of higher exposures to improve efficacy and clinical meaningfulness
- RAPID to utilize a 70 mg repeat dosing regimen
  - Patients who still have symptoms 10 min after their drug administration will take a second dose of study drug
  - Pool the single dose with the repeat dose administrations to maintain power and compare etripamil to placebo

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

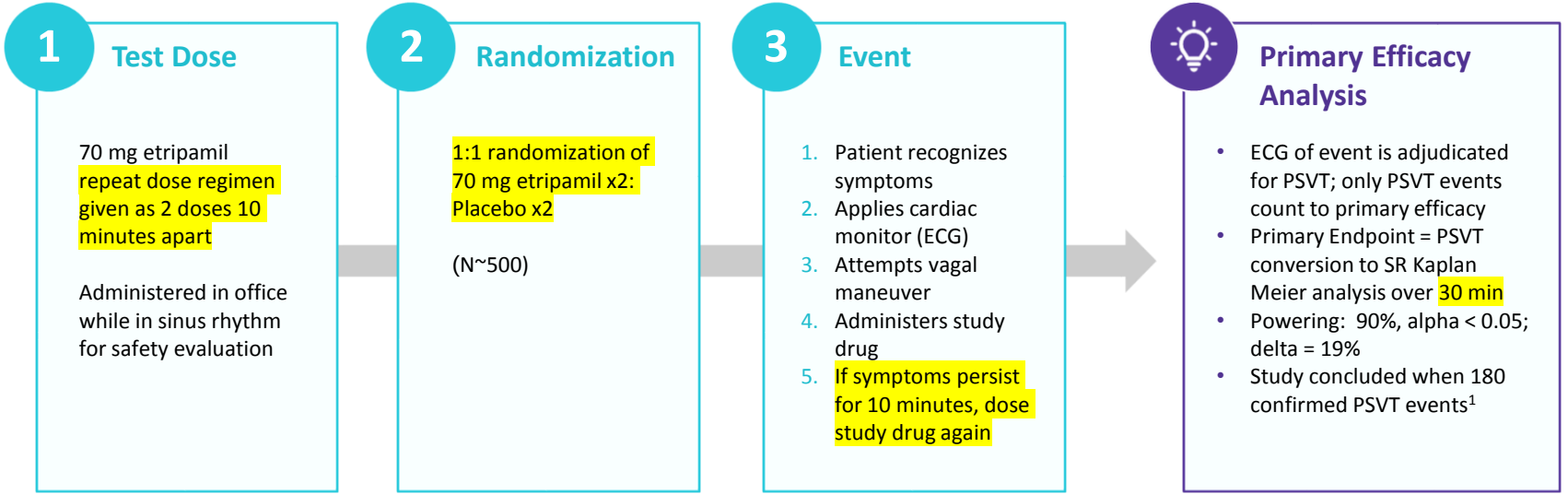
Repeat administration increases both Cmax and AUC



N=7, Error bars are standard error

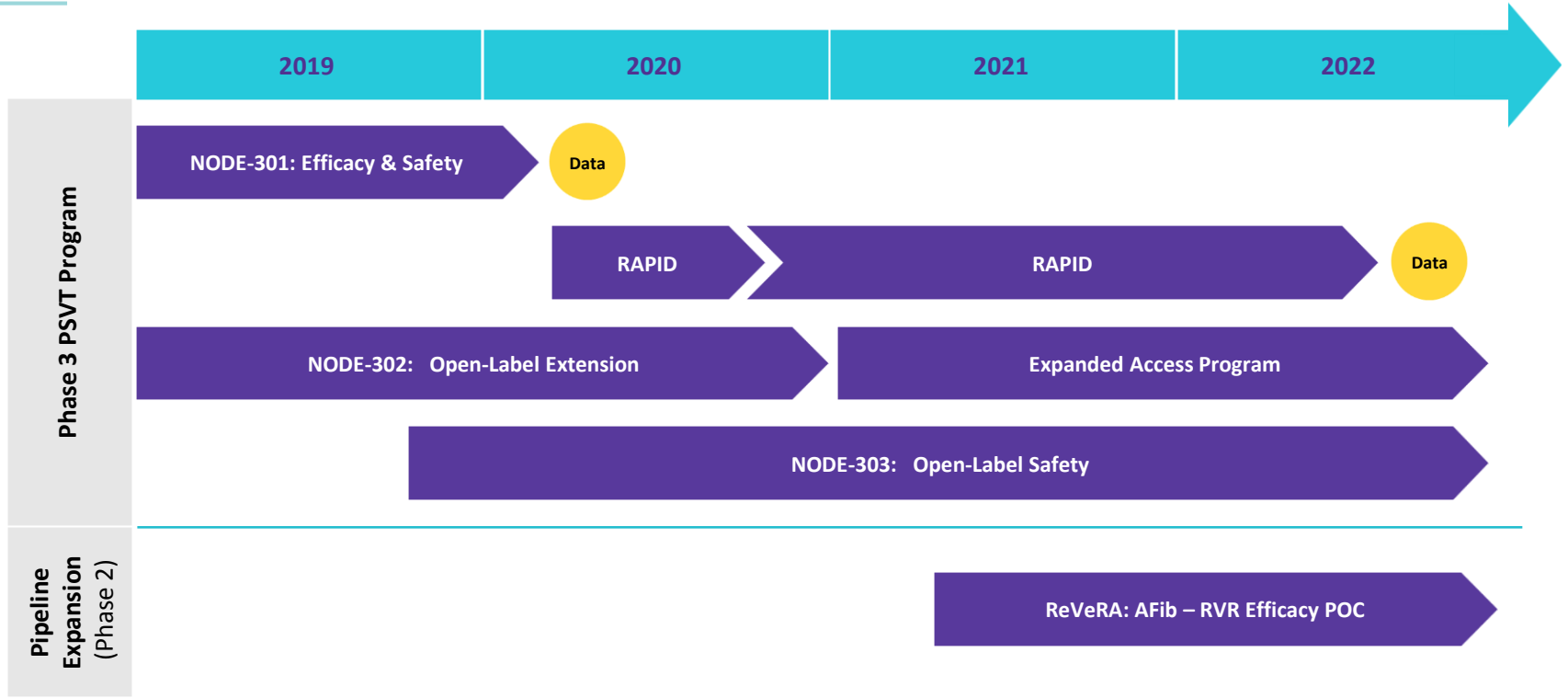
Source: Data on File, Milestone Pharmaceuticals Inc.

RAPID Study Design

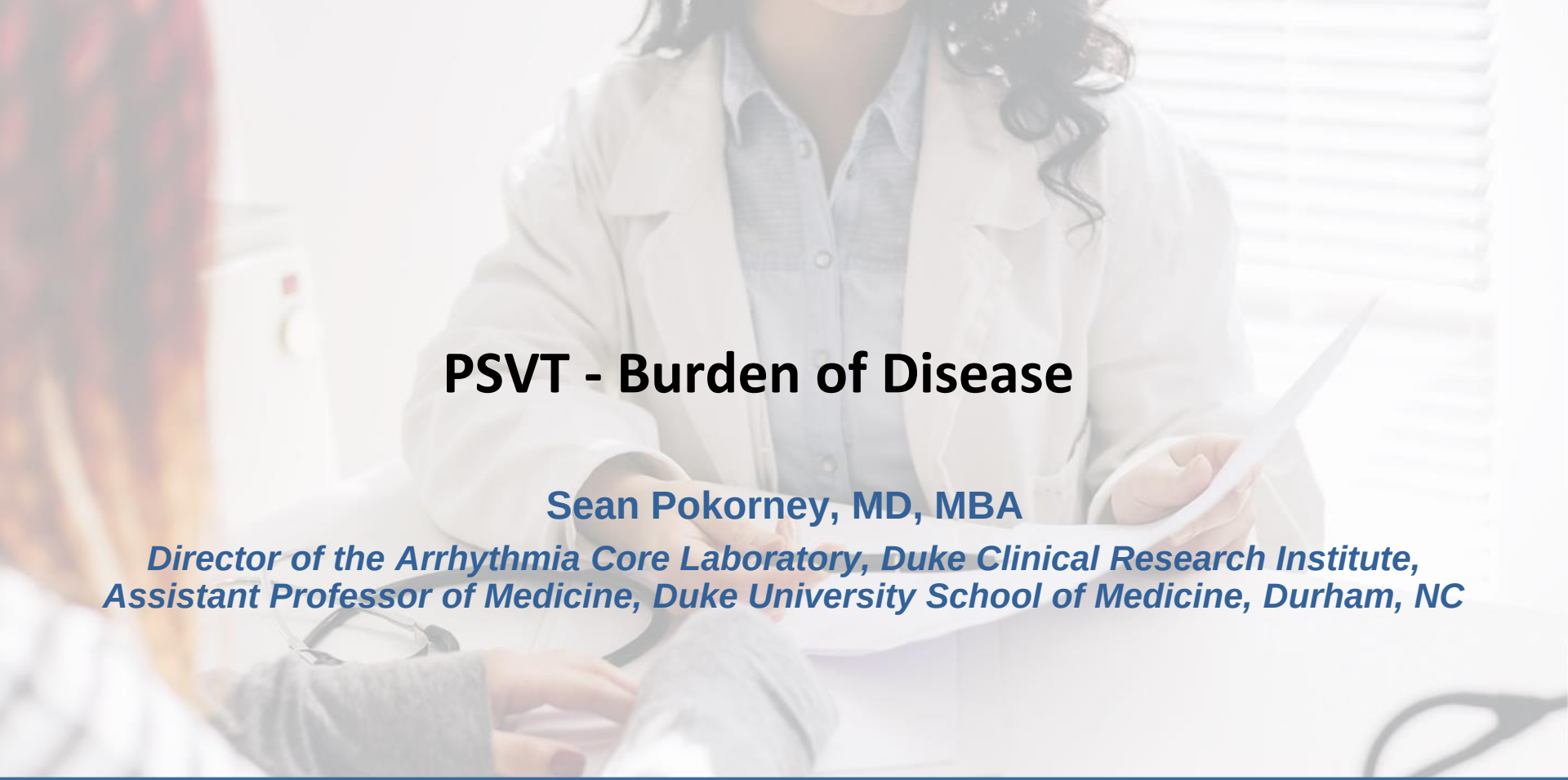


[1] includes ~30 events expected to be treated with the single dose double-blind study drug administration from NODE-301 patients who experienced an event prior to the RAPID study being available

Development Plan for Etripamil



AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; POC = Proof of Concept

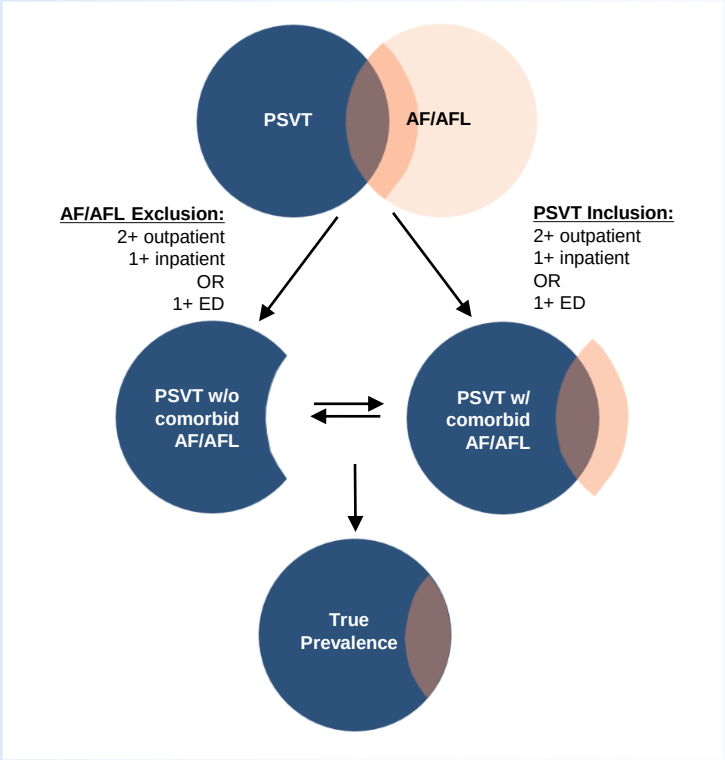


PSVT - Burden of Disease

Sean Pokorney, MD, MBA

Director of the Arrhythmia Core Laboratory, Duke Clinical Research Institute,
Assistant Professor of Medicine, Duke University School of Medicine, Durham, NC

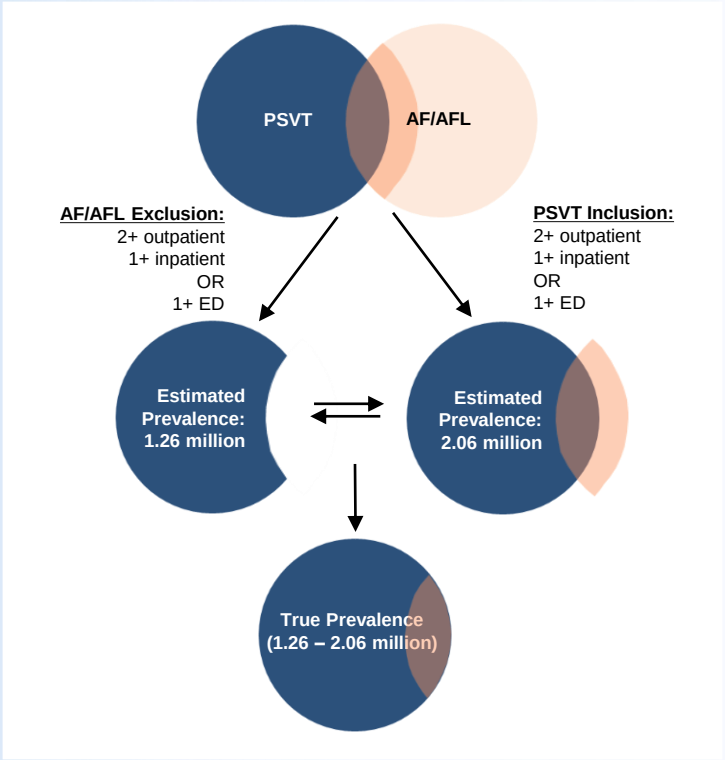
Claims Analyses Provide a Better Approach for Estimating the Prevalence and Incidence of PSVT in the US



- **Literature precedent: MESA and PREEMPT**
- **Analyzed US commercial and Medicare claims data over a 9-year period (5 years of continuous enrollment)**
  - ✓1+ PSVT code required in the ED or inpatient setting
  - ✓2+ PSVT codes required in the outpatient setting *(additional unique patients managed chronically)*

Source: Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, Pokorney SD. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. PMID: 34028109.

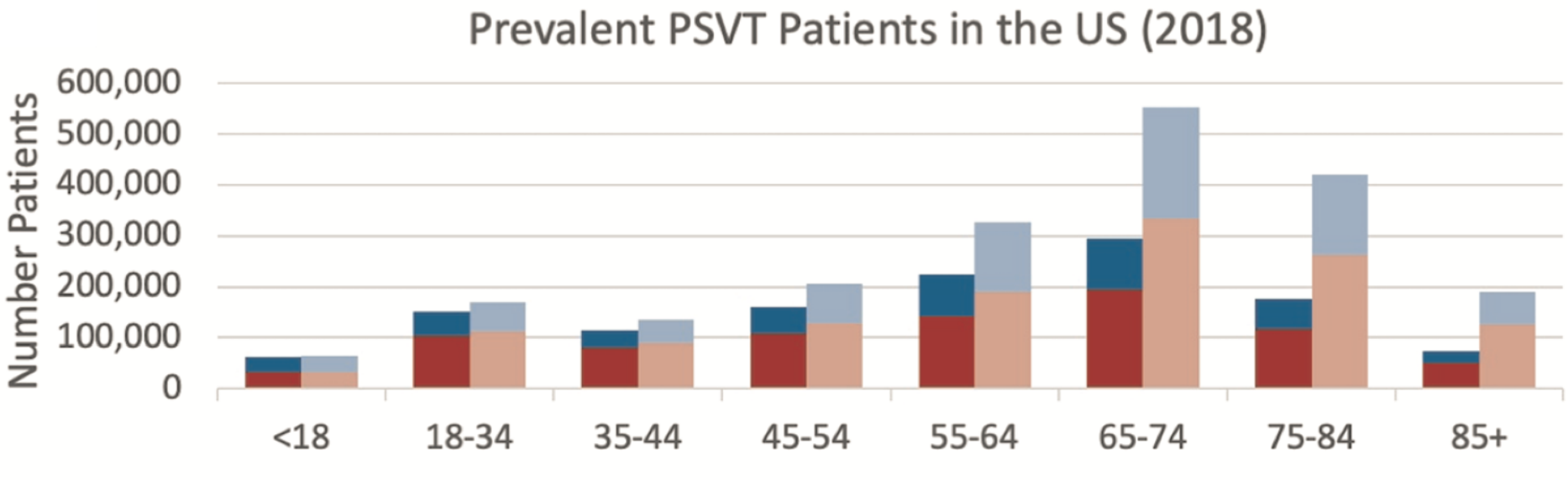
Recent Epidemiology Analyses Suggest a Diagnosed Prevalence of PSVT in the US of 1.3M to 2.1M patients



- **1.3 – 2.1M estimated US prevalence of PSVT**
  - 1.3M: *without* concomitant AF/AFL diagnosis codes
  - 2.1M: *including* concomitant AF/AFL diagnosis codes
- **Excludes patients receiving other diagnosis codes with true PSVT** (e.g., adjudicated in MESA/PREEMPT studies)
  - MESA showed only 39% of adjudicated PSVT had ICD-9 code 427.0

Source: Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, Pokorney SD. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. PMID: 34028109.

PSVT is Prevalent Across Age Ranges and Sex

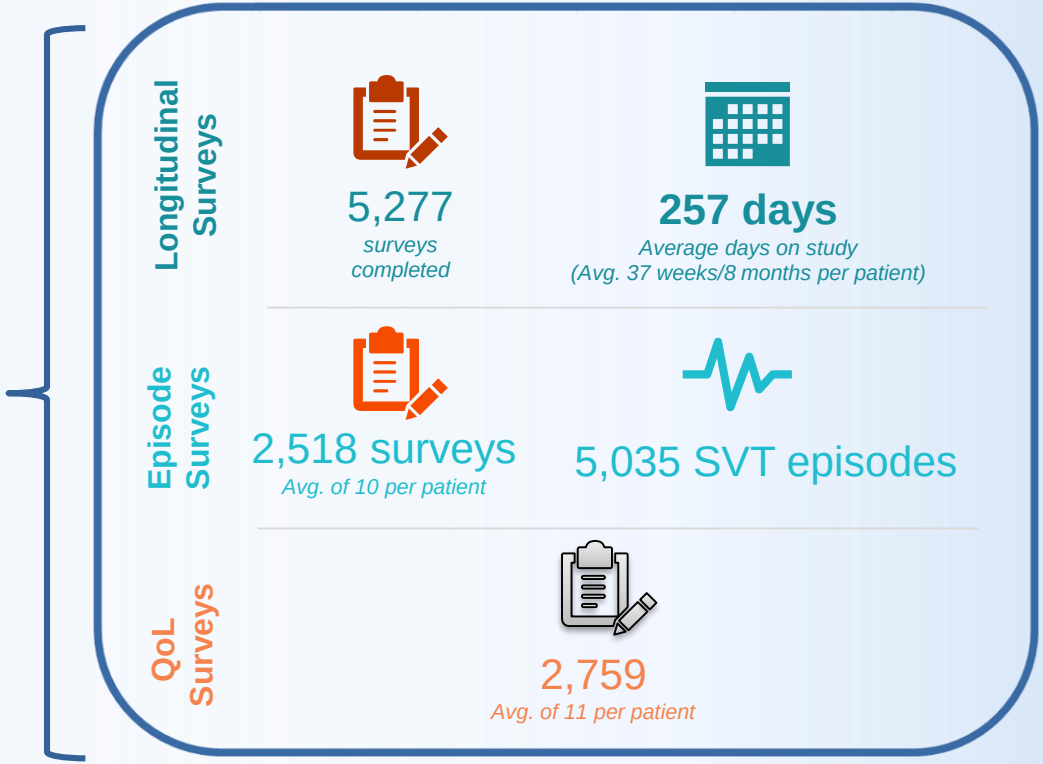


Source: Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, Pokorney SD. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. PMID: 34028109.

New Data Enhances Understanding of Burden of PSVT

Analysis of Prospective Patient Reported Outcomes Longitudinal Data

247 US & UK unablated* PSVT patients



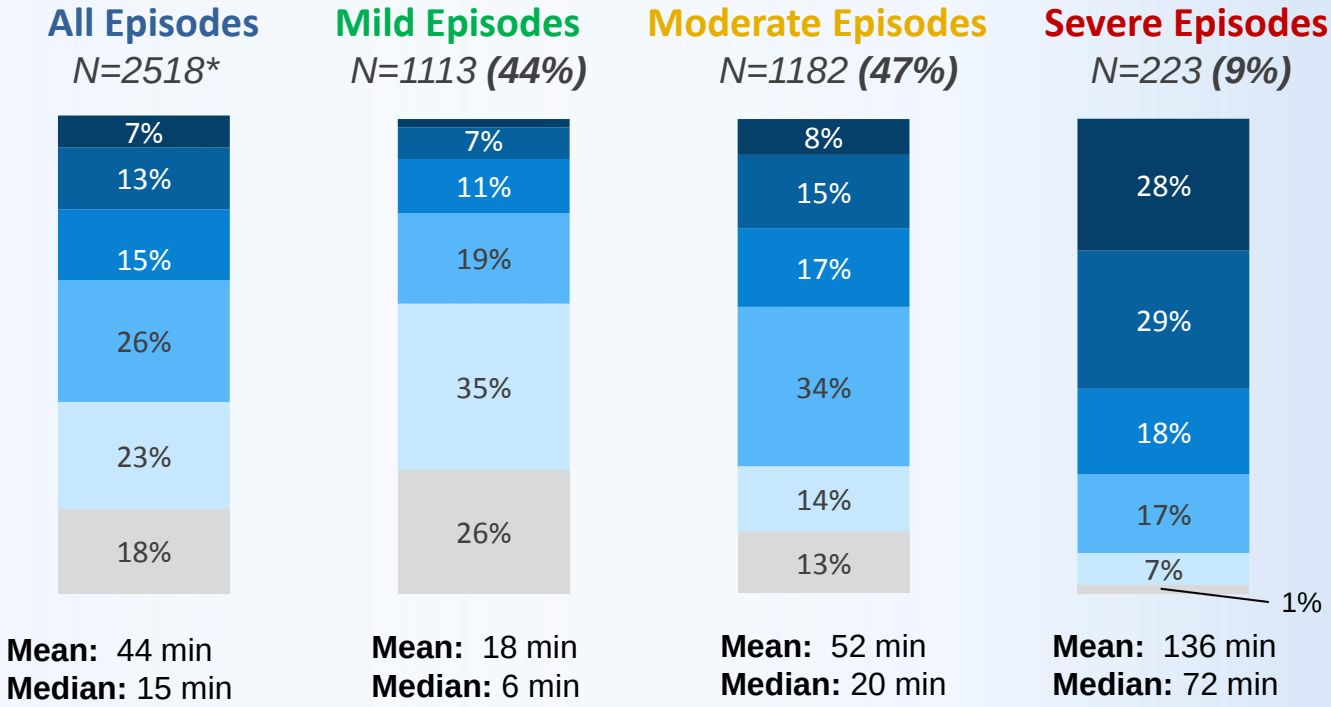
*Unablated prior to starting the research. N=21 patients received ablation while on study.

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

PRO Study Episode Burden – Duration by Episode Severity

Duration by Episode Severity*
% of Episodes

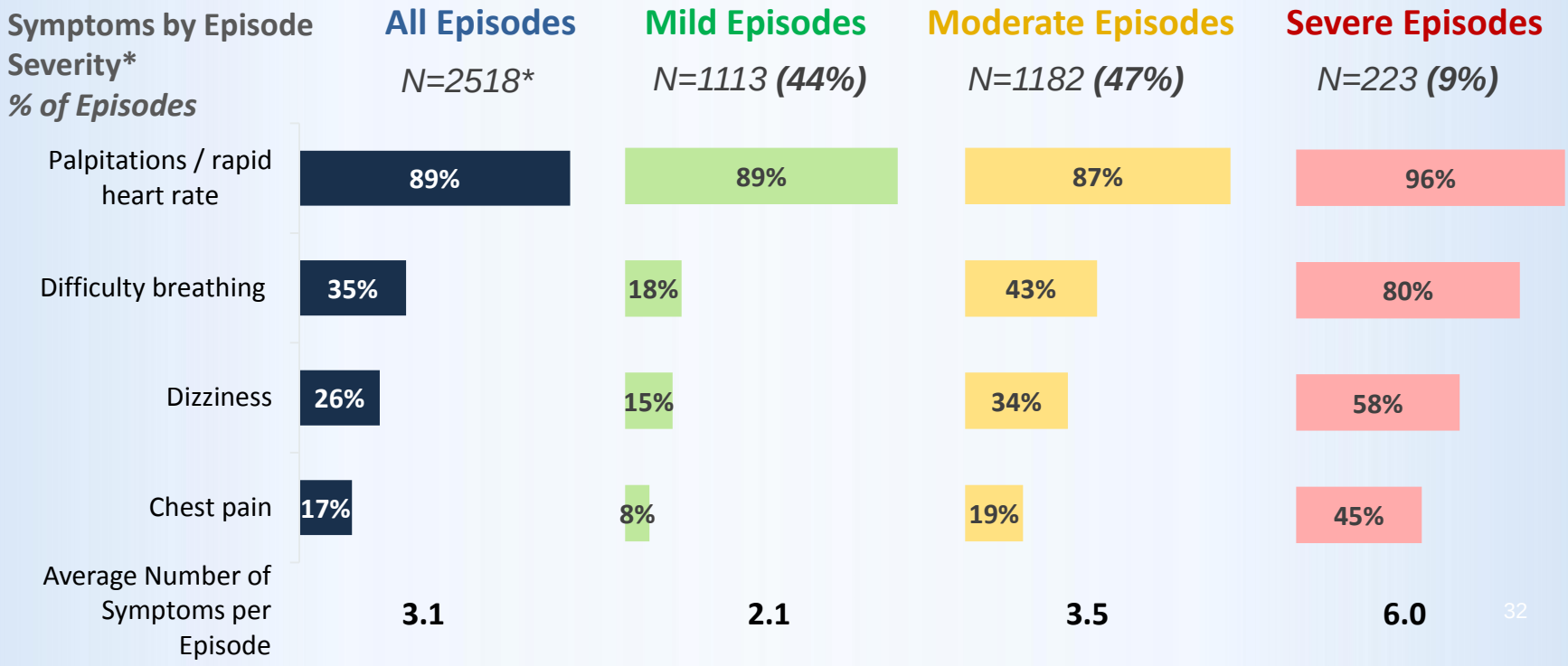
- 2+ hrs
- 1-2 hrs
- 30-59 mins
- 10-29 mins
- 5-9 mins
- 0-4 mins



*Severity as self-reported by patient (mild, moderate, severe)

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

Episode Burden – Symptoms by Episode Severity



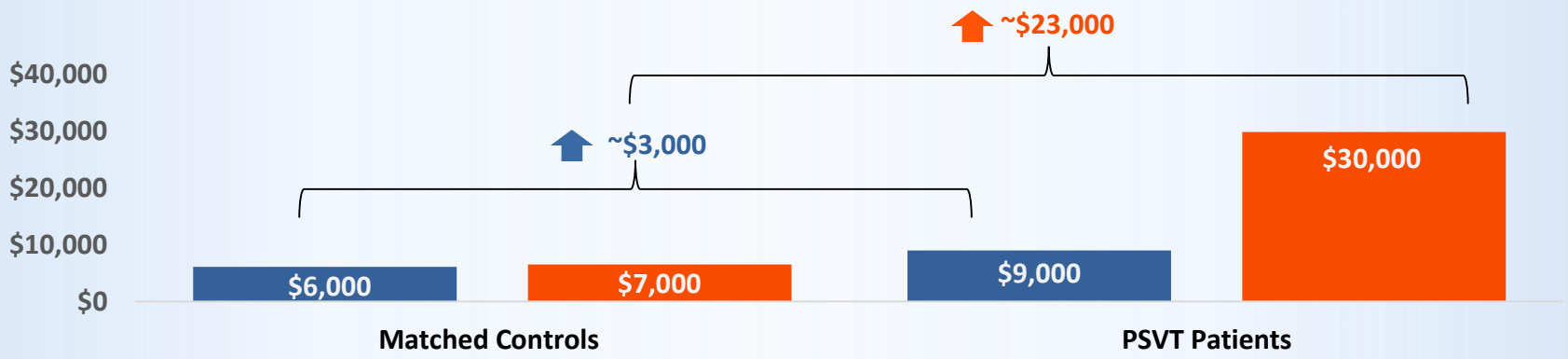
*Severity as self-reported by patient (mild, moderate, severe)

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

PSVT results in significant cost to the healthcare system

Annual US Healthcare Expenditures, Prior to and After PSVT Diagnosis

<65 Year Olds



Rates per PSVT patient

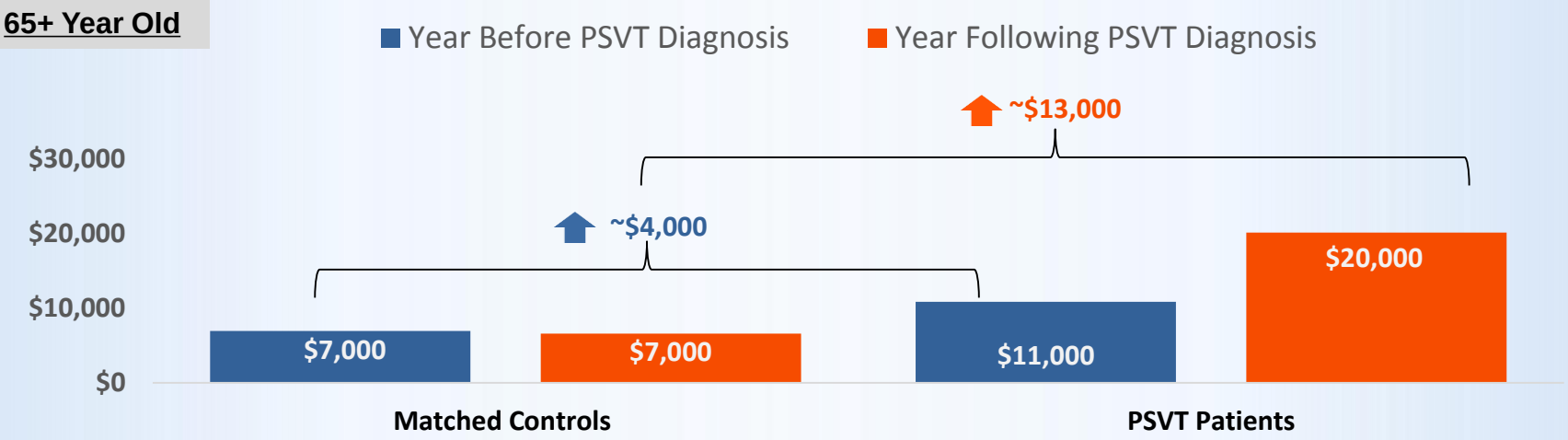
ED visit	**0.32**	**0.77**
Inpatient	**0.08**	**0.35**
Ablation	**-**	**0.14**

Source: Sacks NC, Cyr PL, Preib MT, Everson K, Wood DR, Raza S, Pokorney SD. Healthcare Resource Use and Expenditures in Patients Newly Diagnosed With Paroxysmal Supraventricular Tachycardia. Am J Cardiol. 2020 Jan 15;125(2):215-221. doi: 10.1016/j.amjcard.2019.10.015. Epub 2019 Oct 30. PMID: 31771758.

PSVT results in significant cost to the healthcare system

Annual US Healthcare Expenditures, Prior to and After PSVT Diagnosis

65+ Year Old

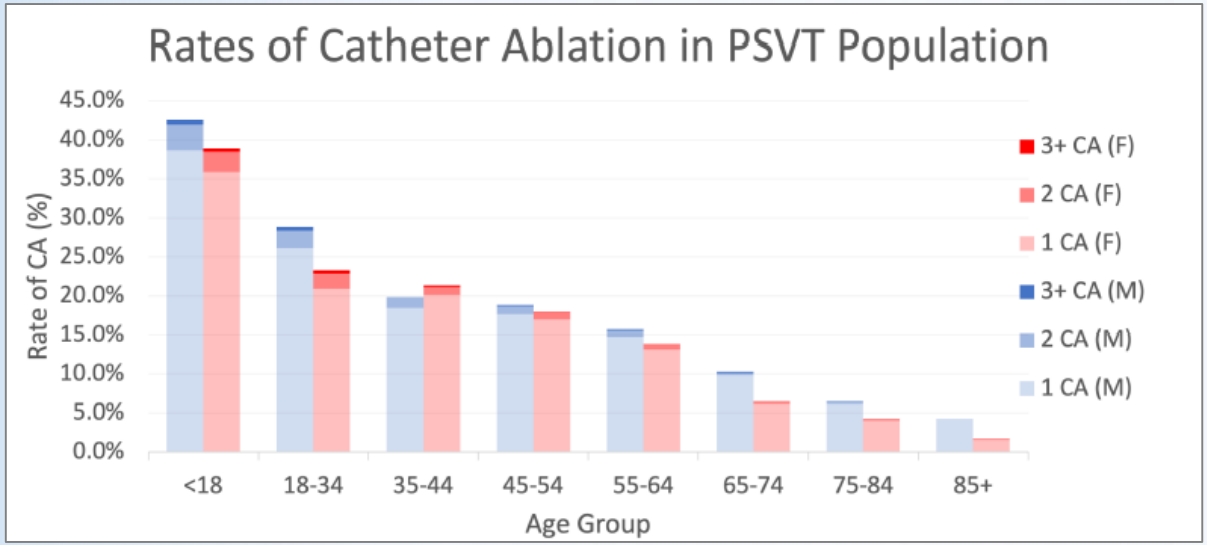


Rates per PSVT patient

ED visit	**0.46**	**0.60**
Inpatient	**0.36**	**0.65**
Ablation	**-**	**0.03**

Source: Sacks NC, Cyr PL, Preib MT, Everson K, Wood DR, Raza S, Pokorney SD. Healthcare Resource Use and Expenditures in Patients Newly Diagnosed With Paroxysmal Supraventricular Tachycardia. Am J Cardiol. 2020 Jan 15;125(2):215-221. doi: 10.1016/j.amjcard.2019.10.015. Epub 2019 Oct 30. PMID: 31771758.

~15% of Patients with PSVT Undergo Ablation



CA = Catheter Ablation; F = Female; M = Male

- ~15% of all PSVT patients received a catheter ablation during the 3-year follow-up period
- Among adult patients, rates of ablation highest in younger and male populations
- Re-ablation rate ~7%, also highest in younger populations
- Significant share of PSVT population is not ablated, with high unmet need for acute at-home treatment

Source: Sacks NC, Cyr PL, Preib MT, Everson K, Wood DR, Raza S, Pokorney SD. Healthcare Resource Use and Expenditures in Patients Newly Diagnosed With Paroxysmal Supraventricular Tachycardia. Am J Cardiol. 2020 Jan 15;125(2):215-221. doi: 10.1016/j.amjcard.2019.10.015. Epub 2019 Oct 30. PMID: 31771758.

Take aways for Scope and Impact of PSVT

- AV nodal-dependent PSVT occurs frequently
- AV nodal-dependent PSVT is prevalent across age ranges and sex
- Patient-perceived severity of PSVT episodes appears correlated with episode duration and number of symptoms
- PSVT management is costly and leads to increased emergency department visits and health-care utilization
- Catheter ablations occur in ~15% of the population

Milestone PHARMACEUTICALS

Etripamil - Commercial Opportunity

Lorenz Muller

Chief Commercial Officer

Etripamil – Addressing Market Needs in PSVT and AFib-RVR

Potential for high receptivity to etripamil across stakeholders

Future with Etripamil – a Potentially Better Treatment Option

Patients

- Self-management of acute episodes
- Reduces ED visits/hospital admissions

Physicians (Cards, EPs, PCPs)

- Better risk/benefit profile
- Expected to have significant adoption in unablated patients

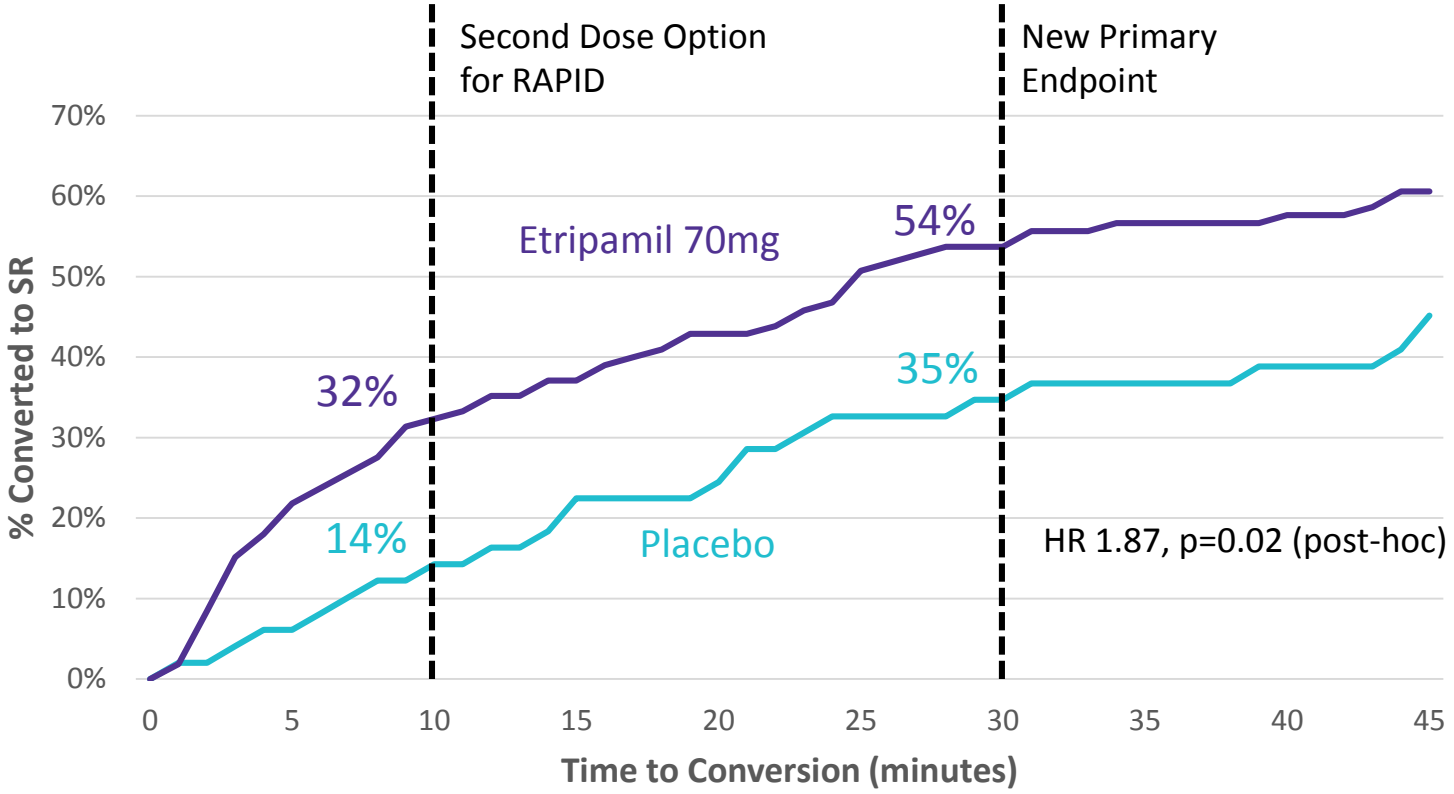
Payers

- Reduction in ED/hospital admissions
- Improvement in patient satisfaction

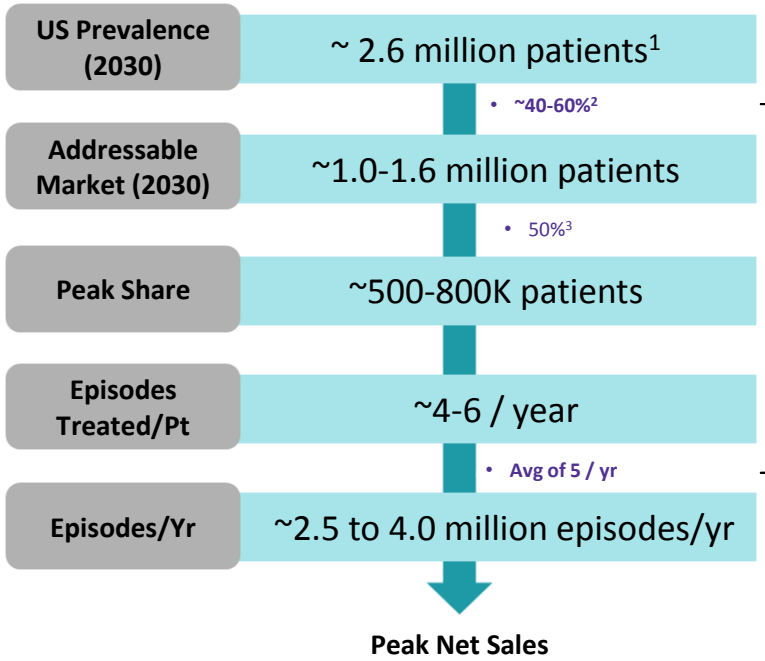
Cards = Cardiologists, EPs = Electrophysiologists, PCPs = Primary Care Providers, PSVT = Paroxysmal Supraventricular Tachycardia, ED = Emergency Department

Sources: Internal market research

NODE-301 Efficacy– Time to Conversion over 45 Minutes



Peak US Market Opportunity for Etripamil in PSVT



Patients with PSVT

~60% with multiple 10+ minute moderate/severe* episodes per year

~45% Experience an average duration ≥30 min / episode

Episodes of PSVT

12-15 median annual episode frequency

60% last at least 10 minutes

35% last at least 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).

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

Q&A

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President and Chief Executive Officer

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Chief Financial Officer and Executive Vice President of Corporate Development

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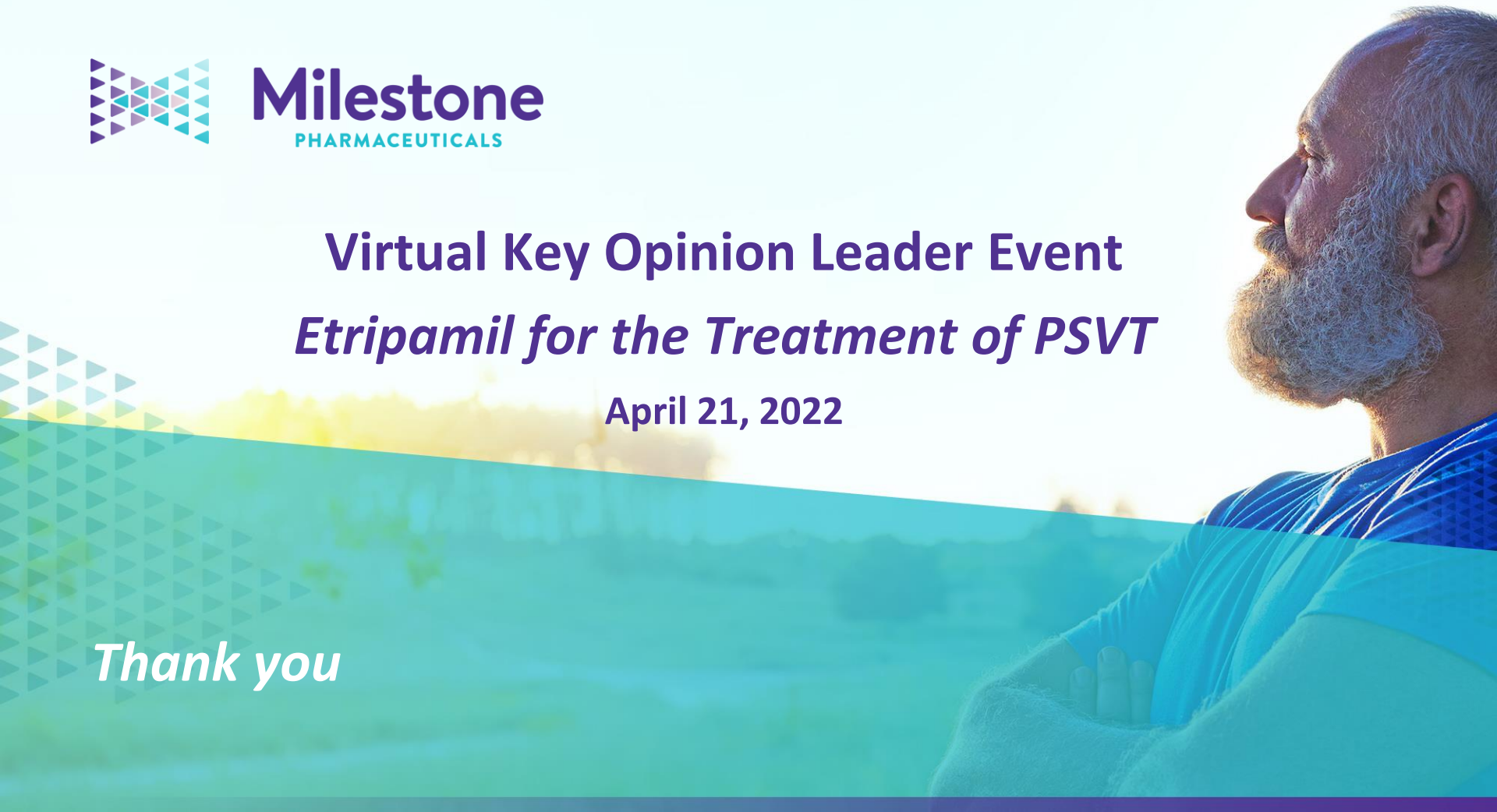
Milestone PHARMACEUTICALS

Virtual Key Opinion Leader Event

Etripamil for the Treatment of PSVT

April 21, 2022



Thank you