UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event reported):
November 12, 2021

MILESTONE PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Québec	**001-38899**	**Not applicable**
(state or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)
1111 Dr. Frederik-Philips Boulevard, Suite 420 Montréal, Québec CA		**H4M 2X6**
(Address of principal executive offices)		(Zip Code)

Registrant's telephone number, including area code: **(514) 336-0444**

Not applicable
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Shares	MIST	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b–2 of the Securities Exchange Act of 1934 (§ 240.12b–2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 2.02. Results of Operations and Financial Condition.

On November 12, 2021, Milestone Pharmaceuticals, Inc. (the "Company") issued a press release announcing its financial results for the third quarter ended September 30, 2021, which also provided a clinical and corporate update. A copy of the press release is attached as Exhibit 99.1 hereto and is incorporated herein by reference.

Item 8.01. Other Events.

In addition, on November 12, 2021, the Company updated its corporate presentation that it intends to use in connection with presentations at conferences and meetings. The full text of the Company's corporate presentation is filed as Exhibit 99.2 hereto and incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release dated November 12, 2021
99.2	Corporate Presentation dated November 12, 2021.
104	Cover Page Interactive Data File—the cover page XBRL tags are embedded within the Inline XBRL document

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

MILESTONE PHARMACEUTICALS INC.

By: /s/ Amit Hasija
Amit Hasija
Chief Financial Officer

Dated: November 12, 2021

Exhibit 99.1

Milestone Pharmaceuticals Reports Third Quarter 2021 Financial Results and Provides Clinical and Corporate Update

Montreal and Charlotte, N.C., Nov. 12, 2021 -- Milestone Pharmaceuticals Inc. (Nasdaq: MIST), a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines, today reported financial results for the third quarter ended September 30, 2021 and provided a clinical and corporate update.

"We continue to make meaningful progress across our etripamil PSVT program. We've advanced our Phase 3 efficacy and safety studies and completed important patient research which enables a deeper understanding and characterization of the burden experienced by patients," said Joseph Oliveto, President and Chief Executive Officer of Milestone Pharmaceuticals. "Additionally, we look forward to presenting data from an analysis of heart rate in patients treated in the NODE-301 trial at the upcoming AHA Scientific Sessions 2021 meeting. We believe these data underscore the potential of etripamil to serve as an important intervention for patients with episodic cardiovascular conditions."

Recent Updates

- **Milestone Remains on Track to Report Topline Data from Pivotal Phase 3 RAPID Trial in the Second Half of 2022.** As previously announced, enrollment continues in the ongoing pivotal Phase 3 RAPID trial of etripamil nasal spray in patients with paroxysmal supraventricular tachycardia (PSVT). Milestone is working closely with study investigators to support patient enrollment and continues to activate new centers. The Company remains on track to report topline data in the second half of 2022.

  The RAPID trial, which is targeting a total of 180 adjudicated PSVT events, is expected to randomize approximately 500 patients 1:1 to receive either etripamil or placebo. To maximize the potential treatment effect of etripamil, patients will be directed to administer a repeat dose of study drug if they do not experience symptom relief within 10 minutes of the first study drug administration. The primary efficacy analysis for both the RAPID trial and the completed NODE-301 trial will be time to conversion of supraventricular tachycardia (SVT) over the first 30 minutes following initial study drug administration, with a target p-value of less than 0.05 for each trial. The RAPID and NODE-301 trials could potentially serve to fulfill the efficacy requirement for a future New Drug Application (NDA) for etripamil in patients with PSVT.

- **Heart Rate Data from NODE-301 Study to be Presented at the American Heart Association (AHA) Scientific Sessions 2021.** New analyses on the impact of etripamil on heart rate in patients with PSVT, from the NODE-301 Study, will be presented at the upcoming AHA Scientific Sessions 2021 meeting. The presentation, titled "Etripamil Nasal Spray Reduces Heart Rate in Patients with Paroxysmal Supraventricular Tachycardia Prior to Conversion to Sinus Rhythm", will be featured during an ePoster session on November 14, 2021 at 11:00 a.m. ET.

- **Analysis of Large Longitudinal Patient Reported Outcome Market Research Study Establishes Disease Burden in PSVT and Market Opportunity for Etripamil.** In the third quarter, Milestone completed an important patient reported outcomes (PRO) market research study in PSVT. The 247 patients who participated in the longitudinal portion of the study represent the broader PSVT population in terms of age, sex, medical history and time since diagnosis. Patients on average participated for 8.5 months and completed a survey every 12 days. In total, over 5,000 episodes were reported and characterized. Of these episodes, approximately 60% lasted longer than 10 minutes and 35% longer than 30 minutes.

Patients who participated in the study demonstrated a wide range of annual SVT episode frequency (0 to >50), with a median frequency of 12-15 episodes per year. Based on internal analysis, Milestone estimates approximately 60% of patients experience multiple 10+ minute episodes each year characterized as moderate or severe in intensity. In addition, approximately 30% of patients experiencing episodes sought medical care for the episode, the majority of which were treated in the emergency department.

- **ReVeRA Phase 2 Proof-of-Concept Trial Continues Recruitment in Patients Experiencing Atrial Fibrillation with Rapid Ventricular Rate (AFib-RVR).** Recruitment is ongoing in ReVeRA, Milestone's Phase 2 proof-of-concept study of etripamil nasal spray in patients experiencing AFib-RVR. Patients are being randomized 1:1 to receive either 70 mg of etripamil or placebo. The Phase 2 double blind, placebo controlled, proof-of-concept in-patient study is designed to assess the safety and efficacy of etripamil nasal spray to reduce the ventricular rate in patients with AFib-RVR. The trial is being conducted in Canada in collaboration with the Montreal Heart Institute and other research centers. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and duration of the effect.

Third Quarter 2021 Financial Results

- As of September 30, 2021, Milestone had cash, cash equivalents, and short-term investments of $126.4 million and 29.9 million common shares issued and outstanding and 12.3 million common shares issuable upon exercise of pre-funded warrants outstanding.

- Research and development expense for the third quarter of 2021 was $9.7 million compared with $8.2 million for the prior year period. The increase reflects higher clinical consulting fees and contract research organization (CRO) costs due to advancing RAPID Phase 3 efficacy and safety trials in etripamil for the treatment of PSVT along with an increase in clinical personnel related costs. For the nine months ended September 30, 2021, research and development expense was $27.8 million compared with $28.7 million for the prior year period. The decrease was due to a reduction in clinical trial expenses of $2.3 million which was partially offset by an increase of $1.3 million in clinical personnel related costs which included a non-cash share-based compensation expense.

- General and administrative expenses for the third quarter of 2021 and 2020 were $3.0 million. For both of the nine month periods ended September 30, 2021 and 2020, respectively, general and administrative expense was $8.6 million.

- Commercial expense for the third quarter of 2021 was $1.6 million compared with $0.9 million for the prior year period. The increase is attributable to investment in commercial activities during the three months ended September 30, 2021 in contrast to the three months ended September 30, 2020, a period during which Milestone reduced commercial spending in order to focus efforts on an optimized clinical development pathway for etripamil after issuing topline results of the first part of the NODE-301 in March 2020. For the nine months ended September 30, 2021, commercial expense was $4.8 million compared with $4.6 million for the prior year period. This change was due to an increased investment in commercialization activities.

- For the third quarter of 2021, operating loss was $14.3 million compared to $12.1 million in 2020. For the nine months ended September 30, 2021, Milestone's operating loss was $26.2 million compared to $41.9 million in the prior year period.

About Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is a condition characterized by intermittent episodes of rapid heart beat that starts and stops suddenly and without warning that affects approximately two million Americans. Episodes of supraventricular tachycardia (SVT) are often associated with palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting, and anxiety. Adenosine and certain calcium channel blockers have long been approved for the treatment of PSVT. However, these medications must be administered intravenously under medical supervision, usually in an emergency department or other acute care setting.

About Atrial Fibrillation with Rapid Ventricular Rate

Atrial fibrillation (AFib) is a common arrhythmia marked by an irregular and often rapid heartbeat. AFib is estimated to affect five million patients in the United States, a prevalence projected by the Centers for Disease Control to increase to twelve million patients within the next 10 years. Atrial fibrillation with rapid ventricular rate (AFib-RVR) is a condition in which patients with AFib experience episodes of abnormally high heart rate, often with symptoms such as palpitations, shortness of breath, dizziness, and weakness. Oral calcium channel blockers and/or beta blockers are commonly used to manage the heart rate in this condition. When episodes do occur, the corresponding symptoms often cause patients to seek care in the acute care setting such as the emergency department, where standard of care procedures include intravenous administration of calcium channel blockers or beta blockers under medical supervision. Milestone’s initial qualitative market research indicates that approximately 40% of patients with AFib experience one or more symptomatic episodes of RVR per year that require treatment, suggesting a target addressable market for etripamil in patients with AFib of approximately two million patients.

About Etripamil

Etripamil, Milestone's lead investigational product, is a novel calcium channel blocker designed to be a rapid-response therapy for episodic cardiovascular conditions. As a nasal spray that is self-administered by the patient, etripamil has the potential to shift the current treatment experience for many patients from the emergency department to the at-home setting. Milestone is conducting a comprehensive development program for etripamil, with Phase 3 trials ongoing in paroxysmal supraventricular tachycardia (PSVT) and now a Phase 2 proof-of-concept trial underway in patients with atrial fibrillation and rapid ventricular rate (AFib-RVR).

About Milestone Pharmaceuticals

Milestone Pharmaceuticals Inc. (Nasdaq: MIST), is a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. Milestone's lead product candidate etripamil is currently in a Phase 3 clinical-stage program for the treatment of paroxysmal supraventricular tachycardia (PSVT) and in a Phase 2 proof-of-concept trial for the treatment of patients with atrial fibrillation and rapid ventricular rate (AFib-RVR). Milestone Pharmaceuticals operates in Canada and the United States. For more information, visit www.milestonepharma.com and follow the Company on Twitter at @MilestonePharma.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "believe," "will," "expect," "continue," "estimate," “potential,” “progress” and similar expressions (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 press release. 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 press release include statements regarding the potential of etripamil to serve as a promising therapy for PSVT patients, the design, progress, timing, scope and results of the RAPID and ReVeRA trials; Milestone’s ability to execute on the remainder of the PSVT program, Milestone’s ongoing plans to study etripamil in atrial fibrillation patients, the sufficiency of Milestone’s current cash resources to support its operations, and estimates about the addressable market and commercial potential for treatments of atrial fibrillation with rapid ventricular rate. 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, and whether the clinical trials will validate the safety and efficacy of etripamil for PSVT or other indications, among others, as well as risks related to pandemics and public health emergencies, including those related to the ongoing COVID-19 pandemic, and risks related the sufficiency of Milestone’s capital resources and its 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, 2020, under the caption "Risk Factors." 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.

INTERIM CONDENSED CONSOLIDATED STATEMENTS OF LOSS AND COMPREHENSIVE LOSS
(Unaudited, in thousands of US dollars, except share and per share data)

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Collaboration revenue	$ —	$ —	$ 15,000	$ —
Operating expenses				
Research and development, net of tax credits	9,733	8,228	27,755	28,722
General and administrative	2,961	2,952	8,612	8,611
Commercial	1,579	905	4,788	4,615
Loss from operations	(14,273)	(12,085)	(26,155)	(41,948)
Interest income, net	48	89	186	630
Loss before income taxes	(14,225)	(11,996)	(25,969)	(41,318)
Income tax benefit	—	17	—	17
Net loss	$ (14,225)	$ (11,979)	$ (25,969)	$ (41,301)
Weighted average number of shares and pre-funded warrants outstanding, basic & diluted	42,182,887	29,774,065	41,707,563	26,329,581
Net loss per share, basic and diluted	$ (0.34)	$ (0.40)	$ (0.62)	$ (1.57)

INTERIM CONDENSED CONSOLIDATED BALANCE SHEETS
(Unaudited, in thousands of US dollars, except share data)

	September 30, 2021	December 31, 2020
Assets		
Current assets		
Cash and cash equivalents	$ 111,426	$ 72,310
Short-term investment	15,000	70,000
Research and development tax credits receivable	275	725
Prepaid expenses	5,968	5,428
Other receivables	89	223
Total current assets	132,758	148,686
Operating lease assets	780	980
Property and equipment	238	308
Total assets	$ 133,776	$ 149,974
Liabilities, and Shareholders' Equity		
Current liabilities		
Accounts payable and accrued liabilities	$ 5,593	$ 5,914
Operating lease liabilities	254	245
Total current liabilities	5,847	6,159
Operating lease liabilities (net of current portion)	512	696
Total liabilities	6,359	6,855
Shareholders' Equity		
Common shares, no par value, unlimited shares authorized 29,869,785 shares issued and outstanding as of September 30, 2021, 29,827,997 shares issued and outstanding as of December 31, 2020	251,766	251,682
Pre-funded warrants - 12,327,780 issued and outstanding as of September 30, 2021 and 11,417,034 as of December 31, 2020	52,927	48,007
Additional paid-in capital	13,793	8,530
Cumulative translation adjustment	(1,634)	(1,634)
Accumulated deficit	(189,435)	(163,466)
Total shareholders' equity	127,417	143,119
Total liabilities and shareholders' equity	$ 133,776	$ 149,974

Contact:

David Pitts
Argot Partners
212-600-1902
david@argotpartners.com


Milestone
PHARMACEUTICALS
Corporate Overview
November 2021
Joseph Oliveto
President & CEO

Disclaimers

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 possibility that data will support FDA approval, (iii) 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, and (iv) the sufficiency of Milestone's capital resources. 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, 2020, under the caption "Risk Factors." 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.

This Presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners. Certain information contained in this Presentation and statements made orally during this Presentation relate to or is based on studies, publications, surveys and other data obtained from third-party sources and Milestone's own internal estimates and research. While Milestone believes these third-party studies, publications, surveys and other data to be reliable as of the date of the Presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent sources has evaluated the reasonableness or accuracy of Milestone's internal estimates or research and no reliance should be made on any information or statements made in this Presentation relating to or based on such internal estimates and research.

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 through mid-2023

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

PSVT & Atrial Fibrillation Populations 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 Market Addressable (2030) (Patient Population)	1.0-1.6 Million[5]	~3-4 Million[4]

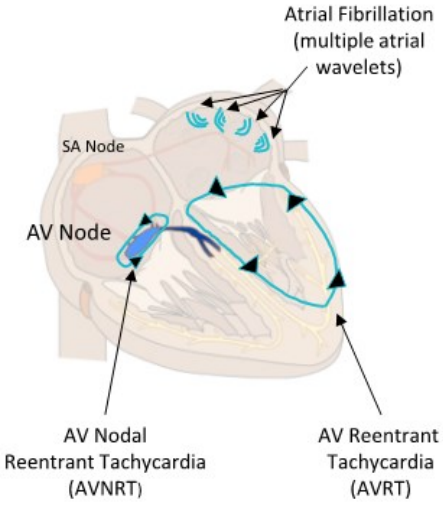
Source(s): **1.** Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Miyasaka et al., Circulation, 2006, 114, 119-125. American Heart Association **2.** HCUP ED & Admissions Data (2016), accessed January 2021. **3.** Rehorn et al. Journal of Cardiovascular Electrophysiology. 2021 Aug; 32(8): 2199-2206. doi: 10.1111/jce.15109. Epub 2021 Jun 14. 2018 prevalence of 2M anticipated to grow at a CAGR of ~2% **4.** 30%-40% of AF patients have >1 symptomatic episode per year of AF with RVR requiring treatment, Triangle Insights Group Market Research, N=25, January 2021. **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.

Atrial Arrhythmias with a Common Patient Burden

Patients with PSVT and AFib-RVR report feeling a loss of control

PSVT (AVNRT and AVRT)	AFib-RVR (a subset of AFib)
Regular rapid heart rate	Irregular rapid heart rate
Typically 150 - 250 bpm	Typically 100 - 175 bpm
Episode frequency and duration is highly variable	

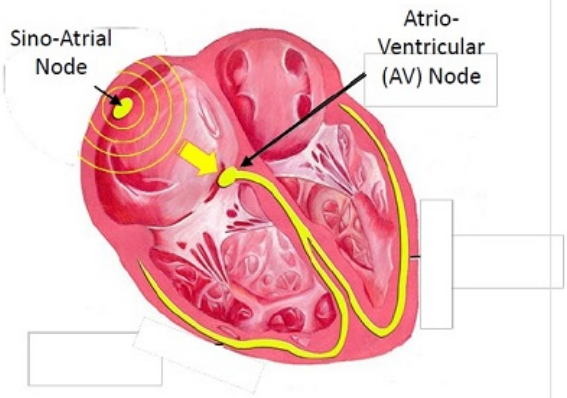
Common Symptoms Include		
	Heart palpitations	Chest pressure or pain
	Shortness of breath	Fatigue
	Light-headedness	Anxiety

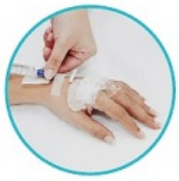


PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

Sources: adapted from https://en.ecgpedia.org/index.php?title=Supraventricular_Rhythms, accessed 2/2021

Role of L-Type Calcium Channel Blockers





IV CCBs like verapamil or diltiazem slow conduction over the AV node…

for PSVT

…to break the tachycardia and return the heart to sinus rhythm

for AFib-RVR

…to reduce the ventricular rate while still in AFib

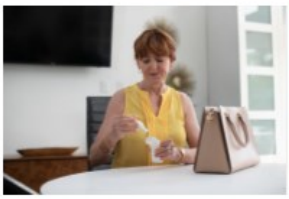
CCBs = Calcium Channel Blockers; PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; IV = Intravenous

Potential Paradigm-Changing Treatment to Empower Patient Control of their Condition

Drawbacks with the current standard of care in the Emergency Department (ED)

- Time consuming
- Anxiety provoking
- Costly
- Often results in a hospital admission
- Experienced by patients as a loss of control

Intervention used by the patient whenever & wherever an episode occurs



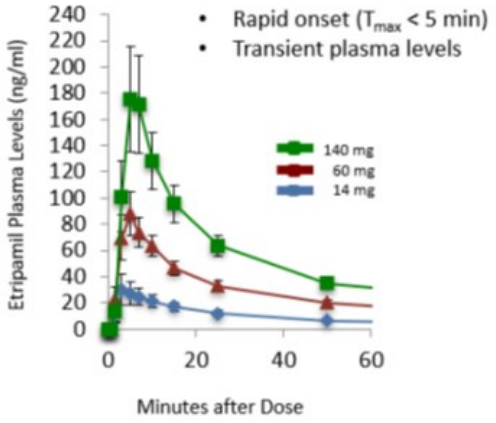
- Reduces ED visits / hospital admissions
- Less need for chronic medications
- Alternative or bridge to ablation procedure

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

Prospectively designed to treat common tachycardias outside the Emergency Department (ED)

	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
- Convenient patient self-administered nasal spray
- Short duration of action



AV = Atrio-ventricular; nM = nanomolar

Error bars indicate standard error of the mean

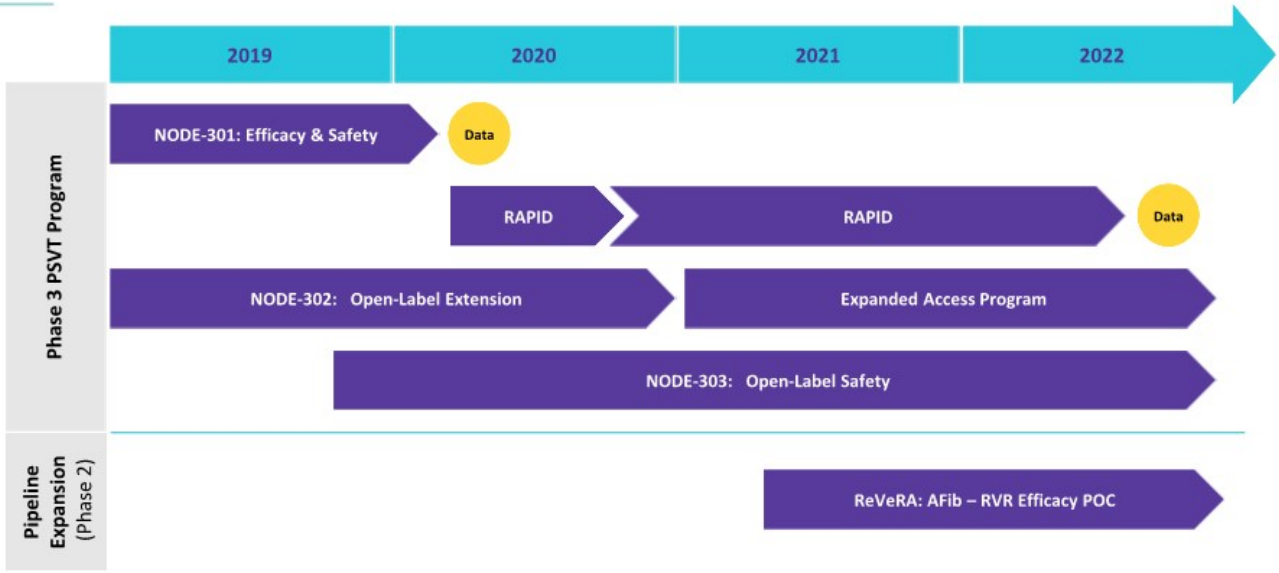
Clinical Program Overview for Etripamil

Clinical development programs designed to support NDA filing in PSVT while concurrently building safety database and running Phase 2 ReVeRA to support AFib-RVR program

NODE-1 PSVT	ReVeRA AFib-RVR	NODE-301 PSVT	RAPID PSVT	NODE-303/302 PSVT
Phase 2	**Phase 2**	**Phase 3**	**Phase 3**	**Phase 3**
Efficacy	Efficacy POC	Efficacy	Efficacy	Safety
Published	Enrolling	Complete	Enrolling	Enrolling/ Complete
Electrophysiology Lab	Emergency Department	At home	At Home	At Home
N= 104 1:1 randomized	N=50 1:1 randomized	N=419 2:1 randomized	N~500 1:1 randomized	N ~1000 Open label

POC = Proof of Concept; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; PSVT = Paroxysmal Supraventricular Tachycardia

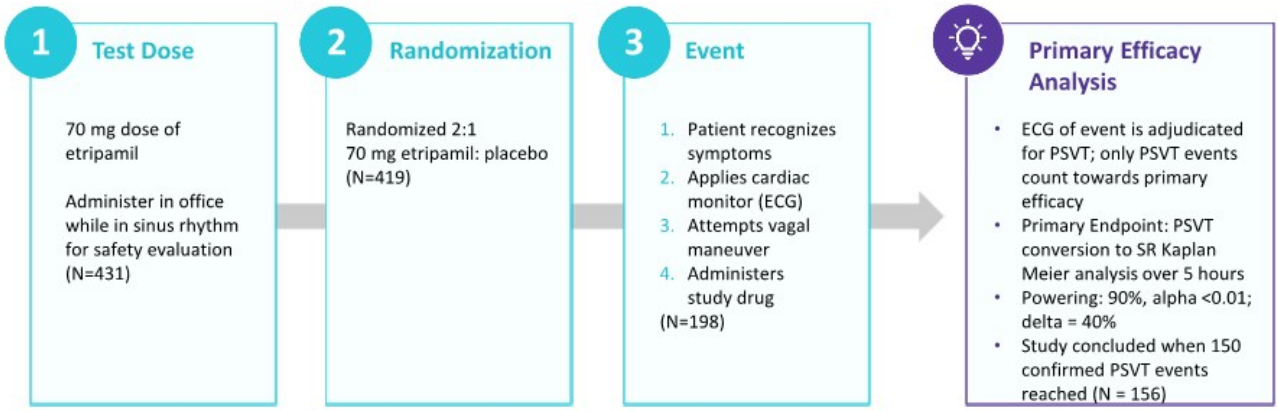
Development Plan for Etripamil



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

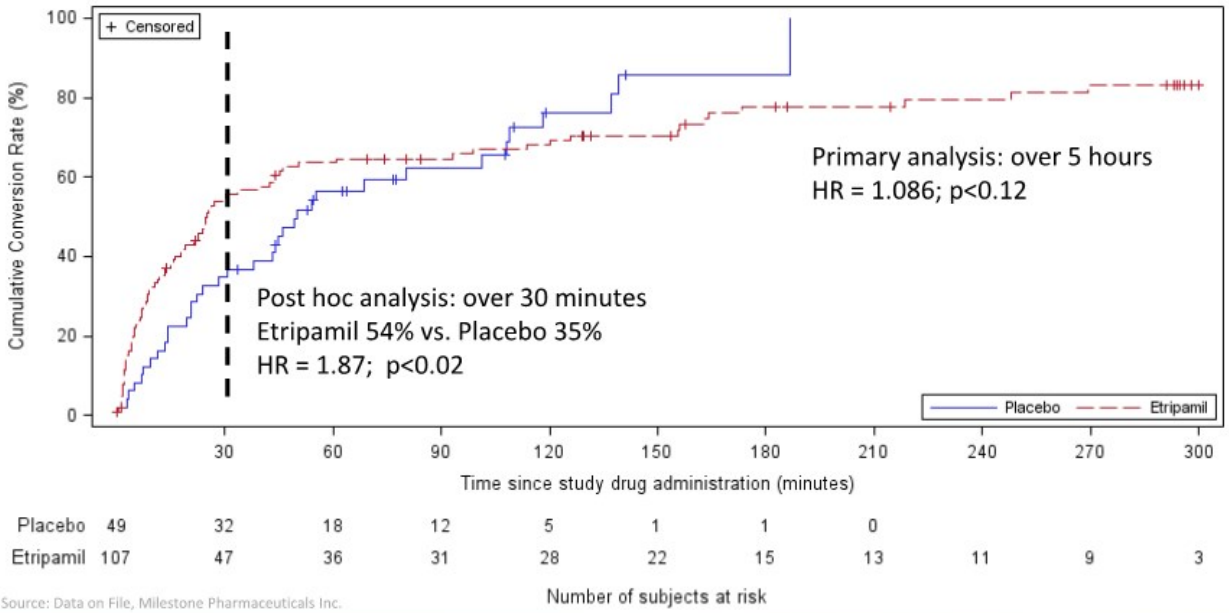
NODE-301 Study Design

NODE-301 patients taking etripamil had no serious adverse events



SR = Sinus Rhythm; ECG = Electrocardiogram; PSVT = Paroxysmal Supraventricular Tachycardia

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



Placebo	49	32	18	12	5	1	1	0			
Etripamil	107	47	36	31	28	22	15	13	11	9	3

Number of subjects at risk

Source: Data on File, Milestone Pharmaceuticals Inc.

NODE-301 Safety Analysis

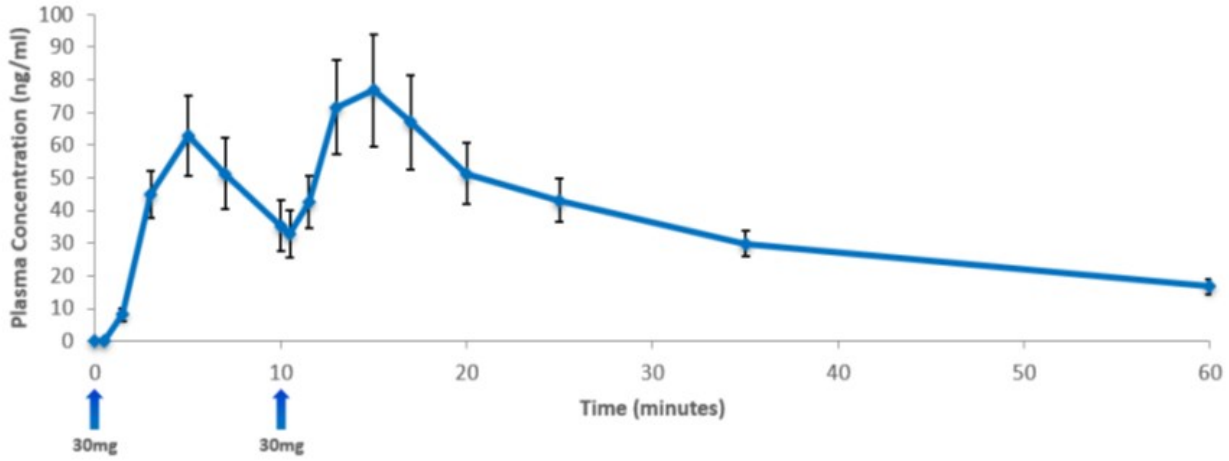
Randomized Treatment Emergent Adverse Events (RTEAE)	Etripamil N=138 (%)	Placebo N=60 (%)
Subjects with any RTEAE	53 (38.4)	12 (20.0)
Maximum severity of RTEAE		
Mild	45 (32.6)	10 (16.7)
Moderate	8 (5.8)	3 (3.3)
Severe	0 (0.0)	0 (0.0)
Most Common Adverse Events (>5%)		
Nasal discomfort	27 (19.6)	4 (6.7)
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.

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

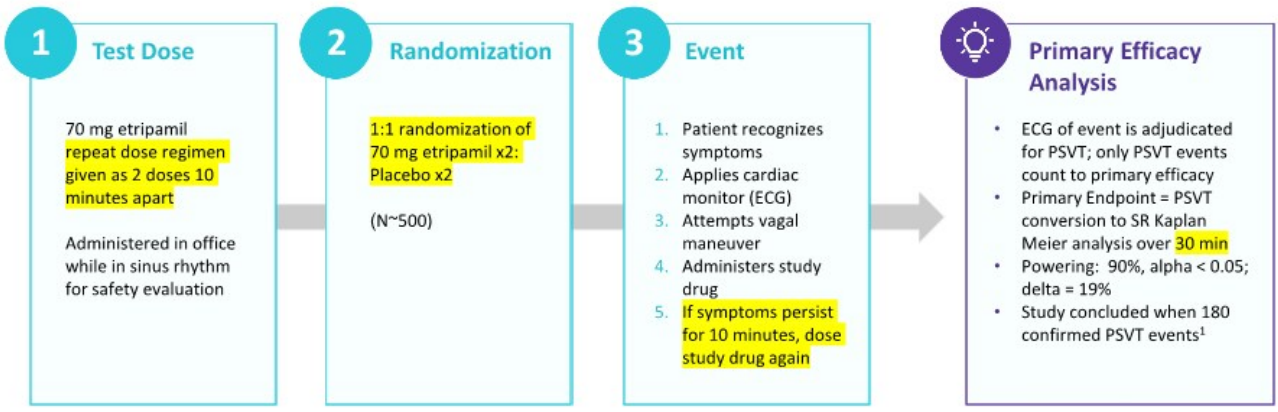
Repeat administration increases both Cmax and AUC



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

ReVeRA – Proof of Concept for AFib with Rapid Ventricular Rate

Clinical development programs designed to support NDA filing in PSVT, while concurrently building safety database and running Phase 2 ReVeRA to support AFib-RVR program

NODE-1 PSVT	ReVeRA AFib-RVR	NODE-301 PSVT	RAPID PSVT	NODE-303/302 PSVT
Phase 2	**Phase 2**	**Phase 3**	**Phase 3**	**Phase 3**
Efficacy	Efficacy POC	Efficacy	Efficacy	Safety
Published	Enrolling	Complete	Enrolling	Enrolling/ Complete
Electrophysiology Lab	Emergency Department	At home	At Home	At Home
N= 104 1:1 randomized	**N=50** 1:1 randomized	**N=419** 2:1 randomized	**N~500** 1:1 randomized	**N ~1000** Open label

SR = Sinus Rhythm; ECG = Electrocardiogram; PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; POC = Proof of Concept

The ReVeRA Trial

Reduction of **Ve**ntricular **R**ate in Patients with **A**trial Fibrillation

1 Patient presents to ED with episode of AFib-RVR

Inclusion:
- Atrial Fibrillation ≥ 1 hour
- Ventricular Rate ≥ 110 bpm

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

2 Dosing & Assessment

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

Efficacy Analysis

- Primary: Maximum reduction in ventricular rate within 60 min
  - N=50: 90% powered to detect 20 bpm difference in max reduction, α=0.05;
- Time from drug administration to lowest ventricular rate
- Time to and duration of ventricular rate reductions
  - <100 bpm, ≥ 10% reduction, ≥ 20% reduction
- Patient satisfaction with treatment (TSQM-9)

CHADs 0 = No Heart Failure/No Hypertension/Age < 65/No Diabetes/No History of Stroke or TIA/No Coronary ischemic disease; OAC = Oral Anti-coagulant; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; TSQM-9, Treatment Satisfaction Questionnaire for Medication; ED = Emergency Department

Milestone
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Commercial Opportunity

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

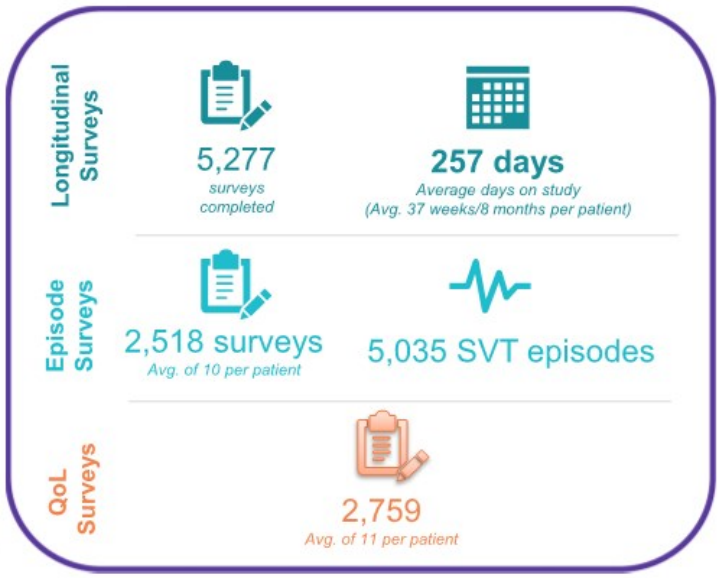
Sources: Internal market research

New Data Enhances Understanding of Burden of PSVT

Analysis of Prospective Patient Reported Outcomes Longitudinal Data

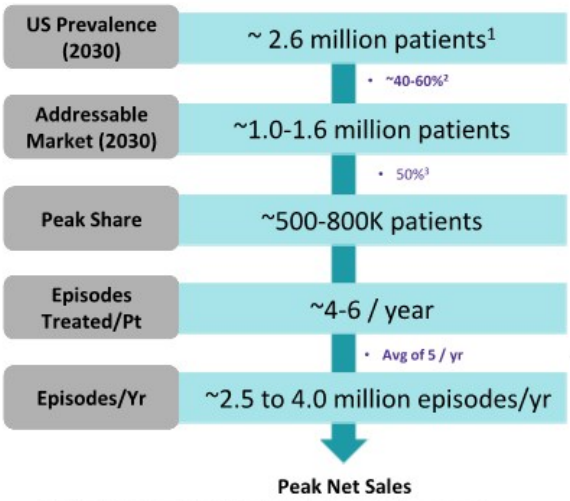
247 US & UK patients

- **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)

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

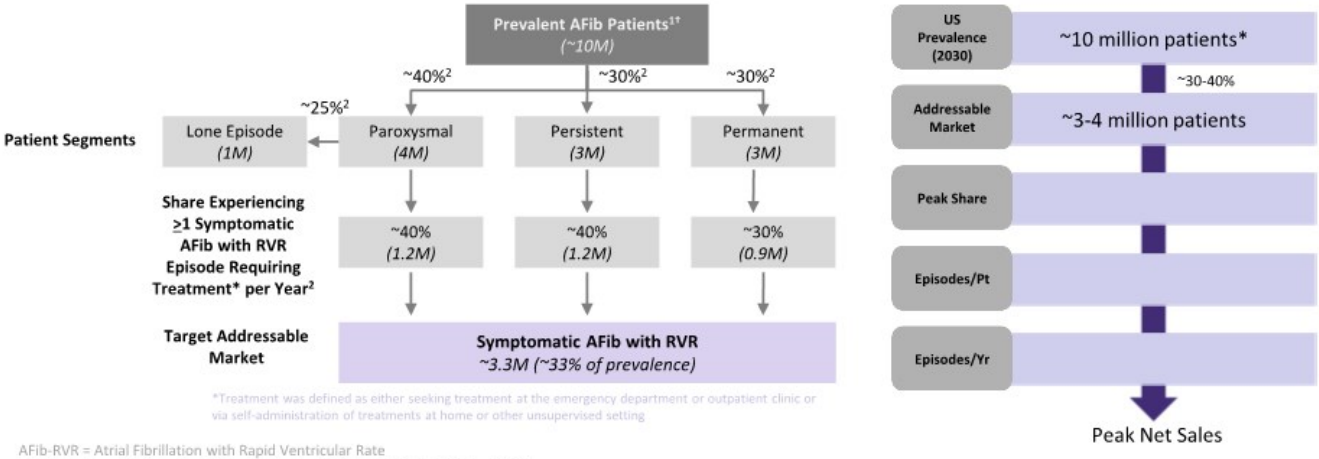
35% last at least 30 minutes

*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).

Peak US Market Opportunity for Etripamil in AFib-RVR

Market research suggests a target addressable market of ~3-4 million patients for AFib-RVR by 2030



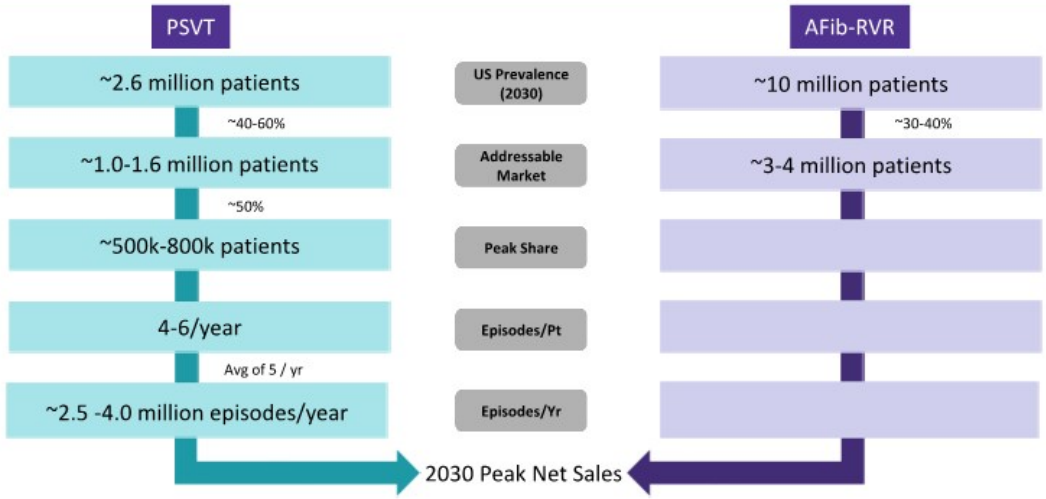
*Treatment was defined as either seeking treatment at the emergency department or outpatient clinic or via self-administration of treatments at home or other unsupervised setting

AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate
*Reflects the midpoint of published estimates (~8M to ~12M by 2025 or 2030)

1. Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Miyasaka et al., Circulation, 2006, 114, 119-125; Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147 ; American Heart Association **2.** HCUP ED & Admissions Data (2016), accessed January 2021. **2.** Quantitative Survey conducted by Triangle Insights, May 2021, N=250 Clinical Cardiologists, Interventional Cardiologists, and Electrophysiologists

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



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

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

Finances – as of September 30, 2021

- Cash, cash equivalents and short-term investments of $126.4M
- Cash funds operations past guidance for top-line data and into mid-2023
- Equity - 42.2M in shares and pre-funded warrants outstanding
  - 29.9M common shares
  - 12.3M pre-funded warrants

Milestone
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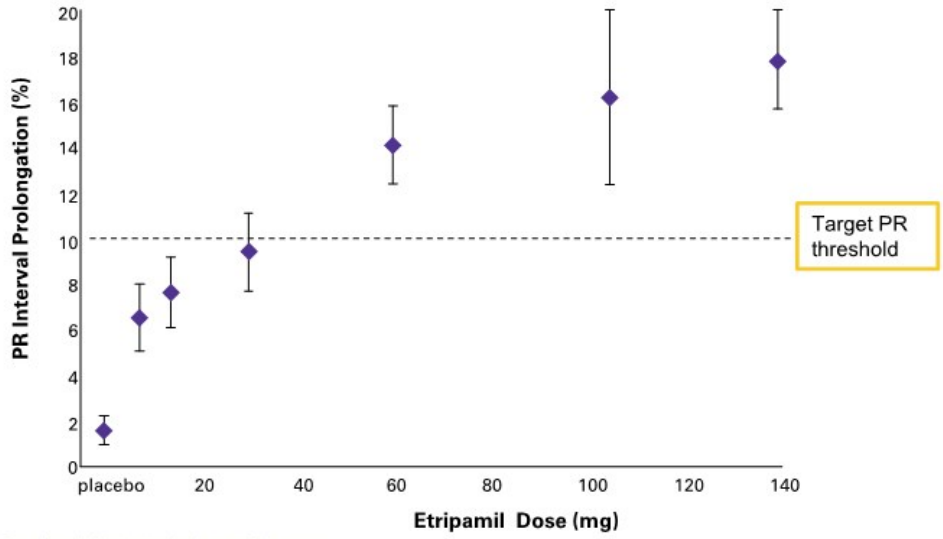
Thank you

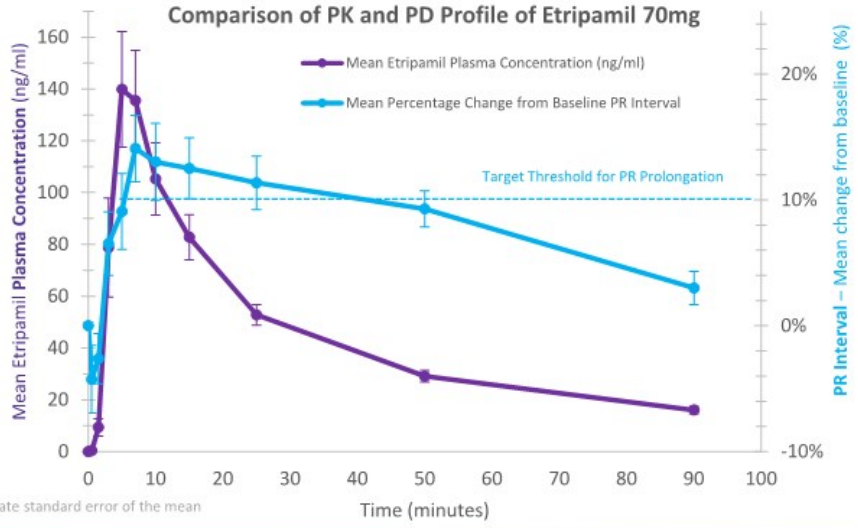
Etripamil Phase 1 Pharmacology
PR Prolongation Used to Select Doses for Phase 2



Error bars indicate standard error of the mean

Etripamil Nasal Spray Pharmacological Results (NODE-102)

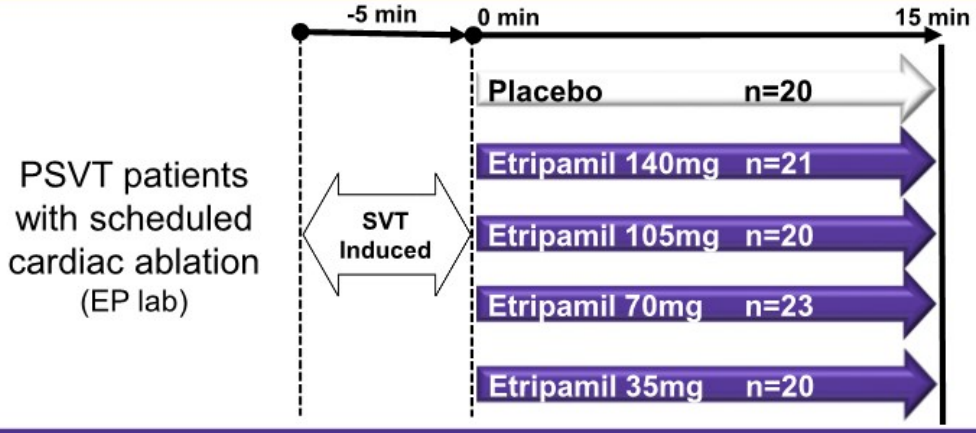
Anticipated therapeutic effect within 45 minutes; peak within 10 minutes



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

Phase 2a/b Study Design

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

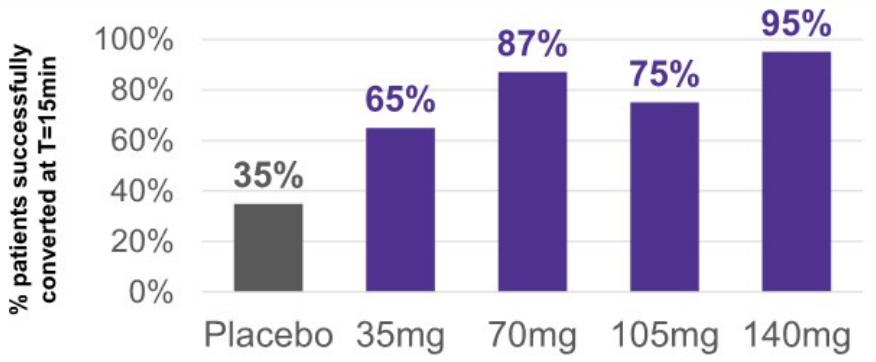


Endpoint: conversion to sinus rhythm within 15 minutes
>80% power to show a 50% absolute difference vs. placebo

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

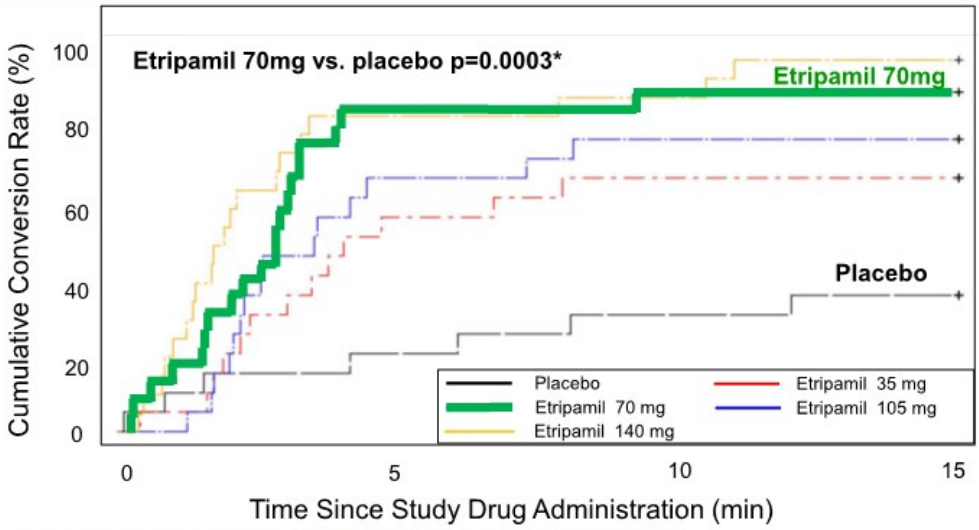


# patients converted at 15 min	7/20	13/20	20/23	15/20	20/21
p-value		0.1128	0.0006	0.0248	<.0001

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 Time to Conversion

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

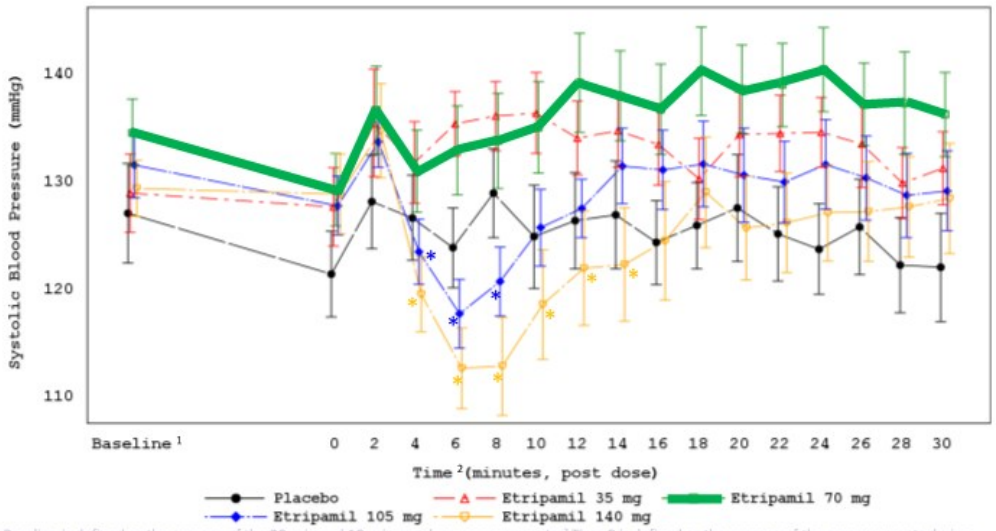


*Hazard Ratio and 95% Confidence Intervals etripamil 70mg vs. placebo; 4.99 (2.09, 11.93)

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

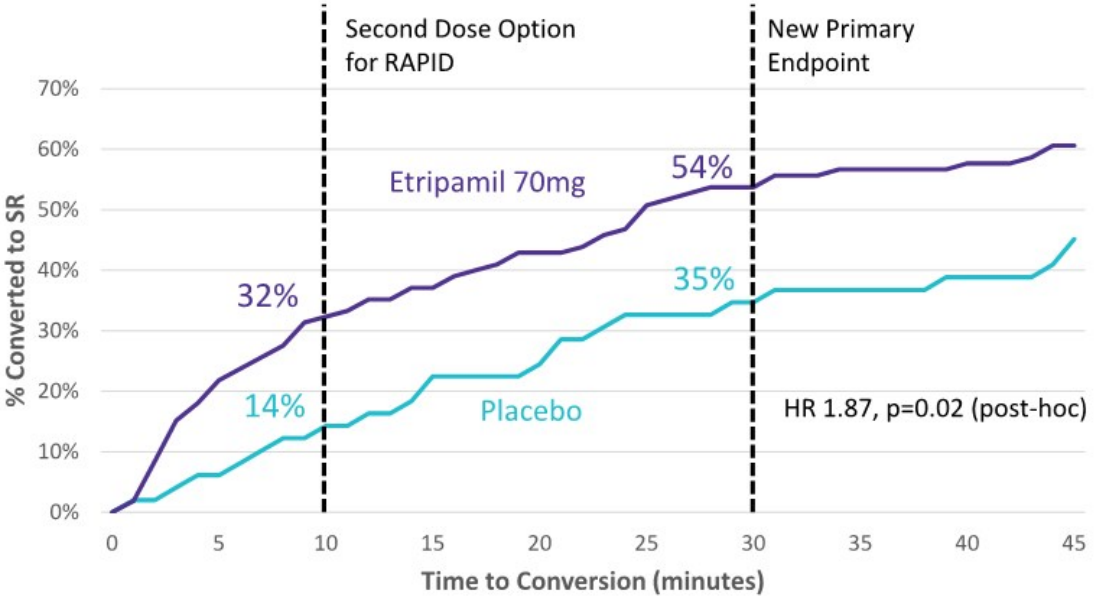
70 mg of etripamil showed no decrease in blood pressure; higher doses transient decreases



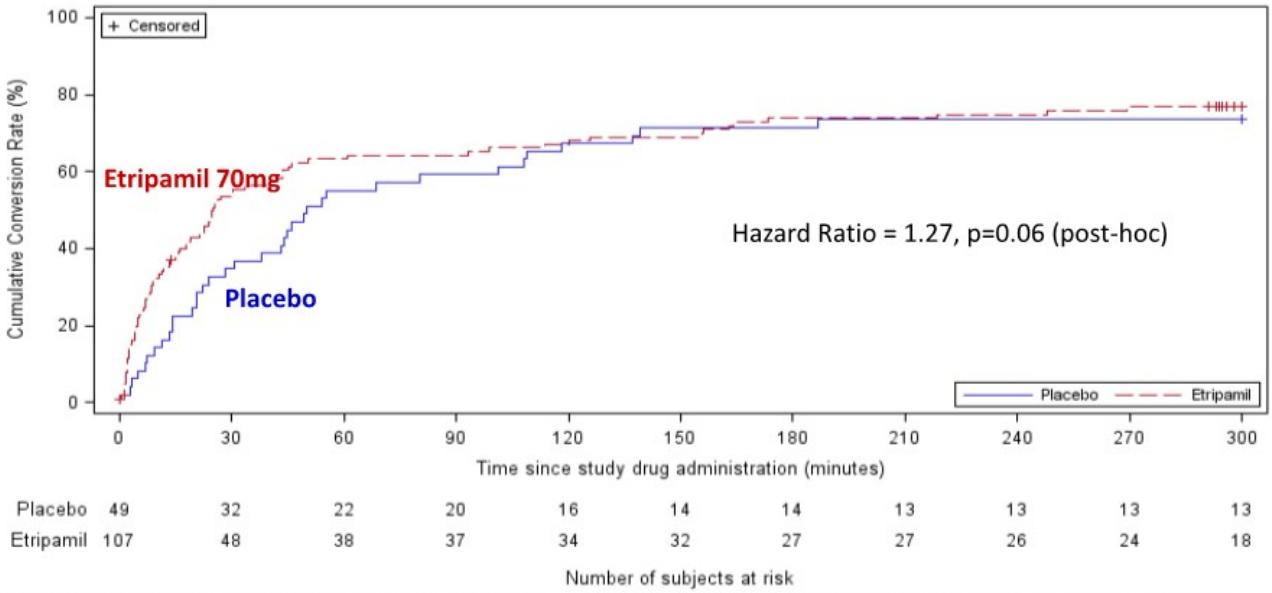
[1] Baseline is defined as the average of the 20-min and 10-min pre-dose measurements. [2] Time 0 is defined as the average of the measurements during supraventricular tachycardia between 5 and 0 min before study drug administration. *p < 0.05 versus baseline.

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

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)



Number of subjects at risk											
Placebo	49	32	22	20	16	14	14	13	13	13	13
Etripamil	107	48	38	37	34	32	27	27	26	24	18

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

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)

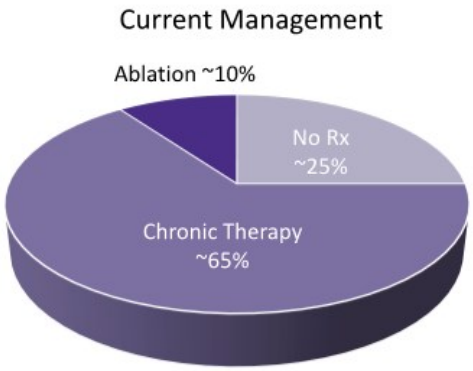
*Patients on study at least 6 months were used to project annual episode frequency. Sample projections were weighted by stated episode frequency from an intake survey

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).

Current US PSVT Market

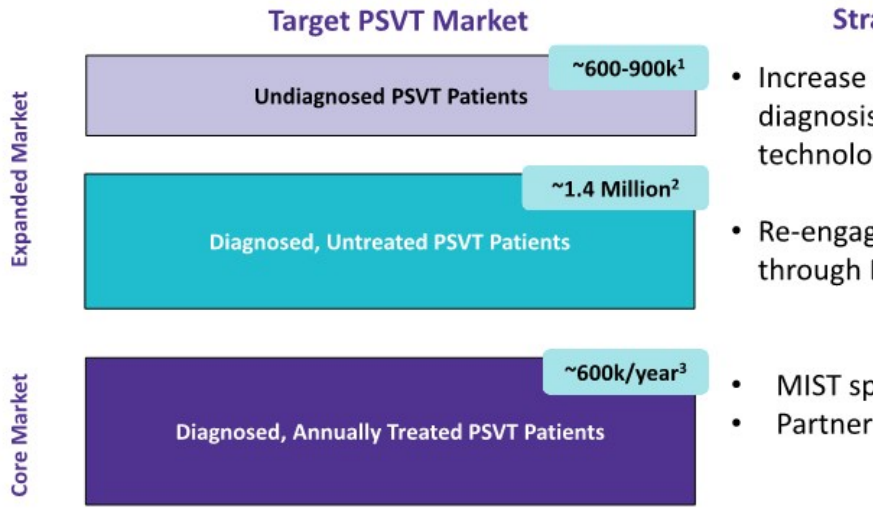
Total annual US healthcare expenditures of ~$3B

- 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



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.

Core PSVT Market is Addressable Now, with Potential for Expansion



Source: 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 2M and annual treatment rate of ~600k 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.

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

Estimating Prevalence, Incidence, and Annually Treated Patients Using Longitudinal Claims Data

- Analyzed commercial and Medicare claims data over a 9-year period, where patients were required to have 5 years of continuous enrollment
  - ✓ 1+ PSVT code required in the ED or inpatient setting (unique patients managed acutely)
  - ✓ 2+ PSVT codes required in the outpatient setting (additional unique patients managed chronically)

Age Group	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Age < 65	271,024	196,653	169,988	155,966	145,485	939,116
Age 65+	377,493	220,596	209,358	188,925	166,286	1,162,658
All Ages	648,518	417,249	379,346	344,891	311,771	2,101,775

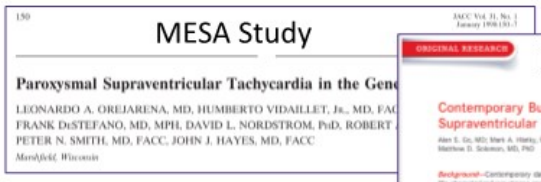
Annually Treated PSVT Patients

Incident PSVT Patients

Prevalent PSVT Patients

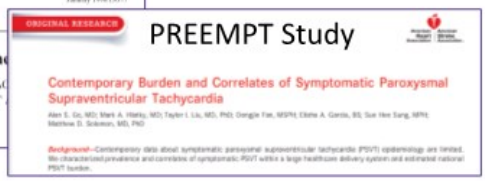
Source: Data on file from IBM Marketscan® Commercial Research Database (<65y) and the Medicare Limited Dataset (≥65y), with demographic, enrollment and claims data for commercially insured (Truven) and Medicare covered patients using PSVT code 427.0 or I47.1 for up to a 9-year interval between 2008 and 2016 inclusive.

Published Disease Data Likely Under-Reports Burden of PSVT


MESA Study

Paroxysmal Supraventricular Tachycardia in the Gene

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


ORIGINAL RESEARCH

PREEMPT Study

Contemporary Burden and Correlates of Symptomatic Paroxysmal Supraventricular Tachycardia

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.