

**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 11, 2023

MILESTONE PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Québec
(state or other jurisdiction of incorporation)

001-38899
(Commission File Number)

Not applicable
(I.R.S. Employer Identification No.)

**1111 Dr. Frederik-Philips Boulevard,
Suite 420
Montréal, Québec CA**
(Address of principal executive offices)

H4M 2X6
(Zip Code)

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

(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
Common Shares

Trading Symbol(s)
MIST

**Name of each exchange on which
registered**
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 7.01. Regulation FD Disclosure.

On November 13, 2023, Milestone Pharmaceuticals Inc. (“Milestone” or the “Company”) provided an updated corporate presentation that may be used in connection with presentations at conferences and investor meetings. The full text of the Company’s corporate presentation is filed as Exhibit 99.1 hereto, and incorporated herein by reference, and may also be accessed through the “Investors & Media” section of the Company’s website at www.milestonepharma.com.

The Company intends to use its website as a means of disclosing material non-public information and for complying with its disclosure obligations under Regulation FD. Such disclosures will be included on its website in the “Investors & Media” section. Accordingly, investors should monitor such portions of its website, in addition to following press releases, filings with the U.S. Securities Exchange Commission (the “SEC”) and public conference calls and webcasts.

The information furnished under this Item 7.01, including Exhibit 99.1, shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, or subject to the liabilities of that section or Sections 11 and 12(a) (2) of the Securities Act of 1933, or the Securities Act. The information in this Item 7.01, including Exhibit 99.1, shall not be deemed incorporated by reference into any other filing with the SEC, made by the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 8.01. Other Events.

On November 11, 2023, the Company issued a press release announcing positive Phase 2 data that show etripamil nasal spray resulted in rapid and statistically superior ventricular rate reduction and improved symptom relief in patients with atrial fibrillation with rapid ventricular rate compared to placebo. A copy of the press release is attached hereto as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits

(d) Exhibits.

Exhibit No.	Description
99.1	Corporate Presentation, dated November 13, 2023.
99.2	Press release, dated November 11, 2023.
104	Cover Page Interactive Data File (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.

Date: November 13, 2023

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



Milestone[™]
PHARMACEUTICALS

Company Overview
CONFIDENTIAL Atrial Fibrillation Program Update

November 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. \ “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “goal,” “intend,” “may,” “objective,” “plan,” “predict,” “; “potential,” “project,” “seek,” “should,” “target,” “will,” “would” (as well as other words or expressions referencing future events, conditions or circumstances) are intende 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 for statements involves risks and uncertainties. Actual results may differ materially from these forward-looking statements. Forward-looking statements contained in this Presen 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 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 condit 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 comm 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 fu candidates and the implementation of Milestone’s business model and strategic plans for its business, etripamil and any future product candidates. Important factors that co 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 clir the lengthy and uncertain regulatory approval process, uncertainties related to the timing of initiation, enrollment, completion and evaluation of clinical trials, including the f 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 pandem 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 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 “F 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 cor 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 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 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 in and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent sour 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 rel such internal estimates and research.

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

Recent Progress and Key Upcoming Events

- 1 **RAPID Study published in The Lancet** – July 2023
- 2 **NDA submission for PSVT** – October 2023
- 3 **Leadership Hired in Med. Affairs, Marketing, Market Access** – 2023
- 4 **Initial data in AFib-RVR (NODE-303 study) presented** – May 2023
- 5 **FDA Guidance (pre-IND meeting) on AFib-RVR Phase 3 Study** – November 2023
- 6 **AFib-RVR Ph2 (ReVeRA study) data presented at AHA** – November 2023
- 7 **Operating runway to mid-2025 via RTW financing** – March 2023

KOL View on Currently Available Approaches / Unmet Need in AFib

- Regardless of rate- or rhythm-control strategy, break-through episodes of AFib-RVR are frequent, symptomatic, highly burdensome, and disruptive
- Current treatment of acute attacks in the emergency department are burdensome and costly
- Expensive and inefficient use of healthcare system resources
- What would be helpful, and is currently missing, is a simple, fast-acting treatment, that could:
 - be self-administered at-home
 - reduce burden of episodes, and reduce trips to ED and calls to phy

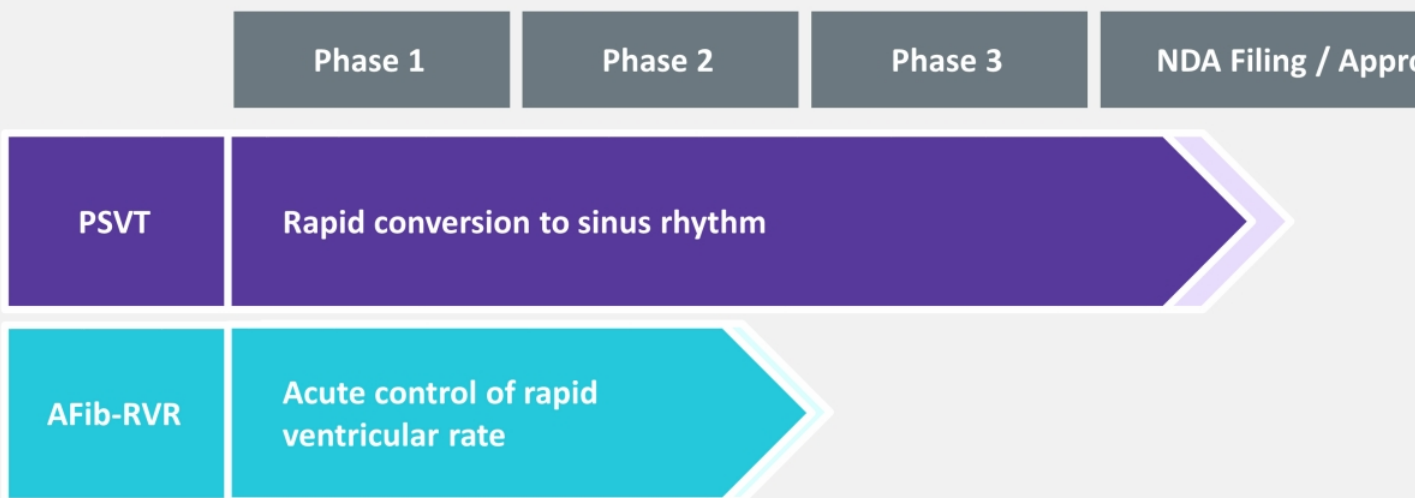
KOL = Key Opinion Leader; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; ED = Emergency Department

Source: Milestone Pharmaceuticals Virtual Key Opinion Leader Event on Etripamil for the Treatment of AFib-RVR, May 22, 2023; <https://investors.milestonepharma.com/ever>

Milestone - Atrial Fibrillation Program Overview

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

Milestone - Atrial Fibrillation Program Overview

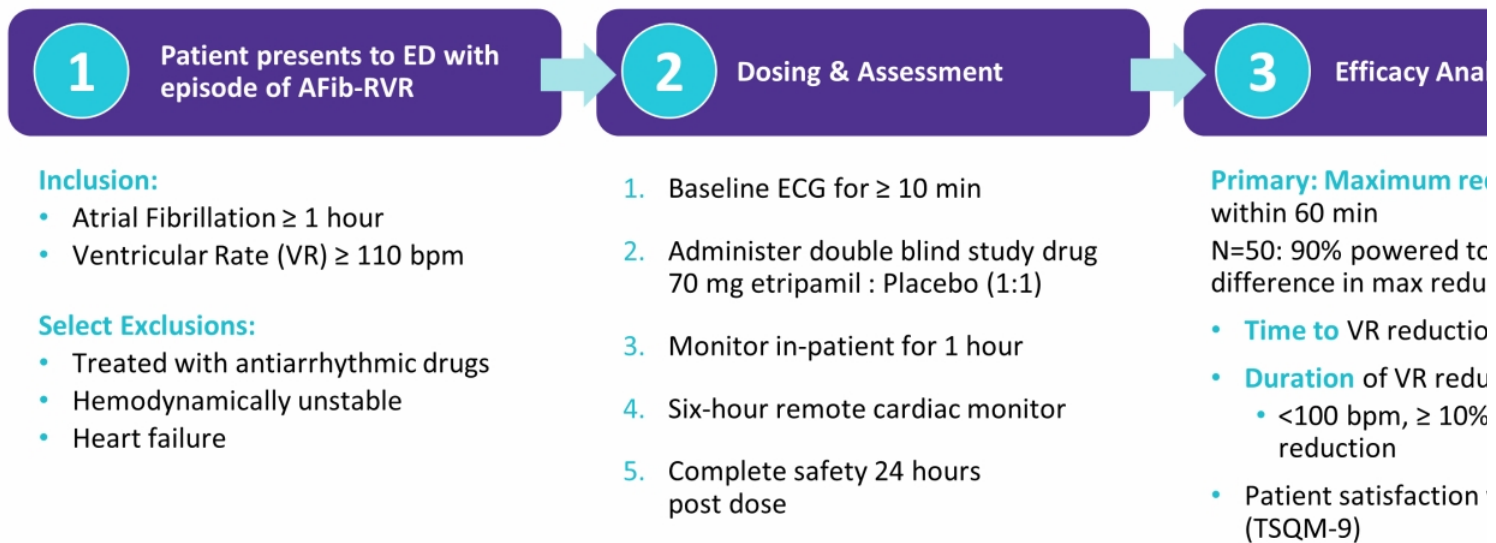
Experience and Successful Progress in PSVT Program Applied to AFib-RVR Program

- Track-record of etripamil NS development in PSVT
- Conducted multi-national PSVT development program in at-home setting with tachycardia symptom prompted, self-administration of etripamil NS
- We demonstrated:
 - ✓ Rapid conversion of PSVT with etripamil NS 70 mg
 - ✓ Optimized efficacy with repeat-dose regimen
 - ✓ Symptomatic improvement
 - ✓ Appropriate Safety & Tolerability Profile shown for approach of symptom-prompted, at-home administration
- Resulted in NDA submission

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

Milestone - Atrial Fibrillation Program Overview

ReVeRA - Phase 2 Proof of Concept Trial of Etripamil in AFib-R in the Emergency Department Setting



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;

Milestone - Atrial Fibrillation Program Overview

ReVeRA was designed to demonstrate:

Sizing of the Study	<ul style="list-style-type: none">• Sized to detect 20-bpm reduction¹ vs placebo (in-line with HCP expectations as clinically meaningful, and similar to IV CCBs); assumed 90% power, $\alpha=0.05$. Target N= 50.
Primary Endpoint	<ul style="list-style-type: none">• Reduction in VR; as measured by difference in maximum reduction from baseline per s over 60 min window
Amount of Reduction Secondary Measures	<ul style="list-style-type: none">• Achievement of responses of VR <100 bpm, or $\geq 20\%$ reduction, or $\geq 10\%$ reduction
Speed of Action Duration of Action	<ul style="list-style-type: none">• Time course plots, Time to VR reduction or to achieve responder status• Duration of VR <100 bpm, or $\geq 20\%$ reduction, or $\geq 10\%$ reduction
Symptomatic Relief	<ul style="list-style-type: none">• Measurements of Satisfaction of Effectiveness and Relief of Symptoms utilizing the TSC
Safety & Tolerability	<ul style="list-style-type: none">• Adverse event collection and ECG monitoring

¹ Reduction = reduction from VR baseline. ² Treatment Satisfaction Questionnaire for Medication-9, a validated patient reported outcome tool. AFib-RVR = atrial fibrillation with rap

ReVeRA Patient Characteristics (Safety Population)¹

Characteristic	Placebo n=29	Etripamil n=27	Total N=56
Age, years			
Mean (SD)	64.59 ± 10.53	64.63 ± 10.61	64.6 (10.47)
Median (range)	66.00 (35.00, 83.00)	64.00 (45.00, 88.00)	65 (35.00, 88.00)
Site Location			
Canada	14 (48.3%)	12 (44.4%)	26 (46%)
The Netherlands	15 (51.7%)	15 (55.6%)	30 (54%)
Sex, female, n (%)	11 (37.9%)	11 (40.7%)	22 (39.3)
Baseline Systolic Blood Pressure (mmHg)			
Mean ± SD (median)	125.59 ± 17.34 (124.00)	130.00 ± 19.78 (126.00)	127.71 ± 18.52 (124.50)
Type of AF			
Paroxysmal	22 (75.9%)	20 (74.1%)	42 (75%)
Persistent	5 (17.2%)	5 (18.5%)	10 (17.9%)
Permanent	2 (6.9%)	2 (7.4%)	4 (7.1%)
Baseline Medications,² n (%)			
Any beta-blocker (BB)	10 (34.5%)	13 (44.8%)	23 (41.1%)
Any NDHP CCB	3 (10.3%)	4 (14.8%)	7 (12.5%)
Any BB or NDHP CCB	13 (44.8%)	15 (55.6%)	28 (50%)
Any Class IC or III antiarrhythmic drug	5 (17.2%)	8 (29.6%)	13 (23.2%)
Anticoagulant, oral	16 (55.1%)	16 (59.3%)	32 (57.1%)

¹ Safety Population (all randomized patients receiving study drug). ² Baseline = medications started at least 1 day prior to study drug administration.
BB = Beta blocker, NDHP = non-dihydropyridine, CCB = calcium channel blocker, Pop = population, SD = standard deviation

ReVeRA Primary Endpoint – Maximum Reduction in VR (60 mi

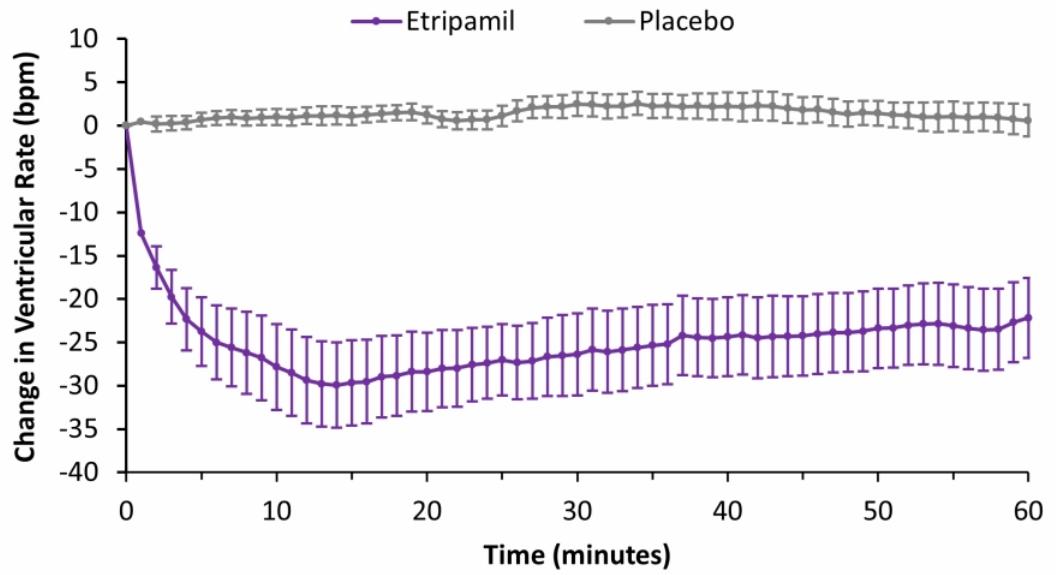
Primary Endpoint achieved with high degree of statistical significance

PRIMARY ENDPOINT: Maximum Reduction in VR from Baseline	Placebo NS,¹ N=25	Etripamil NS, 7 N=24
Baseline Ventricular Rate (SD)	135.54 (13.93)	130.33 (15.1)
Mean (95% CI), bpm	-5.06 (-7.44, -2.67)	-34.97 (-45.13, -
Difference in means (95% CI), bpm	--	-29.91 (-40.31, -
p-value²	--	<0.0001

¹ Efficacy Population (all randomized patients receiving study drug remaining in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug). Maximum reductions determined based on 5-min moving average of VR. ² By ANCOVA. bpm ± SEM. bpm = beats per minute. CI = confidence interval. SD = standard deviation. VR = ventricular rate.

ReVeRA – Mean VR Change from Baseline (60 min)¹

ReVeRA Data Show Substantial & Rapid Reduction in VR for the Etripamil Group

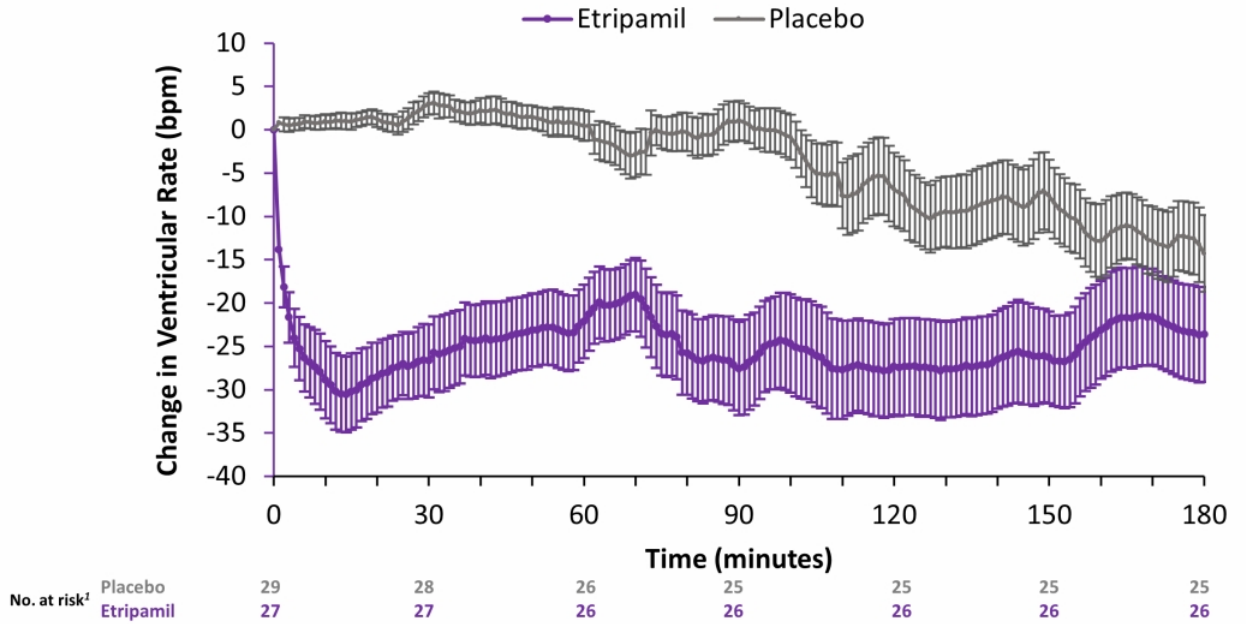


PRIMARY ENDPOINT: Maximum Reduction in VR from Baseline	Placebo NS, N=25 ¹	Etripamil NS, 70 mg, N=24 ¹
Mean (95% CI), bpm	-5.06 (-7.44, -2.67)	-34.97 (-45.13, -24.87)
Difference in means (95% CI), bpm	--	-29.91 (-40.31, -19.52)
p-value ²	--	<0.0001

Note: Data plotted on time course are not those directly used for calculation of Primary Endpoint (by pre-specified plan). X-axis: of plot: time following drug administration; Y-axis: min moving average, bpm \pm SEM. ¹ Efficacy Population (all randomized patients receiving study drug remaining in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug). ² By ANCOVA. Bpm = beats per minute. CI = confidence interval. SEM = standard error of the mean, VR = ventricular rate.

ReVeRA – Mean VR Change from Baseline (180 min)¹

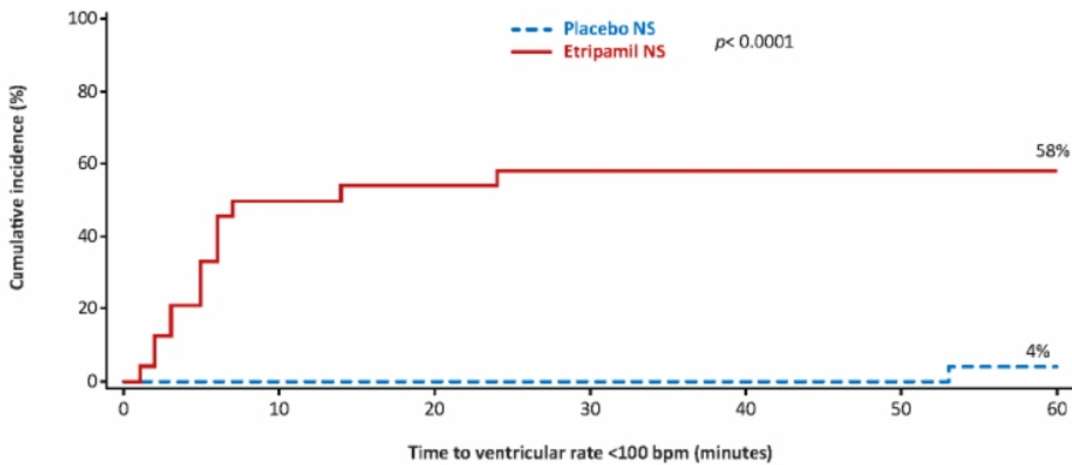
ReVeRA Data Show Lasting Duration of Etripamil Effect, up to 150 min



Separation of Curves: difference between areas under the curves over 180 min **p < 0.00001²**

¹ mITT Population (all randomized patients receiving study drug). ² From t-test of difference between the areas under the curves (AUC) of plots of absolute mean heart rate. X-axis of plot: time following drug administration; Y-axis of plot: 5-min moving average, bpm ± SEM. Bpm = beats per minute; CI = confidence interval. SEM = standard error of the mean.

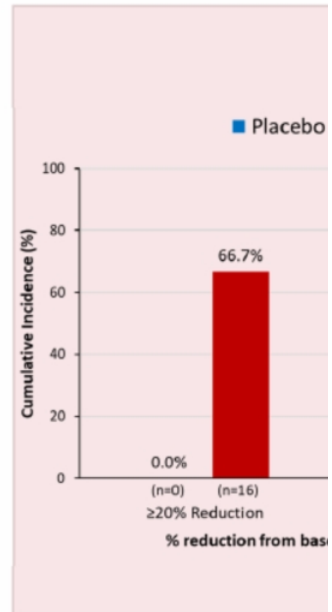
ACHIEVEMENT OF VR <100 BPM OR A REDUCTION OF ≥10% OR ≥20 FROM BASELINE BY 60 MINUTES



No. at risk	0	10	20	30	40	50	60
Placebo NS	25	25	25	25	25	25	24
Etripamil NS	24	12	11	10	10	10	10

Patients Achieving a VR <100 bpm	Placebo NS, n=25 ¹	Etripamil NS, 70 mg, n=24 ¹
n (%)	1 (4.0)	14 (58.3)
p-value ²	—	<0.0001
Median time to achieve VR < 100 bpm	not applicable	7 min

¹ Efficacy Population is comprised of all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. ² By chi-square test. Bpm = beats per minute; NS = nasal spray; VR = ventricular rate



Placebo NS (n=25¹) vs. Etripamil NS

Patients Achieving a ≥20% reduction in VR from baseline, p-value²

Patients Achieving a ≥10% reduction in VR from baseline, p-value²

ReVeRA: TSQM-9 PRO¹ Assessment & Results

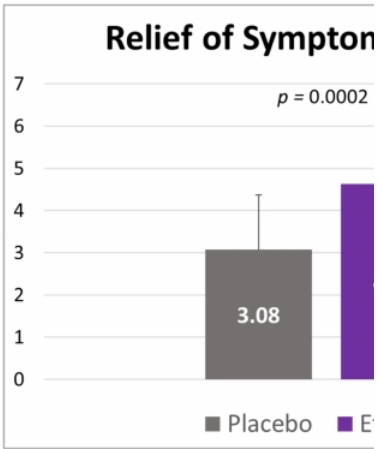
ReVeRA Data Show Significant Improvement in Patient Reported Relief of Symptoms

- TSQM-9 PRO¹ includes an Effectiveness Domain
- Domain includes three questions, each answered on 7-point anchored scale

1	2	3	4	5	6	7
Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied

- The domain score is calculated from its three question scores
 - Domain score is on a 0 to 100-point scale
 - Domain score of 50/100 corresponds to a 4/7 = "Somewhat Satisfied"

	Placebo ² N=25	Etripamil ² N=24	p value ³
Effectiveness Domain Scores, mean (SD)	36.67 (21.64)	62.69 (21.59)	p<0.0001



Delta = 1.55 units on Relief of Symptom

¹ Treatment Satisfaction Questionnaire for Medication-9, a validated Patient-Reported Outcome tool.
² Efficacy Population (all randomized patients receiving study drug remaining in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug). ³ From t-test

ReVeRA Study - Most Common Adverse Events (≥5% frequency)

Patients with ≥1 of most common adverse events (≥5%) ¹	Placebo (N= 29) ²	Etripamil (N=27) ²
Nasal Discomfort	11 (37.9%)	16 (59.3%)
Rhinorrhea	1 (3.4%)	9 (33.3%)
Increased Lacrimation	5 (17.2%)	8 (29.6%)
Throat Irritation	--	5 (18.5%)
Dizziness	3 (10.3%)	3 (11.1%)
Bradycardia	--	2 (7.4%) ³
Epistaxis	--	2 (7.4%)
Nasal Congestion	1 (3.4%)	2 (7.4%)
Nasopharyngitis	--	2 (7.4%)
Nasal Congestion	1 (3.4%)	2 (7.4%)
Oropharyngeal Pain	--	2 (7.4%)
Paresthesia	2 (6.9%)	1 (3.7%)
Intracardiac Thrombus	2 (6.9%)	--

¹ Treatment-emergent adverse events, MeDRA terms. ² Safety Population (all randomized patients receiving study drug). ³ Two patients each with 1 event of brady

ReVeRA Study - Summary of Serious Adverse Events

- One etripamil patient experienced 2 SAEs classified as related to study drug
 - Transient severe bradycardia and syncope, assessed as due to hyper-vagotonia
 - Occurred in a patient with a history of vagal events
 - Fully resolved with placing the patient supine and without sequelae
- Two placebo patients experienced 4 SAEs
 - Patient-1: Intracardiac thrombus, peripheral artery occlusion
 - Patient-2: Myocardial ischemia, atrial fibrillation

SAE = Serious Adverse Event.

ReVeRA demonstrated:

Primary Endpoint: Treatment Effect Size

- Goal: 20 bpm VR reduction¹ vs placebo
- ReVeRA: -30 bpm vs placebo; -35 bpm absolute in etripamil arm

Primary Endpoint: Statistical Significance

- Goal: $p \leq 0.05$
- ReVeRA: $p < 0.0001$

Speed of Action

- Goal: quick on-set
- ReVeRA: quick on-set. Median time to maximum reduction: 13 min in etripamil arm. achievement of responder status (eg, VR <100 bpm)

Duration of Action

- Goal: at least 30 min (for the 1 dose in this study)
- ReVeRA: ~150 min

Symptomatic Relief

- Goal: positive trends, show feasibility of TSQM-9² in AFib-RVR patients
- ReVeRA: Improvement in satisfaction of effectiveness ($p < 0.0001$) & symptom-relief (p and scores apparently exceeding minimally-important-difference benchmarks.

Safety & Tolerability

- Goal: findings aligned with PSVT program experience
- ReVeRA: goals met (with monitored drug administration)

¹ Reduction from baseline. ² Treatment Satisfaction Questionnaire for Medication-9. AFib-RVR = atrial fibrillation with rapid VR, VR = ventricular rate

FDA Pre-IND Guidance for Path to Approval in AFib-RVR¹

- Single study with self-administered etripamil and in an at-home setting, to gain a label indication via supplemental NDA (sNDA)
- Can utilize the safety database from PSVT
- Primary analysis to be on ITT population (all patients who receive drug)
- Reduction in VR may be primary endpoint
- Patient benefit on symptoms, via patient reported outcome (PRO), must be Key Secondary Endpoint:
 - $p < 0.05$ to gain approval
 - Key recommendation: use of anchored 7-point scale; FDA gave latitude on specific PRO
 - FDA expectation of 1-unit improvement in Target population (with verified AFib-RVR)

1) We expect to have additional discussion with FDA regarding the proposed design of our Phase 3 pivotal trial, including whether the proposed Phase 3 p support registration of etripamil for the treatment of AFib-RVR. AFib-RVR = atrial fibrillation with rapid VR. VR = ventricular rate.

Proposed Phase 3 Registrational Study in AFib-RVR¹

- Key Inclusion Criteria: history of symptomatic episodes of AFib-RVR
- Patients self-administer drug at-home for perceived episodes of AFib-RVR
- Dose: etripamil NS 70 mg, repeat-dose regimen
- Target Population = patients with verified AFib-RVR
- ITT Population = patients self-administering study drug for perceived AFib-RVR
- Primary endpoint = change from baseline to nadir VR, same as ReVeRA; etripamil vs
- Key secondary = PRO similar to TSQM Effectiveness Domain or Relief of Symptoms C
- Estimated study size: $N \approx 150-200$ total events, based on²: PRO delta of 1.2 units, 90%
 $p < 0.05$

¹ We expect to have additional discussion with FDA regarding the proposed design of our Phase 3 pivotal trial, including whether the proposed trial will support etripamil for the treatment of AFib-RVR. ² Sizing assumptions also include standard deviation = 1.6 & Target/ITT population ratio of 0.70. AFib-RVR = atrial fibrillation with ventricular rate; ITT = intention to treat; NS = nasal spray; TSQM = Treatment Satisfaction Questionnaire for Medication patient reported outcome tool.

AFib-RVR Program Timeline Projections

- FDA Confirmation of Ph3 Protocol: 1Q 2024
- Study Start: Mid 2024
- Top-Line Data: Mid 2026

Market Opportunity for Etripamil in AFib-RVR

KOL View on Currently Available Approaches / Unmet Need in AFib

- Regardless of rate- or rhythm-control strategy, break-through episodes of AFib-RVR are frequent, symptomatic, highly burdensome, and disruptive
- Current treatment of acute attacks in the emergency department are burdensome and costly
- Expensive and inefficient use of healthcare system resources
- What would be helpful, and is currently missing, is a simple, fast-acting treatment, that could:
 - be self-administered at-home
 - reduce burden of episodes, and reduce trips to ED and calls to phy

KOL = Key Opinion Leader; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; ED = Emergency Department

Source: Milestone Pharmaceuticals Virtual Key Opinion Leader Event on Etripamil for the Treatment of AFib-RVR, May 22, 2023; <https://investors.milestonepharma.com/ever>

Milestone - Atrial Fibrillation Program Overview

PSVT & AFib-RVR Populations in the US

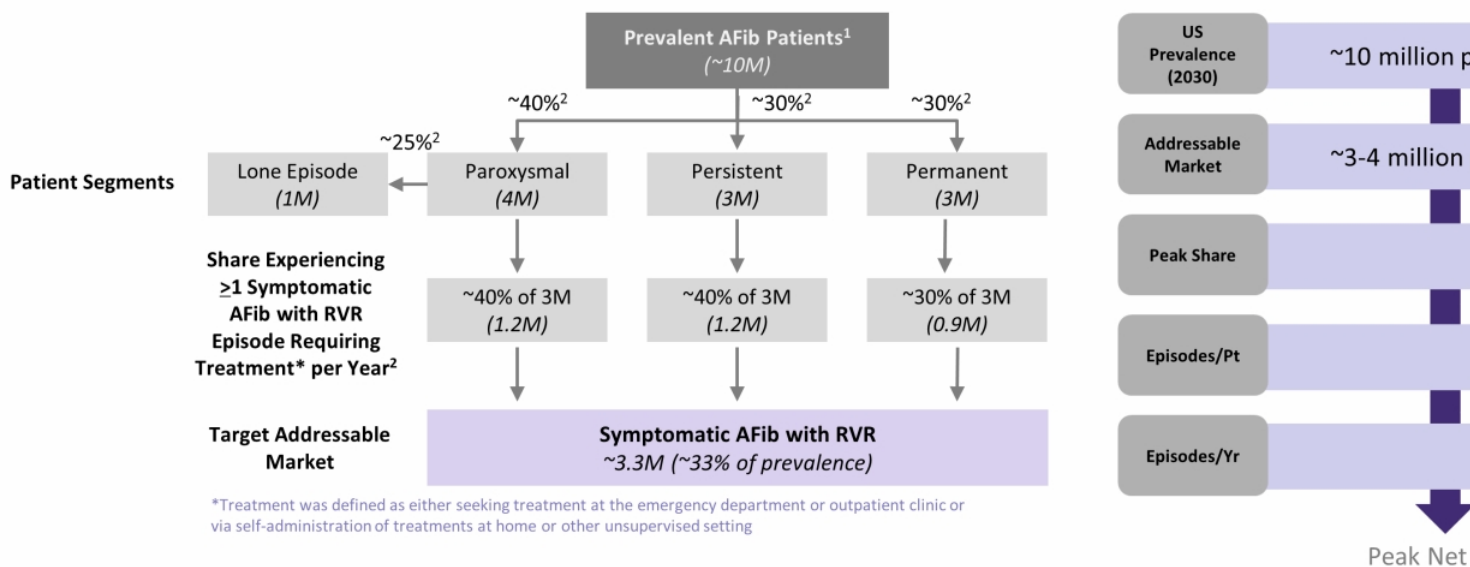
	PSVT	Atrial Fibrillation
Total Patients (2030)	2.6 Million ³	10 Million
Discharged ED Visits & Hospital Admissions (2016) ²	145 Thousand	785 Thousand
Target Addressable Market (2030) Patient Population	1.0-1.6 Million ⁵	AFib-RVR ~3-4 Million

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 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 a CAGR of ~2% 4. Quantitative Survey conducted by Triangle Insights, May 2021, N=250 Clinical Cardiologists, Interventional Cardiologists, and Electrophysiologists. 5. Estim 60% of prevalence) based 2019 market research with patients conducted by BluePrint Research Group, (n=247)

Milestone - Atrial Fibrillation Program Overview

Peak US Market Opportunity for Etripamil in AFib-RVR

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

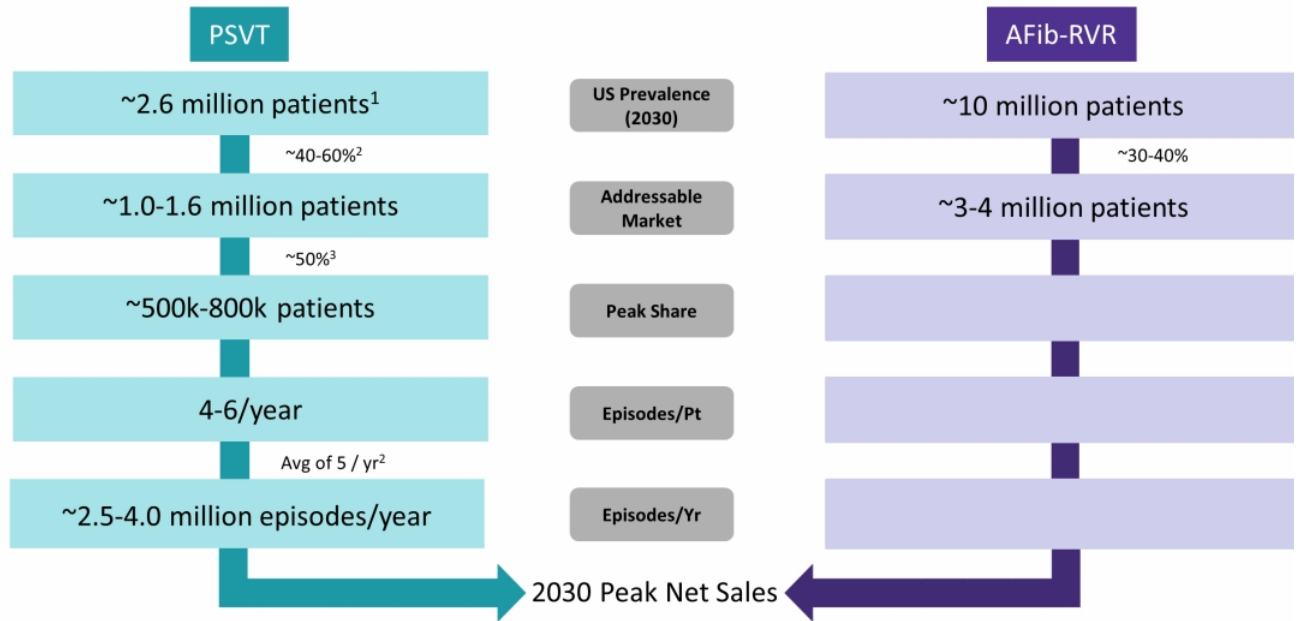


AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

- Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Miyasaka et al., Circulation, 2006, 114, 119-125; 10M estimate reflects the midpoint of published estimates (~8M to ~12M)
- Quantitative Survey conducted by Triangle Insights, May 2021, N=250 Clinical Cardiologists, Interventional Cardiologists, and Electrophysiologists

Milestone - Atrial Fibrillation Program Overview

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

AF – RVR = Atrial Fibrillation with Rapid Ventricular Rate; TAM = Target Addressable Market

Sources: 1. Rehorn et al. Journal of Cardiovascular Electrophysiology. 2021 Aug; 32(8): 2199-2206. doi: 10.1111/jce.15109. ; 2. 2019 market research with patients conducted Research Group, (n=247); 3. 2020 market research with healthcare providers conducted by Triangle Insights Group, (n=250)

Milestone - Atrial Fibrillation Program Overview

Finances – as of September 30, 2023



Cash and short-term investments of \$75.7M



Synthetic Royalty Financing of \$75M available upon approval⁽¹⁾



Cash as of September 30, 2023 together with synthetic royalty financing expected to fund operations into mid-2025



Equity - 43.1M in shares and pre-funded warrants outstanding

- 33.5M common shares
- 9.6M pre-funded warrants

(1) In March 2023, Milestone announced a \$125.0M strategic partnership with RTW Investments. The financing consists of \$50.0M in convertible notes issued in March 2023, and a convertible 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.

Strategic Approach to Value Creation

- 2024 – Financially prudent commercial build to prepare for launch
- 2025 – Staged entry following market access to demonstrate PSVT market potential
- 2026 – Deliver phase 3 data in AFib-RV
 - Fully access cardiology market for PSVT with additional reps/resources
- 2027+ – Expand revenue with AFib-RVR label and additional investments/commercial spend post break even

Milestone Pharma - Targeting Significant 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

- Positive Phase PSVT
- NDA submission
- AFib-RVR program expands market
- Phase 2 data
- Experienced leadership driving commercial success

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

Appendix

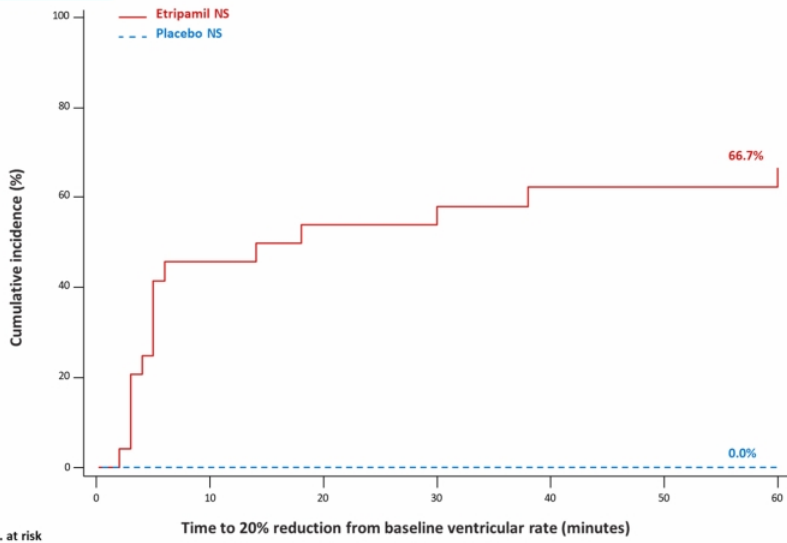
TSQM-9: Effectiveness Domain Questions

Answer scale for
each question:

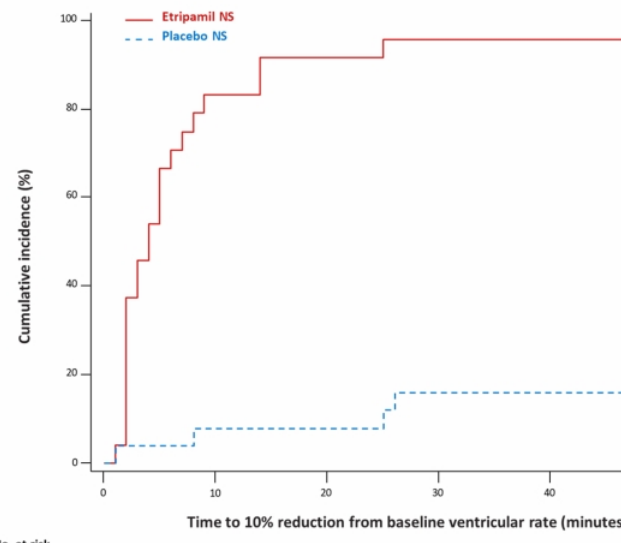
1	2	3	4	5	6	7
Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied

1. How satisfied or dissatisfied are you with the ability of the medication or condition?
2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?
3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

Time from Drug Administration to $\geq 20\%$ and $\geq 10\%$ Reductions from Baseline Ventricular Rate



No. at risk	0	5	10	15	20	30	40	50	60
Placebo	25	25	25	25	25	25	25	25	25
Etripamil	24	13	11	11	9	9	9	9	9



No. at risk	0	5	10	15	20	25	30	40	45
Placebo	25	23	23	21	21	21	21	21	21
Etripamil	24	4	2	1	1	1	1	1	1

	$\geq 20\%$ reduction	$\geq 10\%$ reduction
Difference in achievement of % reduction, p-value ^{1, 2}	<0.0001	<0.0001
Median time to achieve % reduction from baseline VR	Placebo: not achieved Etripamil: 14 min	Placebo: not achieved Etripamil: 4 min

¹ Efficacy Population is comprised of all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. ² By chi-square test



Milestone Pharmaceuticals Presents Positive Results from ReVeRA Phase 2 Study of Etripamil in AFib-RVR at the American Heart Association Scientific Sessions 2023

- Etripamil, an investigational drug, showed statistically significant reduction in ventricular rate by 30 beats per minute for episodes of atrial fibrillation with rapid ventricular rate ($p < 0.0001$) compared to placebo
- Results also showed statistically significant rapid and sustained reductions in ventricular rate and improvement in patient reported symptoms
- Safety and tolerability data were generally consistent with data from studies evaluating etripamil in PSVT
- Results support further clinical development in a Phase 3 clinical trial evaluating patient-administered etripamil for management of AFib-RVR

MONTREAL and CHARLOTTE, N.C., November 11, 2023 /PRNewswire/ -- Milestone Pharmaceuticals Inc. (Nasdaq: MIST) today announced positive Phase 2 data that show etripamil nasal spray resulted in rapid and statistically superior ventricular rate reduction and improved symptom-relief in patients with atrial fibrillation with rapid ventricular rate (AFib-RVR) compared to placebo. Safety and tolerability reported in the 56-patient safety population is generally consistent with that observed in Milestone's much larger Phase 3 paroxysmal supraventricular tachycardia (PSVT) program. The results were presented as a Featured Science presentation at the American Heart Association (AHA) Scientific Sessions 2023 and simultaneously published in *Circulation: Arrhythmia and Electrophysiology*. These data support further development of self-administered etripamil for the treatment of AFib-RVR.

Incidence of atrial fibrillation (AFib) in the United States is expected to grow to approximately 10 million by 2025 and up to about 12 million by 2030.^{1,2,3} Patients with AFib-RVR continue to face a significant unmet need for symptom relief. They can experience the burden of symptomatic acute attacks and our market research indicates 30-40 percent of patients with AFib experience one or more symptomatic episodes of rapid ventricular rate (RVR) per year requiring treatment.

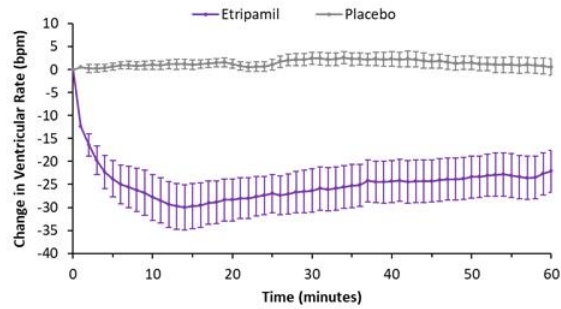
"Breakthrough episodes of rapid ventricular rate in patients with AFib are frequent and often symptomatic and may result in increasing burdens in patients' everyday lives and disruptions to the healthcare system. Today, there is an unmet need for a portable, fast-acting treatment solution that can be easily administered by patients when they experience a sudden episode," said A. John Camm, M.D., lead investigator, British Heart Foundation Emeritus Professor of Clinical Cardiology, The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK. "The results presented and published today from the ReVeRA Phase 2 study are encouraging for patients and healthcare providers who are seeking a treatment solution that delivers significant symptom relief and helps reduce potential visits to the emergency department."

"The results from the ReVeRA study are promising and demonstrate the potential of etripamil nasal spray to rapidly reduce heart rate and provide symptomatic benefit to patients suffering from AFib-RVR," said David Bharucha, MD, PhD, Chief Medical Officer, Milestone Pharmaceuticals. "We believe our recent NDA submission for etripamil for the potential treatment of PSVT, as well as FDA guidance received on AFib-RVR, provide a strong foundation for the continued clinical development of patient-administered etripamil with a Phase 3 study in AFib-RVR."

Randomized, Controlled Study of the Efficacy and Safety of Etripamil Nasal Spray: Findings from Phase 2 ReVeRA-201 Study (AHA Featured Science Session)

The randomized, controlled Phase 2 ReVeRA study treated 56 patients aged 18 years and older presenting in an emergency department or hospital with AFib with a ventricular rate of 110 or more beats per minute (bpm) prior to receiving either etripamil nasal spray or placebo. The study was designed to assess the reduction in ventricular rate (primary endpoint), the time to achieve maximum reduction in ventricular rate, the duration of effect, and patient satisfaction with treatment using the Treatment Satisfaction Questionnaire 9 (TSQM-9) patient reported outcome (PRO) tool (secondary endpoints).

Data from the ReVeRA trial showed that delivery of etripamil nasal spray significantly and rapidly reduced ventricular rate, consistent with the drug's pharmacologic profile. The study achieved its primary endpoint with high statistical significance with patients experiencing a mean ventricular rate reduction of 29.91 bpm (95% confidence interval: -40.31, -19.52; $p < 0.0001$) in the etripamil arm compared to placebo. The absolute maximum reduction in rate was 35 bpm in the etripamil arm, compared with 5 bpm in the placebo arm. The median time to maximum reduction in ventricular rate was 13 minutes in the etripamil arm, and time course graphs of mean ventricular rate reduction illustrate onset of etripamil within minutes after drug administration and lasting approximately 150 minutes compared to placebo.



A greater number of patients receiving etripamil achieved a ventricular rate of less than 100 bpm (58.3%) than those receiving placebo (4%). Furthermore, 67% of patients receiving etripamil achieved at least 20% reductions in ventricular rate and 96% achieved at least 10% reductions in ventricular rate in the first 60 minutes compared to 0% and 20% on placebo, respectively. Using the TSQM-9, compared to placebo, patients treated with etripamil demonstrated significant improvements in two satisfaction ratings: effectiveness ($p < 0.0001$) and relief of symptoms ($p = 0.0002$).

Serious adverse events (SAEs) occurring in the 24 hours after drug were rare, with two occurring in one patient in the etripamil arm (3.7%) and four occurring in two patients in the placebo arm (6.9%). The SAEs in the etripamil arm were transient severe bradycardia and syncope, assessed as due to hyper-vagotonia, which occurred in a patient with a history of vagal events, and fully resolved by placing the patient supine and without sequelae. The most common ($\geq 5\%$) adverse events were mild or moderate in intensity and included nasal discomfort and congestion, rhinorrhea ("runny nose"), and dizziness.

Investor and Analyst Call and Webcast

The Company will host an investor and analyst call and webcast on Monday, November 13, 2023, at 8:00 a.m. Eastern Time. The event will feature a review of the ReVeRA data, an overview of AFib-RVR and current treatment landscape, characteristics of etripamil, and commentary on next steps for Milestone's clinical development program for etripamil. To join the live call by phone, dial (877) 870-4263 (domestic) or (412) 317-0790 (international) and ask to be connected to the Milestone Pharmaceuticals call. To access the live or recorded webcast and accompanying slides, please visit the News & Events section of Milestone's investor relations website at investors.milestonepharma.com.

About Atrial Fibrillation with Rapid Ventricular Rate

An estimated five million Americans suffer from atrial fibrillation (AFib), a common arrhythmia marked by an irregular, disruptive and often rapid heartbeat. The incidence of AFib is expected to grow to approximately 10 million by 2025 and up to about 12 million by 2030.^{1,2,3} A subset of patients with AFib experience episodes of abnormally high heart rate most often accompanied by palpitations, shortness of breath, dizziness, and weakness. While these episodes, known as AFib-RVR, may be treated by oral calcium channel blockers and/or beta blockers, patients frequently seek acute care in the emergency department to address symptoms. In 2016, nearly 800,000 patients were admitted to the emergency department due to AFib symptoms where treatment includes medically supervised intravenous administration of calcium channel blockers or beta blockers, or electrical cardioversion. With little available data for AFib-RVR, Milestone's initial market research indicates that 30 to 40% of patients with AFib experience one or more symptomatic episodes of RVR per year that require treatment, suggesting a target addressable market of approximately three to four million patients in 2030 for etripamil in patients with AFib-RVR.

About Etripamil

Etripamil is Milestone's lead investigational product. It is a novel calcium channel blocker nasal spray under clinical development for elevated and often highly symptomatic heart-rate attacks associated with PSVT and AFib-RVR. It is designed to be a rapid-response therapy that is self-administered by the patient, without the need for direct medical oversight. If approved, etripamil is intended to provide health care providers with a new treatment option to enable on demand care and patient self-management. If approved, the portable treatment, studied as self-administered, may provide patients with active management and a greater sense of control over their condition. CARDAMYST™, the conditionally approved brand name for etripamil nasal spray, is well studied with a robust clinical trial program that includes a completed Phase 3 clinical-stage program for the treatment of PSVT and Phase 2 proof-of-concept trial for the treatment of patients with AFib-RVR.

About Milestone Pharmaceuticals

Milestone Pharmaceuticals Inc. (Nasdaq: MIST) is a biopharmaceutical company developing and commercializing innovative cardiovascular medicines to benefit people living with certain heart conditions. Milestone recently submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for etripamil for treatment of an abnormal heart rhythm, paroxysmal supraventricular tachycardia or PSVT. Find out more at www.milestonepharma.com.

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," "continue," "could," "demonstrate," "designed," "develop," "estimate," "expect," "may," "pending," "plan," "potential," "progress," "will" 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 anticipated growth of incidence of AFib and AFib-RVR by 2030; the ability of etripamil to provide patients with a treatment solution that delivers significant symptom relief and helps reduce potential visits to the emergency department; the ability of etripamil nasal spray to rapidly reduce heart rate and provide symptomatic benefit to patients suffering from AFib-RVR; the continued ability of etripamil provided superior time to conversion to normal heart rhythm compared to placebo; the timing of the anticipated launch of etripamil; the success of the NDA submission for etripamil nasal spray and the timing of the FDA's approval of the NDA; and timing of the Phase 2 proof-of-concept trial of etripamil for the treatment of patients with AFib-RVR. 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, evaluation and results of our clinical trials; risks and uncertainty related to the complexity inherent in cleaning, verifying and analyzing trial data; and whether the clinical trials will validate the safety and efficacy of etripamil for PSVT or other indications, among others, general economic, political, and market conditions, including deteriorating market conditions due to investor concerns regarding inflation and Russian hostilities in Ukraine and ongoing disputes in Israel and Gaza and overall fluctuations in the financial markets in the United States and abroad, risks related to pandemics and public health emergencies, and risks related to the sufficiency of Milestone's capital resources and its ability to raise additional capital in the current economic climate. 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, 2022, and its Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 under the caption "Risk Factors," as such discussion may be updated from time to time by subsequent filings, we may make with the U.S. Securities and Exchange Commission. 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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¹ Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112:1142–1147.

² Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114:199–225.

³ Benjamin, E. J., Muntner, P., et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee (2019). Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*, 139(10), e56–e528.
