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

November 11, 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., Nov. 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.

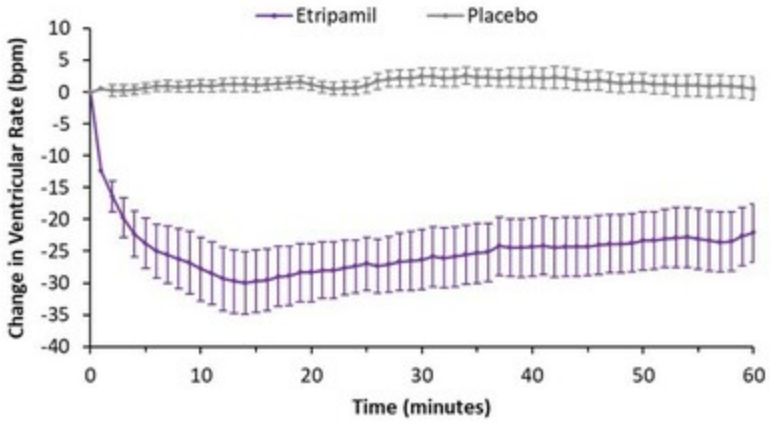
"Breakthrough episodes of rapid ventricular rate in patients with AFib are frequent and often symptomatic and may result in increasing burdens in patients' everyday lives and disruptions to the healthcare system. Today, there is an unmet need for a portable, fast-acting treatment solution that can be 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 (≥ 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 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.

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