Milestone Pharmaceuticals Initiates Pivotal Phase 3 Trial of Etripamil Nasal Spray for Self-Administered Treatment of Atrial Fibrillation with Rapid Ventricular Rate (AFib-RVR)

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ReVeRA-301 Trial is Evaluating the Same 70 mg Repeat-Dose Regimen that is FDA Approved for Paroxysmal Supraventricular Tachycardia (PSVT)

Research Builds on Phase 2 Findings that Etripamil 70 mg Dose Reduced Ventricular Rate and Improved Both Symptom Relief and Treatment Satisfaction in AFib-RVR Population

MONTREAL and CHARLOTTE, N.C., Aug. 21, 2026 (GLOBE NEWSWIRE) -- Milestone® Pharmaceuticals Inc. (Nasdaq: MIST), a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines, today announced that the first patient has been enrolled in the Phase 3 ReVeRA-301 pivotal trial evaluating etripamil for atrial fibrillation with rapid ventricular rate (AFib-RVR). The trial uses the same repeat-dose regimen as the pivotal trials for etripamil, which is FDA-approved for paroxysmal supraventricular tachycardia (PSVT) as CARDAMYST® (etripamil) nasal spray.

“Current management of AFib-RVR in the United States places a substantial burden on both patients and healthcare systems. Because patients experiencing AFib-RVR have no optimally effective self-administered treatment options, many of them require evaluation and treatment in the emergency department,” said James Ip, M.D., Principal Investigator of ReVeRA-301 and Professor of Medicine and Director of Cardiac Pacing and Implantable Devices at Weill Cornell Medicine, and a cardiac electrophysiologist at New York-Presbyterian/Weill Cornell Medical Center. “We are eager to determine if we can clinically validate a safe and effective self-administered treatment option that could reduce reliance on emergency department care for the millions of patients living with AFib-RVR.”

“Enrolling the first patient in the ReVeRA-301 Phase 3 trial marks an important point in the development of etripamil for patients with AFib-RVR,” said David Bharucha, M.D., PhD, FACC, Chief Medical Officer of Milestone Pharmaceuticals. “The FDA approval of etripamil for the treatment of acute, episodic PSVT in adults, and the promising Phase 2 data in patients with AFib-RVR, provide a strong foundation as we advance our clinical development program and evaluate etripamil in this area of substantial unmet medical need. We are activating clinical trial sites across North America and internationally to support efficient enrollment in this event-driven, global Phase 3 study. Today’s announcement is an exciting step forward in our efforts to address a significant unmet need in cardiovascular care.”

“Experiencing AFib-RVR can be very unsettling. It interrupts daily life and may require urgent medical care. The possibility of providing a self-administered treatment for use upon AFib-RVR onset represents an important area of research for patients with this condition,” said Mellanie True Hills, founder and CEO of StopAfib.org. “The start of the ReVeRA-301 study is an exciting milestone for the AFib patient community. We look forward to the knowledge this research may bring us as investigators evaluate a potential new treatment approach.”

About ReVeRA-301
ReVeRA-301 is a Phase 3 multinational, multi-center, randomized, double-blind, placebo-controlled study to evaluate the effects of etripamil nasal spray in approximately 150 patients with atrial fibrillation and RVR. Prompted by symptoms, patients will self-administer, in a medically unsupervised setting (e.g., at home), the same 70 mg dose of etripamil and repeat-dose regimen that supports the current FDA indication for the treatment of PSVT. Based on safety data demonstrated to date, Milestone is currently pursuing a single-study supplemental new drug application (sNDA) registration pathway for the treatment of AFib-RVR. The primary endpoint for ReVeRA-301 is reduction in ventricular rate (VR) within 30 minutes. The study will also evaluate a key secondary endpoint of symptom improvement via patient-reported outcomes. Clinical trial sites and enrollment information can be found at https://clinicaltrials.gov.

The trial advances research from ReVeRA-201, a multicenter Phase 2, randomized controlled study of the efficacy and safety of etripamil nasal spray for the acute reduction of symptomatic AFib-RVR in an emergency room setting. The clinical trial showed that a single dose of etripamil nasal spray at 70 mg reduced VR and improved both relief of symptoms and treatment satisfaction.

About Atrial Fibrillation with Rapid Ventricular Rate (AFib-RVR)
Atrial fibrillation (AFib) is the most common sustained arrhythmia, affecting over 6 million patients in the United States. AFib presents with an irregular heart rate and is classified as paroxysmal, persistent, or permanent. When there is a rapid heart rate during AFib, it is referred to as “atrial fibrillation with rapid ventricular rate (RVR).”

Market research indicates that 30-40% of patients with AFib experience at least one episode of RVR per year requiring urgent medical attention. These episodes commonly cause palpitations, shortness of breath, and weakness. While AFib is rarely life-threatening, it is a serious condition that often requires treatment and increases the risk of serious complications if not properly managed. Current options for acute AFib-RVR management are limited and often involve an emergency department visit for IV beta blockers, IV calcium channel blockers, or electrical cardioversion.

AFib Healthcare Economics
AFib management places a substantial and growing burden on the U.S. healthcare system. Across U.S. studies, incremental annual healthcare costs associated with AFib range from approximately $6,000 to $28,000 per patient, depending on the population, data source, cost categories analyzed, and dollar year reported. U.S. Healthcare Cost and Utilization Project (HCUP) data from 2015-2019 showed an 8.9% increase in emergency department (ED) utilization for AFib from 2015 to 2019. HCUP data from 2016-2020 showed that approximately 0.44% of all ED visits had a primary diagnosis of AFib, with nearly half of these AFib-related ED visits resulting in inpatient admission. The American Heart Association projects that the total U.S. economic burden of AFib will increase from $59.4 billion in 2020 to $174.8 billion by 2050, including an increase in direct healthcare costs from $54.8 billion to $167.3 billion, in 2022 U.S. dollars.

About CARDAMYST

CARDAMYST® (etripamil) nasal spray is approved by the U.S. Food and Drug Administration (FDA) for the conversion of acute symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm in adults. It is a novel calcium channel blocker nasal spray designed as a self-administered rapid response therapy for patients, thereby bypassing the need for immediate medical oversight. The product is intended to provide health care providers with a new treatment option to enable on-demand care and patient self-management. This portable treatment may provide patients with active management and a greater sense of control over their condition. CARDAMYST is well studied with a robust clinical trial program that includes a completed Phase 3 clinical-stage program for the treatment of PSVT. Currently, etripamil is in Phase 2 development for treatment of PSVT in pediatric patients and Phase 3 development for control of acute atrial fibrillation with rapid ventricular rate (AFib-RVR) in adults. For more information, please visit CARDAMYST.com.

Indication
CARDAMYST is indicated for the conversion of acute symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm in adults.

IMPORTANT SAFETY INFORMATION FOR CARDAMYST (etripamil)

What is CARDAMYST?
CARDAMYST is a prescription medicine used to help restore normal sinus heart rhythm in adults who have symptoms of sudden episodes of fast heartbeat called paroxysmal supraventricular tachycardia (PSVT).

It is not known if CARDAMYST is safe and effective in children.

Do not use CARDAMYST if you:

- are allergic to CARDAMYST or any of its ingredients. See the Patient Information for a complete list of ingredients in CARDAMYST.
- have limitations in activities due to heart failure (moderate to severe heart failure).
- have Wolff-Parkinson-White (WPW) syndrome, Lown-Ganong-Levine syndrome, or an abnormal heart rhythm pattern called pre-excitation (delta wave) on an electrocardiogram (ECG).
- have sick sinus syndrome without a permanent pacemaker.
- have second degree or higher atrioventricular (AV) block.

Before using CARDAMYST, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of fainting.
- have low blood pressure.
- are pregnant or plan to become pregnant. It is not known if CARDAMYST will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if CARDAMYST passes into your breast milk. You should stop breastfeeding for 12 hours after treatment with CARDAMYST. During this time, pump and throw away your breast milk. Talk to your healthcare provider about the best way to feed your baby after using CARDAMYST.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

What are the possible side effects of CARDAMYST?

CARDAMYST may cause serious side effects, including:

- **Fainting due to CARDAMYST effects on blood pressure, heart rate, and electrical activity of the heart.** CARDAMYST may cause dizziness and fainting, especially in people with a history of fainting and certain heart problems, or people with a history of fainting during an episode of PSVT. Use CARDAMYST while sitting in a safe area where you will not fall if you become dizzy or lightheaded. Lie down if you feel dizzy or lightheaded after using CARDAMYST. If fainting occurs after using CARDAMYST, caregivers should place you on your back and seek medical help.

The most common side effects of CARDAMYST include:

• nasal discomfort • nasal congestion • runny nose	• throat irritation • nosebleed

These are not all of the possible side effects for CARDAMYST. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see the full Prescribing Information
https://milestonepharma.com/etripamilprescribinginformation.pdf for CARDAMYST.

About Milestone Pharmaceuticals
Milestone Pharmaceuticals Inc. (Nasdaq: MIST) is an emerging commercial-stage biopharmaceutical company advancing innovative cardiovascular medicines to benefit people living with certain heart conditions. Milestone's lead product is CARDAMYST ® (etripamil) nasal spray, a novel calcium

channel blocker, which is FDA-approved for the conversion of acute symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm in adults. Etripamil is also in Phase 3 development for the control of symptomatic episodic attacks associated with AFib-RVR. https://milestonepharma.com/

Cautionary Note on 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," "intend" 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: Milestone's business strategy and plans; the design, timing, and enrollment of the ReVeRA-301 Phase 3 clinical trial for AFib-RVR, including the anticipated number of patients and sites; the potential for etripamil to serve as a treatment option for patients with AFib-RVR, including as a self-administered therapy; the commercialization and market adoption of CARDAMYST; the development of etripamil for additional indications, including Phase 2 development in pediatric PSVT patients; expectations regarding the efficacy and safety of etripamil for AFib-RVR based on Phase 2 findings; the timing and outcomes of future interactions with U.S. and foreign regulatory bodies, including the FDA; projections regarding the economic burden of atrial fibrillation, including estimated healthcare costs and emergency department utilization; and other statements not related to historical facts. 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 Milestone's 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, international tariffs and conflicts, 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 (SEC), including in its annual report on Form 10-K for the year ended December 31, 2025 under the caption "Risk Factors," as such discussions may be updated from time to time by subsequent filings Milestone may make with the SEC. Except as required by law, Milestone assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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