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Milestone Pharmaceuticals Announces Topline Results from First-of-its-kind Phase 3 NODE-301 Trial of Etripamil for At-home Acute PSVT Treatment

March 23, 2020

- Study missed primary endpoint of mean time to conversion of SVT to SR over a five-hour period following dosing ($p=0.12$) –
- Etripamil showed rapid conversion of SVT to SR during the first 45 minutes ($p=0.02$), consistent with its known pharmacology –
- Study demonstrated a positive safety profile showing etripamil was well tolerated in the at-home setting –
- Small number of placebo patients and prolonged efficacy measurement period confounded results –
- Company plans to discuss next steps with regulators and continue its full PSVT clinical program, including NODE-301B, NODE-302 and NODE-303 –
- Company to host conference call today at 5:00 p.m. ET –

MONTREAL and CHARLOTTE, N.C., March 23, 2020 /PRNewswire/ -- Milestone Pharmaceuticals Inc. (Nasdaq: MIST), a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines, today announced topline results from its Phase 3, multicenter, randomized, double-blind, placebo-controlled NODE-301 trial of its investigational new drug, etripamil nasal spray, the Company's novel short-acting calcium channel blocker, in patients with paroxysmal supraventricular tachycardia (PSVT).



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The NODE-301 trial, which enrolled a total of 431 patients across 65 sites in the U.S. and Canada, is an event-driven Phase 3 efficacy trial of etripamil for terminating supraventricular tachycardia (SVT) episodes in the at-home setting. Etripamil (70mg) did not achieve its primary endpoint of time to conversion of SVT to sinus rhythm (SR) compared to placebo over the five hour period following study drug administration (median time to conversion of 25 minutes [95% CI: 16, 43] for etripamil vs. 50 minutes [95% CI: 31, 101] for placebo, $p=0.12$). Despite early activity, including the conversion of 61% of etripamil patients vs. 45% of placebo patients by 45 minutes ($p=0.02$), a time period consistent with etripamil's known pharmacological activity, results from the latter part of the analysis confounded the statistical analysis of the primary endpoint.

The study demonstrated statistically significant improvements in favor of etripamil over placebo in the important secondary endpoint of patient reported treatment satisfaction, as measured by a treatment satisfaction questionnaire for medication (TSQM-9), including global satisfaction ($p=0.0069$) and effectiveness scores ($p=0.0015$), with questions addressing the relief of symptoms commonly associated with an episode of SVT, such as rapid pulse, heart palpitations, anxiety, shortness of breath and dizziness. Additionally, there was a trend in improvement in the percentage of patients seeking rescue medical intervention, including in the emergency department, with etripamil and placebo patients reporting 15% and 27%, respectively ($p=0.12$).

The safety and tolerability data from the NODE-301 study are supportive of at-home use of etripamil, with adverse events (AE) consistent with those observed in prior trials. The most common AEs observed in patients receiving etripamil were local to the nose, including nasal irritation and congestion, and these events were typically transient in nature and most commonly characterized by the patient as mild in severity. There were no significant differences in incidences of severe adverse events or adverse events of interest, such as atrioventricular nodal blocks or blood pressure-related symptoms, across the etripamil and placebo groups.

NODE-301B, which was designed to collect double-blind data from randomized patients who had not yet experienced an event after the NODE-301 trial reached its target number of adjudicated SVT events, continues. These data will be analyzed separately as a second data set. In addition, open-label safety studies of etripamil in subjects with PSVT, NODE-302 and NODE-303, are ongoing with active recruitment underway. The Company is actively monitoring the potential impact of the COVID-19 pandemic on its ongoing trials and will provide updates on any delayed timelines or cost impacts in the future. The Company expects to request a meeting with regulators to discuss the NODE-301 results and its ongoing studies.

"Efficacy signals across the earlier time points in NODE-301, in both primary and secondary endpoints, correlate directly with our understanding of the drug's known pharmacologic activity. We are also encouraged to see very good safety and tolerability across the broad population enrolled in this study. That said, outcomes after 100 minutes, which were affected by a very small number of placebo patients remaining in the study at that time, suggest that the design and analysis plan used in NODE-301 negatively impacted the study's outcome," said Joseph Oliveto, President and Chief Executive Officer of Milestone Pharmaceuticals. "The overall results of the study reinforce our understanding of the promising profile of etripamil and meaningfully inform us how best to prove its efficacy moving forward."

Mr. Oliveto added: "We will continue to execute as prudently possible on the ongoing NODE studies, including NODE-301B, and look forward to reviewing these data with regulators. The ongoing pandemic highlights the need for, and strengthens our commitment to, home use therapies."

"PSVT places a significant burden on patients and the healthcare system, and a fast-acting therapy to resolve its symptoms when and where episodes

occur would have a material impact on both," said Bruce Stambler, MD, FHRS, Piedmont Heart Institute, Atlanta, GA. "NODE-301 is a first-of-its-kind study, and as such encountered a number of challenges relative to studying SVT episodes outside of a controlled electrophysiology laboratory environment. The safety results support at-home use and the multiple efficacy signals show us that, with a confirmatory study, etripamil could fulfill the promise of delivering a fast-acting, patient administered therapy for PSVT."

Conference Call and Webcast

Milestone will host a conference call and webcast to discuss the results of the NODE-301 trial today, March 23, 2020 at 5:00 p.m. ET. To access the live call by phone, dial (800) 529-3311 (domestic) or (470) 495-9164 (international); the conference ID is 6152207. A live audio webcast of the event may also be accessed through the "Investors" section of Milestone's website at www.milestonepharma.com. A replay of the webcast will be available for 30 days following the event.

About NODE-301

The NODE-301 trial is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of etripamil, the Company's lead investigational product. Etripamil is a novel calcium channel blocker in the form of a nasal spray, intended for the acute treatment of PSVT and other episodic cardiovascular conditions wherever they occur. The study is designed for a population of those PSVT patients who historically experience 20 minutes or longer SVT episodes or episodes requiring termination in the emergency department. Following an in-office test dose of etripamil, 97.5% of patients were randomized (2:1) to receive either 70 mg of etripamil or placebo. Upon onset of PSVT symptoms, patients applied a wireless cardiac monitor to their chest to record heart rhythm, performed a vagal maneuver, and, if symptoms persisted, administered study drug. Of the 198 patient-reported events for which study drug was administered, a total of 156 were confirmed to be SVT events by a central independent adjudication committee and used to assess the study's efficacy endpoints.

The primary endpoint of the NODE-301 study is time to conversion of an SVT episode to sinus rhythm after the administration of study drug, as confirmed by a central independent adjudication committee. Secondary study endpoints include relief of symptoms commonly associated with an episode of SVT such as heart palpitations, chest pain, anxiety, shortness of breath, dizziness, or fainting, and rating of treatment satisfaction questionnaire for medication (TSQM).

About Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is a rapid heart rate condition characterized by intermittent episodes of supraventricular tachycardia (SVT) that start and stop suddenly and without warning. Episodes of SVT are often associated with symptoms including palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting, and anxiety. Certain calcium channel blockers have long been approved for the treatment of PSVT as well as other cardiac conditions; however, when calcium channel blockers are used for the termination of SVT episodes, they must be administered intravenously under medical supervision, usually in an emergency department or other acute care setting.

About Etripamil

Etripamil, the Company's lead investigational product, is designed to be a rapid response therapy for episodic cardiovascular conditions. The novel calcium channel blocker is self-administered via a nasal spray which may shift the current treatment paradigm for many patients with PSVT from the emergency department to the at-home setting. Milestone is conducting a comprehensive development program for etripamil, with Phase 3 trials underway in PSVT, and plans to commence a Phase 2 proof-of-concept trial in atrial fibrillation patients with rapid ventricular rate, with subsequent studies expected in other conditions where calcium channel blockers are used.

About Milestone Pharmaceuticals

Milestone Pharmaceuticals is a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. 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 "may," "will," "expect," "plan," "anticipate," "estimate," "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 (i) the design, progress, timing, scope and results of clinical trials, (ii) potential interactions with regulators, and (iii) the possibility that data will support future development. 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 COVID-19, and risks related to 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, 2019, 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.

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