Milestone Pharmaceuticals Announces Regulatory Guidance and Updated Clinical Development Plan for Etripamil in PSVT

July 23, 2020

- Recently completed NODE-301 and ongoing NODE-301B studies can be used as two efficacy studies supporting a future NDA submission (target p-values of <0.05) -

- NODE-301B, renamed the RAPID study, will reopen to enrollment and incorporate a repeat dosing regimen; results anticipated in late 2021/early 2022 -

- Proceeds from $25 million private placement expected to fund planned operations into the second quarter of 2022 -

- Company to host conference call today, July 23, 2020, at 8:30 a.m. ET -

MONTREAL and CHARLOTTE, N.C., July 23, 2020 /PRNewswire/ -- Milestone Pharmaceuticals Inc. (Nasdaq: MIST), a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines, today announced a clinical and regulatory update for its pivotal program with etripamil following recent interactions with the U.S. Food and Drug Administration (FDA). Etripamil nasal spray is the Company's investigational novel short-acting calcium channel blocker for patients with paroxysmal supraventricular tachycardia (PSVT).

"We are pleased with the outcome of our recent interactions with the FDA, as they outline an efficient path to registration for etripamil which eliminates the need to start a new Phase 3 study," said Joseph Oliveto, President and Chief Executive Officer of Milestone Pharmaceuticals. "The FDA agreed with our plan to modify the ongoing NODE-301B study, now known as the RAPID study, to highlight the unique pharmacology of etripamil, including a primary endpoint of time to conversion within 30 minutes. This study, together with our recently completed NODE-301 study, which will also now use a 30 minute endpoint, will serve to fulfill the efficacy requirements for a New Drug Application (NDA) for etripamil in PSVT."

Mr. Oliveto added, "In addition to expanding the RAPID study, the modified design will direct patients to administer an additional dose of study drug 10 minutes after the first dose if they still experience signs and symptoms of a supraventricular tachycardia (SVT) episode. We believe this dosing regimen provides a tailored approach to increase efficacy in patients with more persistent events and improve the overall clinical utility of etripamil. We look forward to reopening enrollment in the RAPID study later this year, with results anticipated in late 2021/early 2022."

The Company announced separately today that it has entered into a securities purchase agreement with existing shareholder RTW Investments, LP for a $25 million private placement. The Company believes that net proceeds from the private placement, together with its existing cash, cash equivalents and short-term investments, will be sufficient to fund its planned operations into the second quarter of 2022. Commenting on the agreement, Mr. Oliveto said, "We are pleased to have the strong, continued support of our largest shareholder, RTW, and to be in a position to fund the RAPID study through to topline data readout."

Regulatory Updates and Clinical Development Plan in Detail

The FDA indicated that two studies, the RAPID study and the completed NODE-301 study, could fulfill the efficacy requirement for the Company's NDA for etripamil in patients with PSVT. The Company proposed and the FDA agreed to the following program changes:

- **Both the RAPID and NODE-301 studies will assess the time to conversion over the first 30 minutes after drug administration as the primary endpoint.** Under an updated statistical analysis plan (SAP), the primary efficacy endpoint for both the RAPID and NODE-301 studies will be defined as time to conversion over the first 30 minutes, with a target p-value of less than 0.05 for each study. This endpoint supports the desire of patients to rapidly address their PSVT symptoms during an episode and ideally avoid visiting the emergency department. Later and earlier time points will also be assessed as part of secondary analyses to fully characterize the efficacy profile of etripamil.

When employing the updated SAP, results from NODE-301 show that 54% of etripamil patients vs. 35% of placebo patients converted within 30 minutes (HR 1.87, p=0.02), which clinicians and cardiovascular thought leaders indicate is a clinically-meaningful outcome given the symptomatic nature of SVT episodes and the lack of approved at-home treatments. Assuming a positive outcome in the RAPID study, this data could serve to fulfill the efficacy requirement for the NDA.

- **RAPID study to reopen enrollment with tailored dosing regimen to optimize clinical utility.** The RAPID study, which was originally designed to collect double-blind data from randomized patients who had not yet experienced an SVT event after the NODE-301 study reached its target number of adjudicated SVT events, will be amended and expanded to serve as a pivotal efficacy and safety study. The study will include the 170 patients who are already enrolled, and will be completed after a total of 180 confirmed SVT events are reached, including those that have already occurred in the study. Additional patients enrolled in the RAPID study will be randomized 1:1.

Based on discussions with the FDA regarding maximizing the treatment effect of etripamil, the RAPID study will allow for an optional repeat administration of study drug (either 70 mg of etripamil or placebo) for patients who have not experienced symptom relief within 10 minutes of the first study drug administration. This tailored regimen, which is similar to current PSVT treatment practices in the emergency department

setting, is enabled by the favorable safety data from the NODE-301 study. The Company expects that the repeat administration could benefit a broader group of patients, including those with more persistent episodes. In the NODE-301 study, 32% of etripamil patients and 14% of placebo patients converted to sinus rhythm within 10 minutes. The FDA agreed that the single and repeat administrations of etripamil will be pooled and compared to placebo for the primary analysis, resulting in no increase in the sample size.

The Company expects to reopen enrollment in the RAPID study later this year, with data anticipated in late 2021/early 2022.

Conference Call

Milestone will host a conference call and webcast to discuss the regulatory guidance and updated clinical development plan today, July 23, 2020 at 8:30 a.m. ET. To access the live call by phone, dial (800) 529-3311 (domestic) or (470) 495-9164 (international); the conference ID is 4085796. 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 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 approved 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 studies underway in PSVT, and plans to commence a Phase 2 proof-of-concept trial in atrial fibrillation patients with rapid ventricular rate, with subsequent trials expected in other conditions where calcium channel blockers are used.

About NODE-301

NODE-301 is a Phase 3, multicenter, randomized (2:1), double-blind, placebo-controlled single administration study of etripamil nasal spray in patients with PSVT. The study targeted a total of 150 adjudicated SVT events. Top line results were reported in March 2020. Despite early activity at 30 minutes, a time period consistent with the relevant pharmacodynamic effect of etripamil, the study did not achieve its primary endpoint of time to conversion of SVT to sinus rhythm (SR) compared to placebo over the pre-specified five hour period following study drug administration (p=0.12). The small number of placebo patients and prolonged efficacy measurement period was found to have confounded the statistical analysis of the results. The study did demonstrate statistically significant improvements in favor of etripamil over placebo in the important secondary endpoint of patient reported treatment satisfaction, as well as a trend toward a reduction in emergency department visits. The Company believes the safety and tolerability data from the NODE-301 study is supportive of at-home use of etripamil, with adverse events consistent with those observed in prior trials.

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 the RAPID study, (ii) potential clinical trials in other cardiac conditions and (iii) the possibility that data will support FDA approval. 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 trial, 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 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 quarterly report on Form 10-Q for the quarter ended March 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.

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

View original content to download multimedia:http://www.prnewswire.com/news-releases/milestone-pharmaceuticals-announces-regulatory-guidance-and-updated-clinical-development-plan-for-etripamil-in-psvt-301098526.html

SOURCE Milestone Pharmaceuticals, Inc.