Windtree Announces Positive Phase 2b Topline Clinical Results with Istaroxime Significantly Improving Cardiac Function and Blood Pressure in Heart Failure Patients in Early Cardiogenic Shock

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Istaroxime treatment significantly improved systolic blood pressure as well as cardiac output and renal function without increasing heart rate or clinically significant arrythmias

NYHA heart failure classification was improved up to 72 hours with a serious adverse event profile generally similar to placebo

WARRINGTON, Pa., Sept. 30, 2024 (GLOBE NEWSWIRE) -- Windtree Therapeutics, Inc. ("Windtree" or the "Company") (NasdaqCM: WINT), a biotechnology company focused on advancing early and late-stage innovative therapies for critical conditions and diseases, today announced positive topline clinical results for its Phase 2b SEISMiC Extension Study of istaroxime in heart failure patients in early cardiogenic shock.

Early cardiogenic shock is caused by a failing heart and is characterized by low blood pressure, leaving the patient at risk of developing inadequate blood flow to vital organs leading to high morbidity and mortality. Istaroxime is a novel first-in-class investigational therapy that is intended to improve systolic contraction and diastolic relaxation of the heart while also increasing blood pressure and maintaining renal function with a generally favorable safety profile. Istaroxime has been studied in four positive Phase 2 trials enrolling patients with acute heart failure and early cardiogenic shock due to heart failure.

The Phase 2b SEISMiC Part B Extension Study in early cardiogenic shock (SCAI Stage B) randomized 30 subjects and was conducted in the United States, Europe and Latin America (3 subjects have been discharged but have not completed their 30-day visit). The study is focused on istaroxime's observed ability to correct low blood pressure and to improve cardiac function and other parameters over 96 hours of close monitoring with the final visit at 30 days. The results build upon the positive results reported previously in the Phase 2b SEISMiC Part A study. The Part B study included hospitalized patients with SCAI Stage B cardiogenic shock with persistent hypotension due to acute heart failure and evaluated two different dose regimens of istaroxime compared to placebo. Patients in the active treatment groups received infusions of istaroxime for up to 60 hours, with one group receiving a decreasing istaroxime dose over time and the second group receiving a constant istaroxime dose. The study tested an extended dosing duration of istaroxime compared to previous studies, where treatment was limited to 24 hours, to determine the potential for additional benefit and, along with dose titration, to determine the optimal dosing regimen for an anticipated late-stage Phase 3 clinical trial. For the primary endpoint evaluating blood pressure, subjects from Part A and Part B of SEISMiC were prospectively combined for analysis. In the analysis of Part B, all istaroxime-treated patients were compared to the placebo group. For certain endpoints in Part B, the dose-response between the two different istaroxime dose regimens was compared.

Topline study results:

- The study met its primary endpoint in significantly improving systolic blood pressure over six hours (SBP AUC), with the combined Part A and Part B SEISMiC istaroxime group performing significantly better compared to the placebo group (62.0±7 vs 36.4±7 mmHg*hr, p = 0.0070). Despite the smaller number of patients in SEISMiC Part B, the SBP AUC was also significantly improved by istaroxime compared to placebo (78.4±12 vs. 39.6±14 mmHg*hr, p=0.0429).
- The improvements in SBP AUC at 24 hours in the combined Part A and Part B analysis were also significantly increased by istaroxime (292.4±24 vs 190.9±26 mmHg*hr, p=0.0031). In Part B alone, the istaroxime group was significantly better compared to the placebo group (299.3±48 vs 139.0±56mmHg*hr, (p = 0.0377). With the longer istaroxime dosing in Part B, the SBP AUC was significantly improved at 48 hours (594.4±95 vs 271.7±110, p = 0.0352) and 60 hours (711.4±119 vs 320.4±138 mmHg*hr, p = 0.0408) as well.

SEISMiC Part B results:

- Cardiac output (the amount of blood pumped by the heart per minute) was improved during the infusion by approximately 15% in the istaroxime group over the course of treatment. Heart rate tended to decrease and there was no statistically significant increase in heart rate versus placebo in the istaroxime group. At 12 and 24 hours, patients in the istaroxime group experienced statistically significant reductions in heart rate (p = 0.0102 and p = 0.0218, respectively). Increasing heart rate contributes to greater cardiac oxygen demand and workload, and therefore can lead to deleterious effects in heart failure patients.
- Pulmonary capillary wedge pressure (PCWP) is elevated in this patient population and also was elevated in our study subjects at baseline. Istaroxime treatment reduced PCWP significantly more than placebo within six hours (-6.6 vs -0.9 mmHg, p = 0.0001) and the effect persisted through 60 hours. PCWP is a measure of cardiac filling pressure and when high contributes to worsening heart failure and pulmonary edema.
- Mixed venous oxygen saturation (SVO2), an assessment of organ perfusion, was significantly improved by 12 hours (mean difference of the istaroxime group compared to placebo was approximately 9%, p=0.0071), and remained significant through 48 hours (p=0.0001). The improvement versus placebo generally persisted through a 60-hour assessment. A low SVO2 can indicate that cardiac output is not high enough to meet the tissue oxygen needs.

- Renal function measured by estimated glomerular filtration rate (eGFR) was improved in this study in the istaroxime group compared to placebo at all time points reaching statistical significance at 48 hours (p =0.0291).
- Clinical signs and symptoms of congestion and heart failure improved in both groups. The New York Heart Association (NYHA) classification of heart failure severity significantly decreased in the istaroxime group at 24 hours (p=0.020), 48 hours (p=0.035), and 72 hours (p=0.010) and was similar to placebo at 96 hours.
- Worsening heart failure reported as a serious adverse event occurred less frequently in the istaroxime group compared to placebo 5.3% versus 18.2%, respectively.

The istaroxime safety profile in Part B was favorable and generally consistent with what has been previously reported in other istaroxime clinical trials. Treatment-emergent adverse events were reported more frequently in the istaroxime group at 78.9% compared to 45.5% in the placebo group, predominantly due to nausea, vomiting, infusion site discomfort and headache that have been observed previously with istaroxime. Serious adverse events were infrequent and occurred at a similar frequency in both the istaroxime and placebo groups (10.5% vs. 27.3%, respectively). Importantly, consistent with previous findings, istaroxime did not increase clinically significant arrythmias compared to the placebo group.

Alexandre Mebazaa. MD, PhD, FESC (Université Paris Cité, France), Professor of Critical Care and heart failure expert, said, “Innovation with drug therapy is needed in cardiogenic shock treatment. Istaroxime has a unique profile. It may be the only drug candidate that has been shown to simultaneously improve blood pressure, cardiac output and renal function without increasing heart rate or risk for cardiac arrhythmias. These are all desirable attributes for a drug treating cardiogenic shock and acute heart failure.”

Dr. Mebazaa will be joining the Company for a **Virtual Investor Day** presentation of the above and other results, a review of the program and the forward-looking strategy, plans and milestones on **Tuesday, October 1 at 3pm ET**. Register for the event here: https://lifescievents.com/event/windtreetx/. The presentation will be made available on Windtree’s website after the meeting.

“We are very pleased with the results of this SEISMiC cardiogenic shock study. Through four positive Phase 2 studies in acute heart failure, with and without early cardiogenic shock, in over 300 patients treated with istaroxime to date, we have observed a unique and attractive profile,” said Craig Fraser, CEO and Chairman of Windtree Therapeutics. “We are excited to pursue the next steps of development to potentially deliver an important therapy for patients that need better treatments for this critical condition.”

About Istaroxime
Istaroxime is a first-in-class dual-mechanism therapy designed to improve both systolic and diastolic cardiac function. Istaroxime is designed as a positive inotropic agent that increases myocardial contractility through inhibition of Na+/K+- ATPase with a complimentary mechanism that facilitates myocardial relaxation through activation of the SERCA2a calcium pump on the sarcoplasmic reticulum enhancing calcium reuptake from the cytoplasm. Data from multiple Phase 2 studies in patients with early cardiogenic shock or acute decompensated heart failure have demonstrated that istaroxime infused intravenously significantly improves cardiac function and blood pressure without increasing heart rate or the incidence of cardiac rhythm disturbances.

About Windtree Therapeutics, Inc.
Windtree Therapeutics, Inc. is a biotechnology company focused on advancing early and late-stage innovative therapies for critical conditions and diseases. Windtree’s portfolio of product candidates includes istaroxime, a Phase 2 candidate with SERCA2a activating properties for acute heart failure and associated cardiogenic shock, preclinical SERCA2a activators for heart failure and preclinical precision aPKCi inhibitors that are being developed for potential in rare and broad oncology applications. Windtree also has a licensing business model with partnership out-licenses currently in place.

Forward Looking Statements
This press release contains statements related to the potential clinical effects of istaroxime; the potential benefits and safety of istaroxime; the clinical development of istaroxime; and our research and development program for treating patients in early cardiogenic shock due to heart failure. Such statements constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The Company may, in some cases, use terms such as “predicts,” “believes,” “potential,” “proposed,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Such statements are based on information available to the Company as of the date of this press release and are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the Company’s current expectations. Examples of such risks and uncertainties include, among other things: the Company’s ability to secure significant additional capital as and when needed; the Company’s ability to achieve the intended benefits of the aPKCi asset acquisition with Varian Biopharmaceuticals, Inc.; the Company’s risks and uncertainties associated with the success and advancement of the clinical development programs for istaroxime and the Company’s other product candidates, including preclinical oncology candidates; the Company’s ability to access the debt or equity markets; the Company’s ability to manage costs and execute on its operational and budget plans; the results, cost and timing of the Company’s clinical development programs, including any delays to such clinical trials relating to enrollment or site initiation; risks related to technology transfers to contract manufacturers and manufacturing development activities; delays encountered by the Company, contract manufacturers or suppliers in manufacturing drug products, drug substances, and other materials on a timely basis and in sufficient amounts; risks relating to rigorous regulatory requirements, including that: (i) the U.S. Food and Drug Administration or other regulatory authorities may not agree with the Company on matters raised during regulatory reviews, may require significant additional activities, or may not accept or may withhold or delay consideration of applications, or may not approve or may limit approval of the Company’s product candidates, and (ii) changes in the national or international political and regulatory environment may make it more difficult to gain regulatory approvals and risks related to the Company’s efforts to maintain and protect the patents and licenses related to its product candidates; risks that the Company may never realize the value of its intangible assets and have to incur future impairment charges; risks related to the size and growth potential of the markets for the Company’s product candidates, and the Company’s ability to service those markets; the Company’s ability to develop sales and marketing capabilities, whether alone or with potential future collaborators; the rate and degree of market acceptance of the Company’s product candidates, if approved; the economic and social consequences of the COVID-19 pandemic and the impacts of political unrest, including as a result of geopolitical tension, including the conflict between Russia and Ukraine, the People’s Republic of China and the Republic of China (Taiwan), and the evolving events in Israel and Gaza, and any sanctions, export controls or other restrictive actions that may be imposed by the United States and/or other countries which could have an adverse impact on the Company’s operations, including through disruption in supply chain or access to potential international clinical trial sites, and through disruption, instability and volatility in the global markets, which could have an adverse impact on the Company’s ability to access the capital markets. These and other risks are described in the Company’s periodic reports, including its Annual Report on

Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, filed with or furnished to the Securities and Exchange Commission and available at www.sec.gov. Any forward-looking statements that the Company makes in this press release speak only as of the date of this press release. The Company assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

Contact Information:
Eric Curtis
ecurtis@windtreetx.com

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