Nuwellis Announces First Patient Enrolled in its Pivotal Trial REVERSE-HF

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REVERSE-HF will evaluate ultrafiltration therapy in comparison to IV diuretics to treat heart failure patients with fluid overload

MINNEAPOLIS, June 29, 2022 (GLOBE NEWSWIRE) -- Nuwellis, Inc. (Nasdaq: NUWE) today announced the first patient has been enrolled in the company's pivotal REVERSE-HF (Ult **r**afiltration V**e**rsus I**V** Diur**e**tics in Wo**rse**ning **H**eart **F**ailure) clinical study. REVERSE-HF will evaluate the clinical outcomes and economic value of its Aquadex® ultrafiltration therapy in comparison to intravenous (IV) diuretics for the treatment of fluid overload in patients with worsening heart failure. The first patient was enrolled by Dr. Sirish Vullaganti, M.D. at Northwell Health in New York City.

"Heart failure is among the leading causes of hospitalizations due to the accumulation of fluid requiring decongestion in the hospital setting. Unfortunately, approximately 1 in 4 patients are readmitted to the hospital within 30 days of discharge," said Dr. Vullaganti. "Some patients do not respond well to intravenous diuretics, and this can prolong hospital stays which can burden both patients and the healthcare system. We should remain open to improving treatment for these patients and this study has the potential to demonstrate that ultrafiltration can improve patient outcomes, overall quality of life and economic benefits to the healthcare system."

Heart failure can disrupt normal kidney functions and lower their ability to remove sodium from the body, resulting in excessive water retention that can ultimately lead to fluid overload. Over 1 million heart failure hospitalizations occur annually in the United States, and fluid overload is the predominant cause in 90% of the patients. Furthermore, nearly one-quarter of heart failure patients will be readmitted to the hospital within 30 days of their initial discharge, and half will be readmitted within 6 months.

REVERSE-HF is a multicenter, open-label, randomized controlled trial that will be conducted across the United States. The study is led by Sean Pinney, M.D., Professor of Medicine and Co-Director of the Heart and Vascular Center at The University of Chicago Medicine, and Maria V. DeVita, M.D., Professor of Medicine at Hofstra School of Medicine/Northwell and Chief of the Division of Nephrology at Lenox Hill Hospital.

"The first patient enrolled in REVERSE-HF marks an exciting milestone in this study," said Nestor Jaramillo, Jr., President and CEO of Nuwellis. "We're grateful to Drs. Vullaganti, DeVita and Pinney for their efforts in getting the study off the ground and gathering additional evidence supporting ultrafiltration to treat these patients. As a company, we are committed to the ultimate goal of making Aquadex therapy the standard of care for fluid management in heart failure patients that are resistant to diuretics. In talking to medical societies, Nuwellis has been told that REVERSE-HF will produce the necessary evidence these societies need to have ultrafiltration included within their medical guidelines. We look forward to forthcoming clinical publications that support our belief that REVERSE-HF will be a very positive study."

The primary effectiveness endpoint of REVERSE-HF will evaluate mortality and heart failure events within 30 days and 90 days as a comparison between Aquadex therapy and IV loop diuretics. The study will assess safety parameters, including, but not limited to, cardiovascular and renal-related adverse events of special interest.

REVERSE-HF will use a newer statistical method that increases precision in demonstrating significance between the ultrafiltration and IV diuretic treatment arms of the study. This statistical method, called Finkelstein-Schoenfeld method of Win-Ratios, has also been used recently to re-evaluate data obtained during the AVOID–HF prospective, multicenter, randomized controlled trial, which was the first to propose that patients should be treated with adjustable ultrafiltration when compared to those receiving adjustable loop diuretics. The AVOID-HF (**A**quapheresis **V**ersus Intraven**o**us Diuret**i**cs an**d** Hospitalization for **H**eart **F**ailure) trial tested the hypothesis that patients hospitalized for heart failure and treated with ultrafiltration would have a longer time to their first heart failure event within 90 days after hospital discharge compared to those receiving IV loop diuretics. AVOID-HF was trending favorably when it was terminated before reaching full enrollment for reasons unrelated to patient safety or clinical futility. The Win-Ratio analysis of AVOID-HF, which showed superiority of ultrafiltration over diuretics, is expected to be published in a peer reviewed journal later this year.

In addition to Northwell Health, Nuwellis is currently partnering with other clinical institutions that will soon be enrolling patients for the REVERSE-HF study as well. The company anticipates at least 12 clinical institutions will ultimately participate in the study.

About Nuwellis
Nuwellis, Inc. (Nasdaq: NUWE) is a medical device company dedicated to transforming the lives of patients suffering from fluid overload through science, collaboration, and innovation. The Company is focused on developing, manufacturing and commercializing the Aquadex SmartFlow® system for ultrafiltration therapy. Nuwellis is headquartered in Minneapolis, with a wholly-owned subsidiary in Ireland.

About the Aquadex SmartFlow® System
The Aquadex SmartFlow system delivers clinically proven therapy using a simple, flexible and predictable method of removing excess fluid from patients suffering from hypervolemia (fluid overload). The Aquadex SmartFlow system is indicated for temporary (up to 8 hours) or extended (longer than 8 hours in patients who require hospitalization) use in adult and pediatric patients weighing 20 kg or more whose fluid overload is unresponsive to medical management, including diuretics. All treatments must be administered by a health care provider, within an outpatient or inpatient clinical setting, under physician prescription, both having received training in extracorporeal therapies.

Forward-Looking Statements
Certain statements in this release may be considered forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including without limitation, statements regarding the new market opportunities and anticipated growth in 2022 and beyond. Forward-looking statements are predictions, projections and other statements about future events that are based on current expectations and assumptions and, as a result, are subject to risks and uncertainties. Many factors could cause actual future events to differ materially from the forward-looking statements in

this release, including, without limitation, those risks associated with our ability to execute on our commercialization strategy, the impact of the COVID-19 pandemic, the possibility that we may be unable to raise sufficient funds necessary for our anticipated operations, our post-market clinical data collection activities, benefits of our products to patients, our expectations with respect to product development and commercialization efforts, our ability to increase market and physician acceptance of our products, potentially competitive product offerings, intellectual property protection, our ability to integrate acquired businesses, our expectations regarding anticipated synergies with and benefits from acquired businesses, and other risks and uncertainties described in our filings with the SEC. Forward-looking statements speak only as of the date when made. Nuwellis does not assume any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

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