Septerna Announces Dosing of the First Participants in Phase 1 Clinical Trial of SEP-631, an Oral Small Molecule MRGPRX2 Negative Allosteric Modulator for the Treatment of Mast Cell-Driven Diseases

08.21.25

Trial Designed to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of SEP-631 in Healthy Volunteers

SOUTH SAN FRANCISCO, Calif., Aug. 21, 2025 (GLOBE NEWSWIRE) -- Septerna, Inc. (Nasdaq: SEPN), a clinical-stage biotechnology company pioneering a new era of G protein-coupled receptor (GPCR) drug discovery, today announced the dosing of the first participants in its Phase 1 clinical trial of SEP-631, a selective oral small molecule Mas-related G protein-coupled receptor X2 (MRGPRX2) negative allosteric modulator (NAM) being developed for the treatment of chronic spontaneous urticaria (CSU) and other mast cell-driven diseases. The Phase 1 single-ascending dose (SAD) and multiple-ascending dose (MAD) clinical trial will evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of SEP-631 in healthy adult volunteers.

“Mast cell-driven diseases represent significant unmet medical needs worldwide, affecting millions of patients who often struggle with inadequate symptom relief with current therapies,” said Jae Kim, M.D., chief medical officer of Septerna. “We are excited to initiate the first-in-human trial for SEP-631, a small molecule NAM that aims to inhibit mast cell activation by selectively blocking MRGPRX2, a GPCR that plays a critical role in mast cell activation and degranulation. SEP-631 has the potential to provide a convenient oral treatment option for patients with CSU and other mast cell-driven diseases. As we initiate this Phase 1 trial, we look forward to further demonstrating the potential of our Native Complex Platform™ to discover new ways to modulate GPCR targets to develop novel medicines for patients in need of better treatment options."

One of the most common mast cell-driven diseases, CSU is a systemic inflammatory skin disease characterized by the spontaneous and persistent recurrence of itchy, painful hives and angioedema. While there is no known trigger, the activation and degranulation of mast cells and release of histamine and other inflammatory mediators lead to these debilitating symptoms. While patients are initially treated with antihistamines, a significant portion do not respond to therapy, underscoring the need for new oral treatment options. Mast cells are also implicated in multiple other diseases, including asthma, atopic dermatitis, interstitial cystitis, and migraine, representing additional potential opportunities for an MRGPRX2-targeted therapy.

The randomized, placebo-controlled Phase 1 SAD / MAD clinical trial is expected to enroll up to approximately 150 healthy adult volunteers. Dosing is underway in the SAD portion of the trial, which will evaluate the safety and tolerability of SEP-631 at escalating oral doses. The MAD portion of the trial will evaluate the safety and tolerability of oral doses of SEP-631 over the treatment period, and PD will be assessed through an icatibant skin challenge.

About SEP-631
Septerna is developing SEP-631, a selective oral small molecule Mas-related G protein-coupled receptor X2 (MRGPRX2) negative allosteric modulator (NAM) for the treatment of patients with chronic spontaneous urticaria (CSU) and other mast-cell driven diseases. MRGPRX2 is known to play an important role in mast cell activation and degranulation which, in combination with other inflammatory mediators, lead to debilitating symptoms for patients. In addition to CSU, MRGPRX2 is highly and uniquely expressed on mast cells implicated in multiple diseases, including asthma, atopic dermatitis, interstitial cystitis, and migraine. In preclinical studies, SEP-631 demonstrated potent and long-lasting inhibition of MRGPRX2 and blocked mediator-induced skin extravasation in mice engineered to express the human MRGPRX2 receptor.

About Septerna
Septerna, Inc. is a clinical-stage biotechnology company with a world-class team of GPCR experts and drug developers advancing cutting-edge science to unlock the full potential of GPCR therapies for patients with significant unmet needs. The company’s proprietary Native Complex Platform™ is designed to enable new approaches to GPCR drug discovery and has led to the development of a diverse pipeline of novel oral small molecule drug candidates. Septerna is advancing programs in endocrinology, immunology and inflammation, metabolic diseases and additional therapeutic areas, both independently and with partners. For more information, please visit www.septerna.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements about Septerna’s beliefs and expectations regarding: the continued advancement of its MRGPRX2 NAM program, including the potential of SEP-631 to provide a convenient oral treatment option for patients with CSU and other mast cell-driven diseases; the role of MRGPRX2 in mast cell-driven diseases; the ability to enroll patients and complete the Phase 1 clinical trial for SEP-631; the safety and efficacy results from conducting its research and

development programs, including potential outcomes from the clinical development of SEP-631; and the potential of its proprietary Native Complex Platform™. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “objective,” “ongoing,” “plan,” “predict,” “project,” “potential,” “should,” or “would,” or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: clinical development outcomes including unexpected safety or efficacy findings; the results of preclinical studies, or clinical studies not being predictive of future results in connection with future studies; the scope of protection Septerna is able to establish and maintain for intellectual property rights covering its Native Complex Platform™ and its product candidates, including SEP-631; and general economic, industry and market conditions. These and other risks and uncertainties are described in greater detail in the section entitled “Risk Factors” in Septerna’s Annual Report on Form 10-K for the year ended December 31, 2024, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Septerna’s views only as of today and should not be relied upon as representing its views as of any subsequent date. Septerna explicitly disclaims any obligation to update any forward-looking statements subject to any obligations under applicable law. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Investor Contact:
Renee Leck, THRUST
renee@thrustsc.com

Media Contact:
Carly Scaduto
carly@carlyscadutoconsulting.com