Septerna Announces Positive Phase 1 Data for SEP-631, an Oral MRGPRX2 NAM for the Treatment of Mast Cell-Driven Diseases, and Outlines Initial Phase 2 Development Strategy

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SEP-631 Demonstrated Robust, Dose-Dependent Inhibition of Icatibant-Induced Skin Wheal Formation, with Complete Inhibition Observed at Doses as Low as 10 mg Once-Daily

Well-Tolerated Across All Doses Studied with an Adverse Event Profile Comparable to Placebo; Pharmacokinetic Profile Supports Once-Daily Oral Dosing

Phase 2 Development Planned to Begin with Chronic Spontaneous Urticaria in the Second Half of 2026

Company to Host Conference Call and Webcast on Monday, March 2, 2026, at 8:00 a.m. ET

SOUTH SAN FRANCISCO, Calif., March 01, 2026 (GLOBE NEWSWIRE) -- Septerna, Inc. (Nasdaq: SEPN), a clinical-stage biotechnology company pioneering oral small molecule GPCR-targeted medicines, today announced positive results from its Phase 1 clinical trial evaluating SEP-631, a potent and selective oral negative allosteric modulator (NAM) of Mas-related G protein-coupled receptor X2 (MRGPRX2). Based on these results, Septerna plans to advance SEP-631 into Phase 2 development for chronic spontaneous urticaria (CSU) and continue evaluation of additional mast cell-driven indications.

“These data mark an important milestone for the SEP-631 program and more broadly for our Native Complex Platform ®, which enables new approaches to GPCR drug discovery by reconstituting functional GPCR complexes outside of cells,” said Jae Kim, M.D., chief medical officer of Septerna. “Importantly, the robust inhibition of icatibant-induced wheal formation observed is consistent with the differentiated insurmountable NAM mechanism we characterized preclinically and provides clinical proof-of-mechanism for the MRGPRX2 pathway. Overall, we believe the strength and consistency of these results position SEP-631 as a potentially differentiated oral treatment for patients living with mast cell-driven diseases. With a clear path into Phase 2 development in chronic spontaneous urticaria, we are focused on translating this early validation into meaningful outcomes for patients and exploring additional high-need indications where MRGPRX2 biology is implicated.”

Phase 1 Results
SEP-631 was evaluated in a randomized, double-blind, placebo-controlled Phase 1 trial in healthy volunteers, including single-ascending dose, multiple-ascending dose and food-effect cohorts. The study assessed safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) activity.

SEP-631 was well-tolerated across all doses studied:

- Adverse event profile comparable to placebo
- No severe or serious adverse events
- No clinically meaningful laboratory or ECG abnormalities

SEP-631 demonstrated a PK profile supportive of convenient once-daily oral dosing, including:

- Half-life of approximately 24 hours
- No clinically meaningful effect of food on exposure, supporting dosing without food restrictions

Pharmacodynamic activity was assessed using icatibant-induced skin wheal formation, an established skin test used to measure mast cell activation and target engagement, as a translational model of MRGPRX2-mediated mast cell activation. Use of short-wave infrared imaging technology enabled accurate and precise measurement of the skin test wheals. SEP-631 produced robust suppression of wheal formation across evaluated dose levels, with complete inhibition observed at doses as low as 10 mg once daily following the 10 µg/mL icatibant challenge. Following the 100 µg/mL icatibant challenge, inhibition was dose-dependent, with progressively greater suppression observed at increasing SEP-631 doses with near to complete inhibition achieved at 90 and 200 mg once daily. These findings are consistent with the insurmountable NAM mechanism of SEP-631 observed preclinically and support potent target engagement and functional blockade of MRGPRX2 signaling in humans, providing clinical proof-of-mechanism.

Phase 2 Development Strategy
Septerna plans to initiate a Phase 2b clinical trial of SEP-631 in chronic spontaneous urticaria (CSU) in the second half of this year, following the completion of ongoing long-term toxicology studies.

The planned Phase 2b study will be a randomized, double-blind, placebo-controlled, global trial evaluating once-daily oral

SEP-631 in adult patients with moderate-to-severe CSU who remain symptomatic despite treatment with second-generation antihistamines. Following the CSU study initiation, the company also plans to pursue an open-label study in chronic inducible urticaria (CIndU), specifically in patients with symptomatic dermatographism.

Beyond urticaria, Septerna is evaluating additional mast cell-driven diseases with high unmet medical need and evidence of MRGPRX2 expression, and has initially prioritized atopic dermatitis, interstitial cystitis, migraine and asthma for further assessment.

Conference Call and Webcast Information
Septerna will host a conference call and webcast on Monday, March 2, 2026, at 8:00 a.m. ET to discuss the Phase 1 results and initial Phase 2 development strategy for SEP-631. The live webcast will be available in the investors section of the company's website at www.septerna.com. A replay will be available shortly after the event and will be archived for at least 30 days.

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 a Phase 1 clinical trial, SEP-631 demonstrated favorable tolerability, once-daily pharmacokinetics and pharmacodynamic evidence of MRGPRX2 pathway inhibition. Septerna plans to advance SEP-631 into Phase 2 development in CSU and chronic inducible urticaria and is evaluating its potential in additional mast cell-driven indications, including atopic dermatitis, interstitial cystitis, migraine and asthma.

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 SEP-631, including the plan to initiate a Phase 2b clinical study in CSU in the second half of 2026 subject to the successful completion of long-term preclinical toxicology studies; the role of MRGPRX2 in mast cell-driven diseases; the potential of SEP-631 to provide a convenient oral treatment option for patients with CSU and other mast cell-driven diseases; expectations regarding the anticipated once-daily dosing frequency of SEP-631; the ability of the SEP-631 Phase 1 safety and efficacy observations to successfully translate into clinical outcomes in patients; the potential of its proprietary Native Complex Platform®; the size and growth potential of the markets for its current and future product candidates; its expectations regarding strategic plans for its business, product candidates, and technology; and the scope of protection it is able to establish and maintain for intellectual property rights covering its Native Complex Platform® and its product candidates. 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: Septerna's product candidates successfully entering and advancing through clinical trials (including SEP-631) including uncertainties related to opening INDs and other regulatory approvals; risks related to clinical development outcomes including unexpected safety or efficacy findings; the results of preclinical studies including the long-term toxicology studies for SEP-631, or clinical studies not being predictive of future clinical outcomes; risks related to the timing of initiating clinical studies and future availability of clinical data; and the scope of protection Septerna is able to establish and maintain for intellectual property rights covering its Native Complex Platform® and its product candidates. 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.

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