Septerna Announces Discontinuation of SEP-786 Phase 1 Clinical Trial and Plans to Advance Next-Generation Oral Small Molecule PTH1R Agonist

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Trial decision follows unanticipated events of elevated unconjugated bilirubin levels

Company advancing multiple next-generation PTH1R agonists with distinct and unrelated chemical structures relative to SEP-786

SOUTH SAN FRANCISCO, Calif., Feb. 18, 2025 (GLOBE NEWSWIRE) -- Septerna, Inc. (Nasdaq: SEPN), a clinical-stage biotechnology company pioneering a new era of GPCR drug discovery, today announced its decision to discontinue the Phase 1 single- and multiple-ascending dose (SAD/MAD) clinical trial of SEP-786 in healthy volunteers. SEP-786 is an oral small molecule agonist of the parathyroid hormone 1 receptor (PTH1R) being developed for the treatment of hypoparathyroidism.

Septerna's decision follows the observation of two unanticipated severe (Grade 3) events of elevated unconjugated bilirubin in the MAD portion of the Phase 1 trial, both of which were without elevations in ALT, AST, and GGT liver enzyme levels. Dosing was discontinued for both study participants, and the bilirubin elevations were reversible. Importantly, there were no events of liver injury, cholestasis, or hemolysis across all participants, and there were no serious adverse events (SAEs) in the Phase 1 trial.

"After careful evaluation of SEP-786 and in the context of our robust PTH1R agonist program, we've made the decision to discontinue the SEP-786 Phase 1 trial. We observed early signals of on-target pharmacological activity with SEP-786, with increases in serum calcium and corresponding decreases in endogenous PTH, reinforcing our commitment to developing an oral small molecule PTH1R agonist for hypoparathyroidism," said Jeffrey Finer, M.D., Ph.D., CEO and co-founder of Septerna. "Strategically, for each of our programs, we identify a diverse portfolio of follow-on compounds that are chemically distinct. We have multiple attractive PTH1R agonists from which we plan to select a next-generation candidate to accelerate toward the clinic later this year to quickly regain momentum with our PTH1R program."

In completed 28-day preclinical toxicology studies, SEP-786 was generally well-tolerated, without predicted risk of bilirubin elevation. In response to these Phase 1 events, Septerna has initiated non-clinical studies to investigate the underlying mechanism behind the observed effect.

"Our extensive preclinical research and toxicology studies did not predict the risk of this off-target effect of SEP-786," said Jae B. Kim, M.D., Chief Medical Officer of Septerna. "We plan to expeditiously progress our PTH1R program with a next-generation candidate. In addition, we are on-track with SEP-631, our selective oral small molecule MRGPRX2 negative allosteric modulator for mast cell diseases, which we are preparing for clinical initiation later this year. We look forward to sharing more on our progress in the future."

The Company's cash, cash equivalents, and marketable securities totaled $137.5 million as of September 30, 2024. Together with the $302.6 million in net proceeds from the company's IPO completed in October 2024, Septerna expects its current cash position to support its planned operations into at least the second half of 2027.

About Septerna
Septerna, Inc. is a clinical-stage biotechnology company pioneering a new era of GPCR drug discovery powered by its proprietary Native Complex Platform™. Its industrial-scale platform aims to unlock the full potential of GPCR therapies and has led to the discovery and development of its deep pipeline of oral small molecule product candidates focused initially on treating patients in three therapeutic areas: endocrinology, immunology and inflammation, and metabolic diseases. Septerna was launched by preeminent drug discovery company builders and scientific leaders in the biochemistry, structural biology, and pharmacology of GPCRs. 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 development and advancement of Septerna's oral small molecule GPCR-targeted programs; its ability to demonstrate, and the timing of, preclinical proof-of-concept in vivo and ex vivo for multiple programs including Septerna's plan to select a next-generation PTH1R product candidate to accelerate toward the clinic later this year; its ability to advance any product candidates that it may identify and successfully complete any clinical studies; the initiation, timing, progress, and results of conducting its research and development programs including its plans to initiate a clinical trial for SEP-631 later this year; the potential of its proprietary Native Complex Platform™; its expectations regarding the implementation of its business model, strategic plans for its business, product candidates, and technology, and the accuracy of its estimates regarding expenses and capital requirements, including its expected cash runway into at least the second half of 2027. 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: uncertainties related to Septerna's product candidates entering clinical trials; the authorization, initiation, and successful completion of preclinical and Investigational New Drug (IND)-enabling studies to support future clinical development of potential product candidates (including those for the PTH1R program), including uncertainties related to opening INDs and obtaining regulatory approvals; risks related to 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; Septerna's ability to identify and enter into future license agreements and collaborations; 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 most recent Quarterly Report on Form 10-Q, 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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