Septerna Presents Preclinical Data at ENDO 2024 Highlighting Therapeutic Potential of its GPCR Drug Discovery Platform

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Oral, small molecule parathyroid hormone 1 receptor (PTH1R) agonist maintained serum calcium control over 28-day dosing in a preclinical hypoparathyroidism model

PTH1R program for hypoparathyroidism expected to enter Phase 1 in late 2024

Oral, thyroid stimulating hormone receptor (TSHR) antagonist improved thyroxine (T4) hormone levels and histological parameters associated with Graves' disease in a preclinical model

SOUTH SAN FRANCISCO, Calif. – June 3, 2024 – Septerna, a biotechnology company discovering and advancing novel, oral small molecule medicines targeting G protein-coupled receptors (GPCRs), today presented preclinical data from the company's parathyroid hormone 1 receptor (PTH1R) program and its thyroid stimulating hormone receptor (TSHR) program which validate the application of the Native Complex Platform™ for drug discovery in endocrine disorders. The data were presented in two poster presentations and a rapid-fire oral presentation during the Endocrine Society's Annual Meeting (ENDO 2024) held June 1-4, 2024, in Boston, MA.

Data from the PTH1R program showed small molecule agonists of PTH1R engaged endogenous pathways in the kidney and bone similar to native PTH peptide and demonstrated sustained control of serum calcium and phosphate levels over 28 days with daily oral administration. These results suggest that oral small molecule PTH1R agonists may be suitable alternatives to injectable PTH peptides for the treatment of hypoparathyroidism. The company plans to initiate a Phase 1 trial with its lead PTH1R agonist candidate in healthy volunteers in late 2024.

"Our PTH1R agonist is the only small molecule in development to behave similarly to native PTH, and we are excited about its potential to reshape the treatment paradigm for hypoparathyroidism as we advance into the clinic later this year," said Jeffrey Finer, M.D., Ph.D., Chief Executive Officer and Co-founder of Septerna. "We are also pleased to showcase data from our TSHR antagonist program demonstrating its ability to target the known drivers of Graves' disease, an indication for which there are currently no disease-modifying oral small molecules. Together, these data validate the ability of our Native Complex Platform™ to unlock difficult-to-drug GPCRs and to discover novel small molecules to address numerous endocrine disorders."

Summary of PTH1R Data

The rapid-fire oral presentation and poster, entitled "Characterization of a Novel Oral Small Molecule PTH1R Agonist: Proof of Concept for an Alternative to Injectable Peptide-based Therapy for Hypoparathyroidism," were presented by Jun Zhang, Ph.D., Senior Director of Disease Biology for Septerna.

- To assess PTH1R engagement in key target tissues, primary tissue from the renal cortex and tibial bone was assessed following *in vivo* treatment with PTH peptide and Septerna's small molecule PTH1R agonist. The results suggest that PTH1R-regulated genes were similarly impacted by both PTH peptide and small molecule agonists.
- Oral administration of a single dose of Septerna's PTH1R agonist in a surgical rat model that mimics hypoparathyroidism in patients resulted in significant upregulation of serum calcium levels for a period of 24 hours in a dose dependent manner. The data also demonstrated sustained control of serum calcium and phosphate levels over 28 days with daily oral administration. The window of calcium upregulation is comparable to injectable PTH peptides currently in development to treat hypoparathyroidism.

Summary of TSHR Data

Additionally, a poster entitled "A Novel, Oral Small Molecule Antagonist Targeting TSHR Improves Hyperthyroidism in an *in vivo* Model of Graves' Disease" was presented.

Data from the TSHR program demonstrated that Septerna's small molecule TSHR antagonist blocks the stimulating effects of autoantibodies known to drive Graves' disease (GD). Sustained treatment with the TSHR antagonist reduced the overall size of the thyroid gland and improved histological parameters associated with GD, providing proof-of-concept that potent small molecules directly targeting TSHR function have the potential to ameliorate the effects of hyperthyroidism in GD. The company is advancing several lead molecules toward the selection of a development candidate for GD and Graves' ophthalmopathy (also known as thyroid eye disease or TED).

About Septerna
Septerna, Inc. is a biotechnology company focused on advancing novel, oral small molecule medicines targeting the entire class of G protein-coupled receptors (GPCRs). The company's Native Complex Platform TM recapitulates GPCRs with their native

structure, function, and dynamics outside of the cellular environment to rapidly apply new technologies for industrial-scale drug discovery to address both validated GPCRs and many GPCRs that have been undruggable and unexploited to date. Septerna is building a pipeline of GPCR-targeted, oral small molecule drug candidates, led by its program targeting the parathyroid hormone 1 receptor (PTH1R) for the treatment of hypoparathyroidism. Septerna was launched in 2022 by scientific founders who have made groundbreaking GPCR discoveries. For more information, please visit www.septerna.com.

About the PTH1R Program and Hypoparathyroidism
Septerna is developing a novel, first-in-class, oral small molecule parathyroid hormone 1 receptor (PTH1R) agonist designed to treat patients with hypoparathyroidism, a harmful condition characterized by a deficiency of the parathyroid hormone (PTH). Hypoparathyroidism results in a wide range of debilitating symptoms, including fatigue, brain fog, muscle weakness, tissue calcification, and in severe cases can lead to seizures, heart arrhythmias, and kidney failure. Current available treatments include supplements that only partially address PTH deficiency, or PTH peptide replacements, which require daily injections. Septerna's investigational PTH1R agonist has been shown to normalize serum calcium levels in preclinical studies and has the potential to be the first oral alternative to injectable treatments for hypoparathyroidism.

About the TSHR Program and Graves' disease
Septerna is developing a novel, investigational, oral small molecule thyroid stimulating hormone receptor (TSHR) antagonist for the treatment of Graves' disease and thyroid eye disease (TED). Graves' disease is an autoimmune condition in which the body produces antibodies that bind to and activate the TSH receptor on thyroid cells. These antibodies stimulate the thyroid gland to produce too much thyroid hormone, resulting in hyperthyroidism. Additionally, in TED, the antibodies stimulate TSH receptors on cells behind the eyes, causing swelling of the eye muscles, which can result in eye bulging, pain and impaired vision. Current standard-of-care treatments for Graves' disease are inadequate and focus on the thyroid (surgery, radioactive iodine, and antithyroid medicines) while failing to prevent progression to TED. Septerna's TSHR program is designed to block the activity of all Graves' autoactivating antibodies as a single oral therapeutic.

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