Seaport Therapeutics Presents New Preclinical Data on SPT-320 (Glyph Agomelatine) at the Society of Biological Psychiatry (SOBP) Annual Meeting

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SPT-320, an oral prodrug of agomelatine, increased lymphatic transport to over 50 percent compared to less than one percent for agomelatine alone

SPT-320 increased plasma exposure of agomelatine by over 10-fold compared to agomelatine alone, demonstrating the delivery of therapeutically relevant agomelatine exposures at lower doses to potentially reduce or eliminate liver enzyme elevations

Company is progressing SPT-320 into the clinic as a novel treatment for generalized anxiety disorder

Boston, MA – April 24, 2025 – Seaport Therapeutics, a clinical-stage biopharmaceutical company that is advancing novel neuropsychiatric medicines with a proven strategy and team, today announced the presentation of new preclinical data from SPT-320 at the Society of Biological Psychiatry (SOBP) Annual Meeting held on April 24-26 in Toronto, Canada. SPT-320 is a novel oral prodrug of agomelatine in development for the treatment of generalized anxiety disorder (GAD). The new findings demonstrate the potential of SPT-320 to deliver therapeutically relevant levels of agomelatine at lower doses, minimizing the impact on the liver, and addressing a key limitation that has previously held back agomelatine's development in GAD.

Agomelatine, a clinically validated melatonin receptor agonist and serotonin 2C receptor antagonist, is an effective anxiolytic and antidepressant approved for the treatment of GAD in Australia and major depressive disorder (MDD) in Australia and the European Union (EU). In GAD, agomelatine has demonstrated statistically significant separation from placebo in four out of four third-party placebo-controlled studies and has better efficacy and tolerability – including reduced risk of abuse potential, sexual dysfunction, and weight gain – than standard of care drugs, like benzodiazepines or selective serotonin reuptake inhibitors (SSRIs). However, since over 90 percent of unmodified agomelatine is lost to first-pass liver metabolism, its use has been limited by dose-dependent liver enzyme elevations and the need for frequent liver monitoring. Using Seaport's proprietary Glyph™ platform, SPT-320 is designed to overcome this limitation by shifting absorption toward the intestinal lymphatics, avoiding first-pass metabolism, and increasing systemic exposure of agomelatine.

In newly presented data from a series of preclinical proof-of-concept studies, SPT-320 exhibited enhanced lymphatic absorption and provided significantly higher systemic exposures of agomelatine compared to agomelatine alone. Specifically, oral dosing of SPT-320 resulted in over 50 percent of agomelatine being transported through the mesenteric lymphatics versus less than one percent for orally dosed agomelatine alone. The data also show that the oral dosing of SPT-320 increased plasma exposure of agomelatine by over 10-fold versus agomelatine alone, which would allow for a reduced dose, potentially eliminating liver enzyme elevations.

"We demonstrate, for the first time, that SPT-320 has the potential to deliver therapeutically relevant levels of agomelatine with a substantially lower dose, which could significantly reduce the impact on the liver while preserving the validated efficacy of agomelatine," said Daniel Bonner, Ph.D., Co-Founder and Senior Vice President, Platform, at Seaport Therapeutics. "These positive results further validate our Glyph prodrug platform and support initiating clinical development of SPT-320."

The successful validation of SPT-320's pharmacological profile in preclinical models supports Seaport's progression into Phase 1 trials to further evaluate the safety, tolerability, and pharmacokinetics of SPT-320.

About SPT-320

SPT-320 is a novel oral prodrug of agomelatine has the potential to be the first new treatment for generalized anxiety disorder (GAD) in decades. Using the Glyph^{TM} platform, SPT-320 was designed to bypass first-pass liver metabolism in order to lower the dose, reduce liver exposure, and reduce or eliminate the need for liver enzyme monitoring. Agomelatine is a clinically validated anxiolytic and antidepressant approved for GAD in Australia and major depressive disorder (MDD) in Australia and the European Union (EU). The use of agomelatine has been limited by high first-pass liver metabolism resulting in liver enzyme elevations in some patients and frequent, burdensome liver enzyme monitoring requirements.

About the Glyph^{TM} Platform

Glyph is Seaport's proprietary technology platform which uses the lymphatic system to enable and enhance the oral administration of drugs. With the Glyph platform, drugs are absorbed like dietary fats through the intestinal lymphatic system and transported into circulation. The Glyph platform has the potential to be widely applied to many therapeutic molecules that have high first-pass metabolism leading to low bioavailability and/or side effects, including liver enzyme elevations or hepatotoxicity. For each program, Seaport uses Glyph to create sets of prodrugs with differentiated profiles, including lymphatic transport and conversion characteristics, as potential candidates to advance into preclinical and clinical proof-of-concept studies. Seaport exclusively

licensed this technology from Monash University based on the pioneering research of the Porter Research Group. Advanced initially at PureTech Health and now at Seaport, Glyph has been applied to create therapeutic candidates for the Company's pipeline resulting in new intellectual property, including composition of matter. The group and its collaborators have published research in *Nature Metabolism*, *Frontiers in Pharmacology*, *Journal of Controlled Release* and *Molecular Pharmaceutics* supporting the Glyph platform's capabilities. See Glyph in action here.

About Seaport Therapeutics

Seaport Therapeutics is a clinical-stage biopharmaceutical company advancing the development of novel neuropsychiatric medicines in areas of high unmet patient needs. The Company has a proven strategy of advancing clinically validated mechanisms previously held back by limitations that are overcome with its proprietary Glyph technology platform. All the therapeutic candidates in its pipeline of first and best-in-class medicines are based on the Glyph platform, which is uniquely designed to enable oral bioavailability, bypass first-pass metabolism and reduce liver enzyme elevations or hepatotoxicity and other side effects. Seaport is led by an experienced team that invented and advanced important neuropsychiatric medicines and is guided by an extensive network of renowned scientists, clinicians, and key opinion leaders. For more information, please visit www.seaporttx.com.