PureTech Founded Entity Seaport Therapeutics Announces First Patient Dosed in Phase 2b BUOY-1 Study of GlyphAllo™ (SPT-300) in Major Depressive Disorder (MDD), With or Without Anxious Distress

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BUOY-1 builds on successful Phase 1 and Phase 2a data with GlyphAllo - a novel oral prodrug of allopregnanolone and a potential first-in-class treatment for MDD

Allopregnanolone has demonstrated rapid antidepressant and anxiolytic activity in clinical settings, but its clinical scope was previously constrained by limitations that Glyph™ is specifically designed to solve

PureTech Health plc (Nasdaq: PRTC, LSE: PRTC) ("PureTech"), a clinical-stage biotherapeutics company, noted that its Founded Entity, Seaport Therapeutics, ("Seaport") a clinical-stage biopharmaceutical company that is advancing novel neuropsychiatric medicines with a proven strategy and team, today announced that the first patient has been dosed in the Phase 2b BUOY-1 study of GlyphAllo™ (SPT-300 or Glyph Allopregnanolone) in major depressive disorder (MDD) with or without anxious distress.

GlyphAllo is a novel, "Glyphed" oral prodrug of allopregnanolone, an endogenous molecule that has been shown to dampen stress. Allopregnanolone has been clinically validated in third-party trials as a rapidly acting antidepressant with anxiolytic effects, but its scope of clinical use was previously constrained by limitations that the Glyph™ platform is specifically designed to solve. GlyphAllo has the potential to be a first-in-class treatment for patients with MDD, including those with or without anxious distress.

The full text of the announcement from Seaport is as follows:

Seaport Therapeutics Announces First Patient Dosed in Phase 2b BUOY-1 Study of GlyphAllo™ (SPT-300) in Major Depressive Disorder (MDD), With or Without Anxious Distress

BUOY-1 builds on successful Phase 1 and Phase 2a data with GlyphAllo - a novel oral prodrug of allopregnanolone and a potential first-in-class treatment for MDD

Allopregnanolone has demonstrated rapid antidepressant and anxiolytic activity in clinical settings, but its clinical scope was previously constrained by limitations that Glyph™ is specifically designed to solve

Boston, MA - July 17, 2025 - Seaport Therapeutics ("Seaport" or the "Company"), a clinical-stage biopharmaceutical company that is advancing novel neuropsychiatric medicines with a proven strategy and team, today announced that the first patient has been dosed in the Phase 2b BUOY-1 study of GlyphAllo™ (SPT-300 or Glyph Allopregnanolone) in major depressive disorder (MDD) with or without anxious distress. GlyphAllo is a novel, "Glyphed" oral prodrug of allopregnanolone, an endogenous molecule that has been shown to dampen stress. Allopregnanolone has been clinically validated in third-party trials as a rapidly acting antidepressant with anxiolytic effects, but its scope of clinical use was previously constrained by limitations that the Glyph™ platform is specifically designed to solve. GlyphAllo has the potential to be a first-in-class treatment for patients with MDD, including those with or without

anxious distress.

"The initiation of BUOY-1 marks a significant milestone for Seaport's pipeline, bringing us closer to a potential new treatment for major depression, which impacts around 280 million people globally - nearly 60 percent of whom also experience anxious distress," said Daphne Zohar, Co-Founder and Chief Executive Officer at Seaport Therapeutics. "This is an important step on our journey to deliver new treatments for patients living with depression, anxiety, and other neuropsychiatric conditions."

BUOY-1 is a global, randomized, double-blind, placebo-controlled study that will evaluate the efficacy, safety, and tolerability of GlyphAllo in adults with MDD, with or without anxious distress, a subtype of depression characterized by significant anxiety. The study is expected to enroll up to approximately 360 patients, randomized 1:1 to receive either GlyphAllo or placebo once-daily over a six-week treatment period. The primary endpoint of the study is the change from baseline at six weeks in the Hamilton Depression Rating Scale-17 (HAM-D-17), a gold-standard depression severity rating scale. Following the initial treatment period, eligible patients may enter an open-label extension phase, during which all participants will receive GlyphAllo for up to an additional six weeks.

"CNS clinical trials are inherently complex, and we are applying our team's extensive expertise to implement a high-quality study," said Antony Loebel, M.D., Chief Medical Officer, President of Clinical Development at Seaport Therapeutics. "We are confident that our rigorous clinical trial execution, including an emphasis on the quality of patient enrollment, will build on a proven mechanism and established clinical efficacy, to increase our likelihood of success in developing an effective treatment for patients with depression."

The BUOY-1 study builds on a foundation of positive clinical data from Phase 1 and Phase 2a studies of GlyphAllo in healthy volunteers. In Phase 1, GlyphAllo demonstrated approximately nine times greater allopregnanolone exposure than that previously reported following oral dosing of allopregnanolone and reached similar exposures to the efficacious doses of IV-infused allopregnanolone. The two key measures used to determine allopregnanolone-associated brain activity, EEG beta frequency power and reduction in saccadic eye velocity, confirmed that GlyphAllo engaged with its target in a dose-dependent manner. The overall safety data, pharmacokinetics, and pharmacodynamic findings, along with non-clinical studies, support six-week dosing of GlyphAllo in BUOY-1.

In a Phase 2a proof-of-concept study in healthy volunteers using the Trier Social Stress Test (TSST), a validated clinical model of anxiety, GlyphAllo significantly reduced the stress hormone salivary cortisol at all post-TSST timepoints compared to placebo, meeting the primary endpoint with a p-value of 0.0001 and demonstrating that GlyphAllo regulates hypothalamic-pituitary-adrenal axis reactivity to acute stress. GlyphAllo was generally well-tolerated, with adverse events that were mostly mild and transient.

About the Glyph™ 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 otherwise leading to low bioavailability and/or side effects, including liver enzyme elevations or hepatotoxicity. For each program, Seaport leverages its Glyph platform to create unique 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 GlyphAllo™ (SPT-300 or Glyph Allopregnanolone)

GlyphAllo (SPT-300 or Glyph Allopregnanolone), an oral prodrug of allopregnanolone, is in clinical stage development for the treatment of major depressive disorder (MDD) with or without anxious distress. Allopregnanolone, an endogenous molecule that has been shown to dampen stress, has antidepressant and anxiolytic activity and sleep-promoting effects but poor oral bioavailability due to substantial first-pass hepatic metabolism. Allopregnanolone was previously only approved as an intravenous infusion, which limited the scope of its clinical use. A synthetic analog of allopregnanolone was previously evaluated in MDD and showed promise but may not retain the activity, potency and the breadth of the natural biological response of endogenous allopregnanolone. In a Phase 1 clinical study, GlyphAllo demonstrated oral bioavailability, tolerability and γ-aminobutyric-acid type A ($GABA_A$) receptor target engagement in healthy volunteers. In a Phase 2a clinical study, GlyphAllo demonstrated initial proof-of-concept in the Trier Social Stress Test, a validated clinical model of anxiety in healthy volunteers. GlyphAllo is currently being evaluated in the Phase 2b BUOY-1 study for MDD, with or without anxious distress.

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.

About PureTech Health

PureTech is a clinical-stage biotherapeutics company dedicated to giving life to new classes of medicine to change the lives of patients with devastating diseases. The Company has created a broad and deep portfolio through its experienced research and development team and its extensive network of scientists, clinicians, and industry leaders that is being advanced both internally and through its Founded Entities. PureTech's R&D engine has resulted in the development of 29 therapeutics and therapeutic candidates, including three that have been approved by the U.S. Food and Drug Administration. A number of these programs are being advanced by PureTech or its Founded Entities in various indications and stages of clinical development, including registration-enabling studies. All of the underlying programs and platforms that resulted in this portfolio of therapeutic candidates were initially identified or discovered and then advanced by the PureTech team through key validation points.

For more information, visit www.puretechhealth.com or connect with us on X (formerly Twitter) @puretechh.

Cautionary Note Regarding Forward-Looking Statements

This press release contains statements that are or may be forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation those related to Seaport's development plans for its pipeline of neuropsychiatric therapeutics based on the Glyph™ Platform, the potential of GlyphAllo™ and the Glyph platform, the design and expected safety and efficacy outcomes of the BUOY-1 study, the broader applicability of the platform, the addressable market for Seaport's product candidates, if approved, potential benefits to patients, and Seaport's and our future prospects, developments and strategies. The forward-looking statements are based on current expectations and are subject to known and unknown risks, uncertainties and other important factors that could cause actual results, performance and achievements to differ materially from current expectations, including, but not limited to, those risks, uncertainties and other important factors described under the caption "Risk Factors" in our Annual Report on Form 20-F for the year ended December 31, 2024, filed with the SEC and in our other regulatory filings. These forward-looking statements are based on assumptions regarding the present and future business strategies of the Company and the environment in which it will operate in the future. Each forward-looking statement speaks only as at the date of this press release. Except as required by law and regulatory requirements, we disclaim any obligation to update or revise these forward-looking statements, whether as a result of new information, future events or otherwise.

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Sources:

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