PureTech Founded Entity Seaport Therapeutics Announces Positive Proof of Concept Topline Results from Ongoing Phase 1 Trial of GlyphAgo™ in Healthy Volunteers

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PureTech Health plc

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PureTech Health plc (Nasdaq: PRTC, LSE: PRTC) ("PureTech" or the "Company"), a hub-and-spoke biotherapeutics company dedicated to giving life to science and transforming innovation into value, notes that its Founded Entity, Seaport Therapeutics, today announced positive topline data from portions of its ongoing Phase 1 proof-of-concept clinical trial evaluating GlyphAgo™ (SPT-320™ or Glyph Agomelatine). GlyphAgo is a novel, Glyphed oral prodrug of agomelatine in development for generalized anxiety disorder (GAD) and the second clinical-stage candidate from Seaport's pipeline.

Based on the data shared today, Seaport announced plans to advance GlyphAgo into two parallel trials, a Phase 2a proof-of-pharmacology trial to evaluate the potential sleep benefit of GlyphAgo in patients with GAD and a Phase 2b randomized placebo-controlled trial in GAD that is designed to be registration-enabling.

The GlyphAgo program and the underlying Glyph platform were initially advanced at PureTech, applying the Company's strategy of identifying clinically validated pharmacology and overcoming key limitations through targeted innovation. The Glyph platform and related programs are now being advanced by PureTech's Founded Entity, Seaport Therapeutics.

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

Seaport Therapeutics Announces Positive Proof of Concept Topline Results from Ongoing Phase 1 Trial of GlyphAgo™ in Healthy Volunteers

GlyphAgo achieved therapeutic exposures of agomelatine at doses projected to avoid liver enzyme elevations and reduce or eliminate the need for liver function testing that has previously limited agomelatine's clinical use

GlyphAgo demonstrated a statistically significant 6.8-fold increase in bioavailability compared to unmodified agomelatine in healthy volunteers, exceeding the program's 2-fold target to mitigate liver exposure

GlyphAgo substantially reduced pharmacokinetic (PK) variability by 10-fold compared to unmodified agomelatine

GlyphAgo was well-tolerated across all evaluated doses, and no serious or severe adverse events or liver-related adverse effects were reported

BOSTON, April 2, 2026 – Seaport Therapeutics ("Seaport" or the "Company"), a clinical-stage therapeutics company advancing novel neuropsychiatric medicines with a proven strategy and team, today announced positive topline data from its single-ascending dose (SAD) and crossover portions of its Phase 1 proof-of-concept clinical trial evaluating GlyphAgo™ (SPT-320™ or Glyph Agomelatine), a novel, Glyphed oral prodrug of agomelatine in development for generalized anxiety disorder (GAD). The clinical proof-of-concept topline results demonstrated that GlyphAgo exceeded the program's target of a 2-fold increase in bioavailability compared to unmodified agomelatine, achieving therapeutic levels of agomelatine at substantially lower doses that reduce liver exposure and are projected to reduce or eliminate the need for liver function testing.

In the head-to-head crossover portion of the trial, GlyphAgo demonstrated a 6.8-fold increase in bioavailability of agomelatine compared to unmodified orally administered agomelatine. GlyphAgo also showed significantly lower (10-fold) PK variability compared to unmodified agomelatine. The crossover portion included participants who were taking estrogen-containing oral contraceptives that are known to increase agomelatine exposure due to liver drug-drug interaction. In contrast, GlyphAgo exposure was unaffected by oral contraceptives, further supporting the ability of GlyphAgo to bypass first-pass liver metabolism. GlyphAgo demonstrated a 9.6 to 14.5-fold increase in dose-normalized exposure compared to agomelatine in a separate SAD portion of the trial in which no participants were on oral contraceptives. GlyphAgo was well tolerated and no liver-related adverse events (AEs) were observed. The completed SAD and crossover portions of the trial, which included approximately 130 participants, conclude the PK proof-of-concept objectives of the trial, while the ongoing multiple-ascending dose (MAD) portion of this trial – conducted with only GlyphAgo – is intended to further characterize the safety and PK of repeat-dosing of GlyphAgo.

"These topline data, from a well-powered Phase 1 trial, strengthen our conviction in GlyphAgo's potential and provide further clinical validation for the Glyph platform," said Daphne Zohar, Co-Founder and Chief Executive Officer at Seaport Therapeutics. "Based on these data, we plan to advance GlyphAgo into two parallel trials, a Phase 2a proof-of-pharmacology trial to evaluate the potential sleep benefit of GlyphAgo in patients with GAD, and a Phase 2b trial in GAD, that is a randomized placebo-controlled trial designed to be registration-enabling. We believe that GlyphAgo has the potential to bring patients with generalized anxiety disorder what could be the first new therapy in decades in the U.S. for this underserved and debilitating disorder."

Agomelatine, a clinically validated MT1/MT2 melatonin receptor agonist and serotonin 2C (5-HT2C) 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).

Agomelatine's label in both Australia and the EU requires liver function testing before initiating treatment, during treatment, and upon increasing the dose. Agomelatine is not approved in the U.S.

"In GAD, agomelatine has demonstrated robust and statistically significant separation from placebo in four third-party placebo-controlled studies [1-4] and has been observed in meta-analysis to have better efficacy and tolerability than selective serotonin-reuptake inhibitors or benzodiazepines," said Steven Paul, M.D., Co-Founder and Board Chair at Seaport Therapeutics. "Despite this positive profile, over 90 percent of unmodified agomelatine is lost to first-pass metabolism and its use has been limited by dose-dependent liver enzyme elevations. The enhanced pharmaceutical properties of GlyphAgo and resulting markedly reduced inter-individual variability in systemic exposure to agomelatine support our clinical development of GlyphAgo in GAD."

Using Seaport's proprietary Glyph ^{TM} platform, GlyphAgo is designed to enhance lymphatic absorption and avoid first-pass liver metabolism, thereby enhancing oral bioavailability and reducing side effects. By leveraging an alternative absorption pathway via the intestinal lymphatic system used by dietary fats, GlyphAgo is designed to increase systemic exposure of agomelatine, enabling exposure levels of agomelatine that are effective in GAD but at a lower dose that reduces liver exposure and reduces or eliminates the need for liver function testing. Based on the data that Seaport has generated to date, GlyphAgo has the potential to become a leading treatment for GAD.

"Agomelatine combines a differentiated mechanism with a favorable efficacy and tolerability profile in GAD, but its potential has been previously limited by first-pass liver metabolism and the need for burdensome liver testing," said Daniel Bonner, Ph.D., Co-Founder and Senior Vice President, Platform, at Seaport Therapeutics. "These results show that GlyphAgo exceeded the targeted improvement in bioavailability, achieving robust exposure, and a more consistent PK profile at a substantially lower dose of agomelatine."

Phase 1 Trial Design

The Phase 1 proof-of-concept trial is being conducted in multiple parts to evaluate the safety, tolerability, and PK of GlyphAgo and to compare the PK of GlyphAgo to agomelatine alone. The trial includes single and multiple-ascending dose cohorts, as well as a crossover portion, (including both food-effect and within-participant comparison between GlyphAgo and agomelatine), using both open-label and placebo-controlled designs. In the SAD portion of the Phase 1 trial, healthy volunteers received a single administration of either ascending doses of GlyphAgo or a 25 mg dose of agomelatine, an approved efficacious dose in Australia and the EU, to assess PK parameters, including area under the curve (AUC), a measure of overall exposure, and Cmax, or peak plasma concentrations. In the SAD portion, participants were healthy volunteers with no evidence of liver impairment who were not taking any medications or supplements known to alter the PK of agomelatine, including fluvoxamine or estrogen-containing oral contraceptives. In the crossover portion, participants were randomized to one of two sequences designed to assess the food effect on a single dose level of GlyphAgo and compare it with a 25 mg dose of agomelatine. Both sequences evaluated GlyphAgo under fed and fasted conditions before agomelatine, a structure chosen to avoid confounding GlyphAgo safety results with agomelatine's known liver toxicity.

Topline Results

Crossover Portion

- GlyphAgo demonstrated a 6.8-fold increase in dose-normalized AUC compared to agomelatine (90% confidence interval, 4.7 to 10.0x; geometric means). In this portion of the trial, exposure provided by GlyphAgo and unmodified agomelatine were compared head-to-head within the same participants.
- Statistically significantly lower PK variability (10-fold lower geometric CV% of AUC_{0-24}) was observed between participants dosed with GlyphAgo compared to agomelatine 25 mg ($p< 0.0001$).
- It was observed that there is no food effect on agomelatine exposure with GlyphAgo treatment.
- No clinically significant changes in liver-related laboratory parameters were observed, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin.
- GlyphAgo achieved a 1.9-fold increase in dose-normalized maximum plasma concentration (Cmax) compared to agomelatine (90% confidence interval, 1.2 to 3.0x).
- This portion included participants (23%) taking estrogen-containing oral contraceptives, which are known to increase exposure of agomelatine due to liver drug-drug interaction[5]. No effect of estrogen-containing oral contraceptives on GlyphAgo was observed.

SAD Portion

- GlyphAgo demonstrated a 9.6 to 14.5-fold increase in dose-normalized AUC compared to agomelatine and a 2.3 to 3.7-fold increase in dose-normalized Cmax across the doses studied. Participants in the SAD portion were not taking concomitant estrogen-containing oral contraceptives.
- Across all evaluated dose levels, GlyphAgo was well tolerated, with no serious or severe AEs observed and no clinically significant changes in liver-related laboratory parameters, including ALT, AST, or bilirubin.
- All treatment groups (GlyphAgo, agomelatine, and placebo) were well-tolerated, with no serious or severe AEs observed.
- GlyphAgo AUC_{0-24} and Cmax increased dose-dependently over the range of doses studied, supporting PK and dose selection for subsequent studies.

Seaport plans to present additional analyses from the Phase 1 trial, including the results from the MAD portion, at future upcoming scientific meetings.

About GlyphAgo (SPT-320 or Glyph Agomelatine)

GlyphAgo is a novel, Glyphed oral prodrug of agomelatine, a clinically validated anxiolytic and antidepressant that is approved for the treatment of GAD in Australia and MDD in Australia and the EU. Using Seaport's proprietary Glyph platform, GlyphAgo is designed to avoid first-pass liver

metabolism and increase systemic exposure of agomelatine, enabling exposure levels of agomelatine that are effective in GAD but at a lower dose that reduces liver exposure and reduces or eliminates the need for liver function testing. Based on internal analyses, Seaport believes a two-fold increase in the bioavailability of agomelatine with GlyphAgo dosing will reduce or eliminate liver enzyme elevations. Based on the data generated to date, Seaport believes GlyphAgo has the potential to become a leading treatment for GAD.

About Seaport Therapeutics

Seaport Therapeutics is a clinical-stage therapeutics 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 Health is a hub-and-spoke biotherapeutics company dedicated to giving life to science and transforming innovation into value. We do this through a proven, capital-efficient R&D model focused on opportunities with validated pharmacology and untapped potential to address significant patient needs. This strategy has produced dozens of therapeutic candidates, including three that have received U.S. FDA approval. By identifying, shaping, and de-risking these high-conviction assets, and scaling them through dedicated structures backed by external capital, we accelerate their path to patients while creating sustainable value for shareholders.

For more information, visit www.puretechhealth.com or connect with us on LinkedIn and 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 those related to Seaport's development plans for its pipeline of neuropsychiatric therapeutics based on the Glyph™ Platform, the potential of GlyphAgo™ (SPT-320™ or Glyph Agomelatine) and the Glyph platform, 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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