Seaport Therapeutics Announces Science Translational Medicine Peer-Reviewed Publication Featuring GlyphAllo (SPT-300) as the First Triglyceride-Mimetic Prodrug to Achieve Therapeutically Relevant Drug Levels in Humans

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Newly published findings further support clinical validation of Seaport's proprietary Glyph™ platform to enable oral dosing

Data supported advancement of ongoing Phase 2b clinical trial of GlyphAllo in major depressive disorder (MDD)

BOSTON, March 25, 2026 – Seaport Therapeutics ("Seaport" or the "Company"), a clinical-stage therapeutics company focused on inventing and developing new medicines for patients with depression, anxiety, and other debilitating neuropsychiatric disorders with a proven strategy and team, today announced the first comprehensive disclosure of first-in-human clinical and preclinical data for GlyphAllo™ (SPT-300 or Glyph Allopregnanolone), a novel, Glyphed oral prodrug of allopregnanolone, published in *Science Translational Medicine*, tracing the program's pathway from discovery through initial proof-of-concept . The peer-reviewed article, titled "An oral allopregnanolone prodrug bypasses liver metabolism via lymphatic transport enabling bioavailability in animals and humans," details the design, optimization, and clinical translation of GlyphAllo, and further supports clinical validation of Seaport's proprietary Glyph™ platform.

"Allopregnanolone is an endogenous molecule with a rapid onset of action and well established, clinically validated antidepressant, anxiolytic, and sleep-promoting effects, as demonstrated in third-party clinical trials for the treatment of postpartum depression, a form of depression that shares symptomatology with MDD," said Steven Paul, M.D., Co-Founder and Board Chair at Seaport Therapeutics, and author on the paper. "GlyphAllo is our lead investigational product candidate designed to overcome the bioavailability limitations of allopregnanolone and deliver rapid and durable clinical effects. With the now optimized pharmaceutical properties of GlyphAllo, we can now study an oral prodrug of allopregnanolone as a potential new treatment for MDD."

The newly published research details the discovery process driving the creation of GlyphAllo, in which simple triglyceride-mimetic (TG-mimetic) allopregnanolone prodrug candidates with direct conjugation of a desired drug with lipophilic moieties were synthesized, screened, and evaluated across preclinical models. Multiple prodrug candidates demonstrated robust lymphatic transport and plasma release profiles consistent with achieving therapeutically relevant allopregnanolone exposure after oral dosing. The data further demonstrated that Glyph enabled and enhanced the oral administration of molecules historically limited by high first-pass metabolism. The paper describes how Seaport used the Glyph platform to optimize GlyphAllo, demonstrating enhanced oral bioavailability in preclinical models, with oral dosing resulting in robust lymphatic transport and systemic exposure. These data supported the selection and advancement of GlyphAllo into Phase 1 and Phase 2a clinical development.

Translation of these findings into humans was confirmed in Phase 1/2a clinical development, which demonstrated dose-dependent, therapeutically relevant allopregnanolone levels and pharmacodynamic effects in healthy volunteers. In Phase 1, GlyphAllo was generally well-tolerated following single- and multiple-ascending oral doses ranging from 70–1000 mg and provided therapeutically relevant plasma exposures of allopregnanolone. In the Phase 2a initial proof-of-concept trial using the Trier Social Stress Test (TSST), a validated clinical model of anxiety, a single 375 mg dose of GlyphAllo significantly reduced levels of salivary cortisol versus placebo (p=0.0001), demonstrating that GlyphAllo potently blunted the acute physiological stress response.

"This pioneering work, published in *Science Translational Medicine*, a premier, high-impact journal, positions GlyphAllo as a compelling drug candidate and supports further investigation of its potential to address MDD, including in patients with or without anxious distress," said Michael Chen, Ph.D., Co-Founder and Chief Scientific Officer at Seaport Therapeutics, and senior author of the paper. "Importantly, these findings also further support the broad compatibility of the Glyph platform to transform promising small molecules with pharmacokinetic limitations into prodrugs with the right properties."

Collectively, the results support the continued development of GlyphAllo as a potential differentiated therapy for MDD. In July 2025, Seaport initiated BUOY-1, a global, randomized, double-blind, placebo-controlled Phase 2b trial evaluating the efficacy, safety, and tolerability of GlyphAllo in adults with MDD, with or without anxious distress. Beyond GlyphAllo, the publication highlights the broad translatability of the Glyph platform, demonstrating an efficient, repeatable approach to creating and validating Glyph molecules that can overcome pharmacokinetic barriers, with potential applications extending beyond neuropsychiatry into oncology, immunology and inflammation, metabolic disease, and obesity.

In addition to Dr. Paul and Dr. Chen, the research was led by Seaport authors Jamie Simpson, Ph.D., lead author of the publication, original co-inventor of the Glyph technology and Head of Chemistry, and Daniel Bonner, Ph.D., Co-Founder, Senior Vice President, Platform. The research was conducted in collaboration with Monash University under the direction of Christopher Porter, Ph.D., an original co-inventor of the Glyph technology and Director of the Monash Institute of Pharmaceutical Sciences.

Read the paper here: www.science.org/doi/10.1126/scitranslmed.adu2352

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*, *Molecular Pharmaceutics*, and *Science Translational Medicine* supporting the Glyph platform's capabilities. See Glyph in action here.

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's experienced team of industry leaders has a proven track record of building successful companies that have developed and commercialized innovative neuropsychiatric medicines. The Company has focused its strategy on 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 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.