Unlocking Medicines for Neuropsychiatry by Enhancing Oral Absorption Using a Lymphatic-targeting Prodrug Technology

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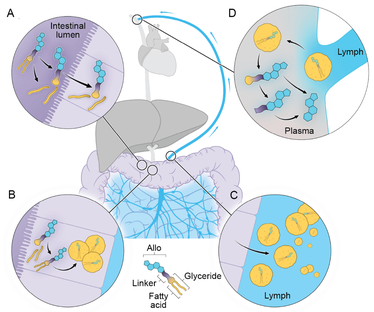
SEAPORT THERAPEUTICS

Introduction

- Depression and anxiety are disabling mental health conditions with a significant need for new treatment options
- Allopregnanolone is an endogenous neurosteroid that has been clinically validated as a rapidly acting antidepressant with anxiolytic and sleep-promoting effects through its pharmacology as a $GABA_A$ receptor positive allosteric modulator
- However, unmodified allopregnanolone has poor oral bioavailability from substantial first-pass metabolism, limiting its clinical use
- GlyphAllo™ (SPT-300 or Glyph Allopregnanolone), an oral prodrug of allopregnanolone, is designed using the Glyph™ platform to overcome this limitation by shifting absorption to the intestinal lymphatics to avoid first-pass metabolism and enhance oral bioavailability



The Glyph platform, a lymphatic-targeting prodrug technology, shifts absorption to the intestinal lymphatics.

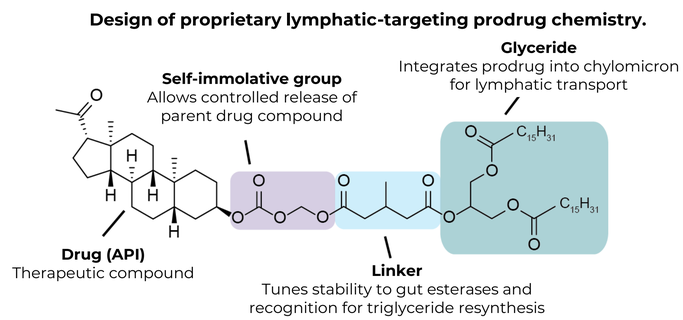
(A) A Glyph prodrug enters the intestinal lumen where it is hydrolyzed.
(B) The hydrolyzed prodrug is then re-esterified and assembled into chylomicrons.
(C) The chylomicrons exit enterocytes and are taken up into the lymph for transport to the circulation via mesenteric and thoracic lymph.
(D) Once the chylomicrons reach the plasma, the active pharmaceutical ingredient is released along with prodrug intermediates.

- Here, we present the initial proof-of-concept results from a phase 1 and 2a clinical trial of oral GlyphAllo in healthy volunteers

Methods

- A series of lymphatic-targeting triglyceride-mimetic allopregnanolone prodrugs was screened for in vitro plasma release and in vivo lymphatic absorption across species

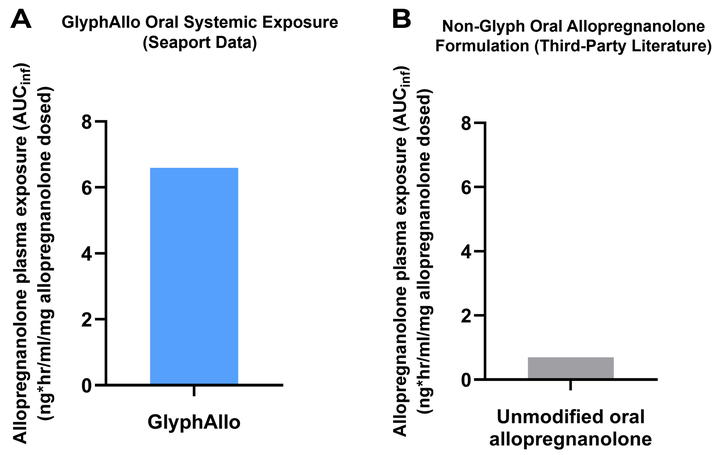
Design of proprietary lymphatic-targeting prodrug chemistry.



- Safety, tolerability, pharmacokinetics, and pharmacodynamics of GlyphAllo was evaluated in a multipart, phase 1 clinical trial (NCT05129865) of 189 healthy volunteers
- Pharmacodynamic assessments included the quantitative EEG (qEEG) and video-oculography for saccadic eye velocity (SEV)
- GlyphAllo's potential to reduce physiological stress in healthy volunteers was evaluated in an initial proof-of-concept phase 2a (NCT05129865) pharmacodynamic trial using the Trier Social Stress Test, a clinically validated model of anxiety

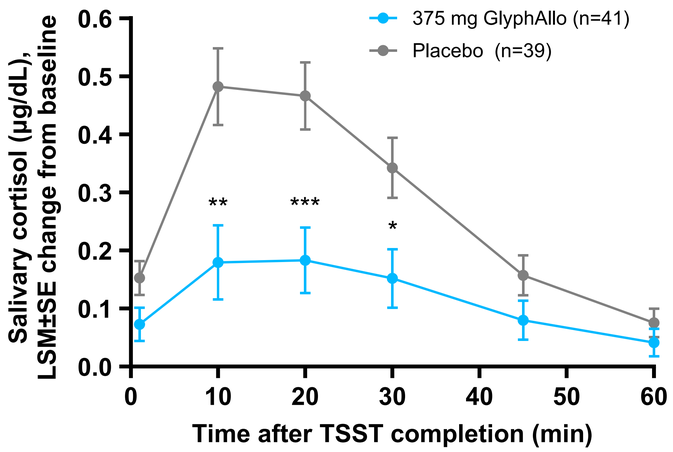
Results

Figure 1. (A) GlyphAllo enhanced oral bioavailability of allopregnanolone compared to (B) third-party literature of non-glyph oral allopregnanolone.



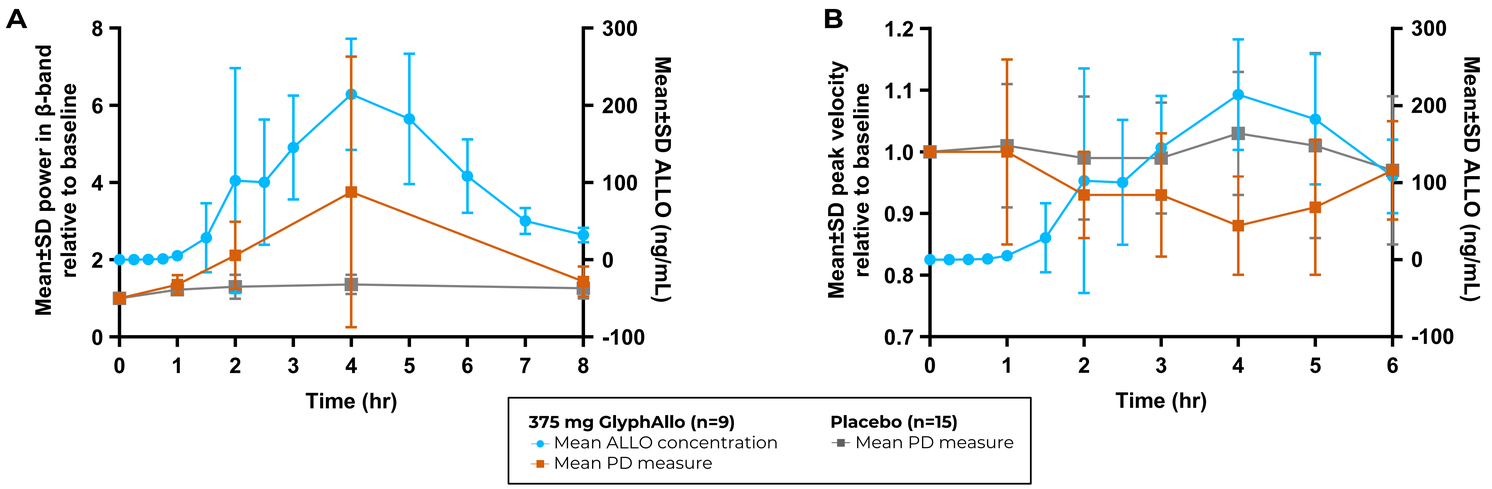
Not a head-to-head comparison.

Figure 2. GlyphAllo administration significantly blunted salivary cortisol concentrations compared to placebo following completion of the TSST.



*P<0.05, **P<0.01, P<0.001 vs placebo.

Figure 3. GlyphAllo demonstrated therapeutically relevant allopregnanolone exposures and pharmacodynamic signals which peaked at 3 to 5 hours post dose and returned to baseline by 6 to 8 hours.



ALLO, allopregnanolone; PD, pharmacodynamic; qEEG, quantitative electroencephalogram; SEV, saccadic eye velocity; TSST, Trier Social Stress Test.

Discussion

- In a phase 1 clinical trial, GlyphAllo was generally well tolerated and enhanced oral bioavailability of allopregnanolone in healthy volunteers compared to previously published values of allopregnanolone[1]
- These data validate the Glyph platform's ability to redirect absorption to the intestinal lymphatics and confirm that the pharmacodynamic activity of GlyphAllo is consistent with the known profile of allopregnanolone
- GlyphAllo has the potential to be a novel treatment mechanism for major depressive disorder with benefits for anxious distress and has the potential to avoid side effects associated with standard-of-care drugs
- A phase 2b, placebo-controlled trial (BUOY-1) is underway to evaluate the efficacy and safety of GlyphAllo in patients with major depressive disorder, with or without anxious distress (NCT07065240), with the option to roll over into the 6-week open-label extension trial (NCT07161700)
- GlyphAllo's development and demonstration of enhanced oral bioavailability provides an initial proof-of-concept supporting the wider applicability of the lymphatic-targeting prodrug approach to other therapeutic molecules with previous limitations

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References: 1. Simpson JS et al. Sci. Transl. Med. 2026;18(842). Comparative values from brexanolone NDA 211371 Multi-disciplinary Review and Evaluation, FDA CDER, 2018.
Disclosures: AL, SY, DKB, JSS, and MCC are currently employed by Seaport Therapeutics.
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