GlyphAllo, a Novel, Orally Bioavailable Prodrug of Allopregnanolone, Induces an EEG Profile Consistent with $GABA_A$ Positive Allosteric Modulation in Healthy Volunteers

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Introduction

- Allopregnanolone is an endogenous neuroactive steroid that exhibits antidepressant and anxiolytic effects through its pharmacology as a $GABA_A$ positive allosteric modulator (PAM)
- Allopregnanolone has been reported to increase EEG β power, an established marker of $GABA_A$ receptor engagement, and induce an overall EEG profile different from other $GABA_A$ PAMs[1,2]
- Due to poor oral bioavailability from substantial first-pass hepatic metabolism, unmodified allopregnanolone must be administered via intravenous infusion for the treatment of postpartum depression, limiting broader clinical use to other indications
- GlyphAllo™ (SPT-300 or Glyph Allopregnanolone) is an oral prodrug of allopregnanolone designed with the Glyph™ platform, a lymphatic–targeting prodrug technology, which enhances oral bioavailability of allopregnanolone and enables once daily dosing as an oral capsule[3]
- Here, we assessed the ability of GlyphAllo to modulate electroencephalography (EEG) activity consistent with the known effects of allopregnanolone

Methods

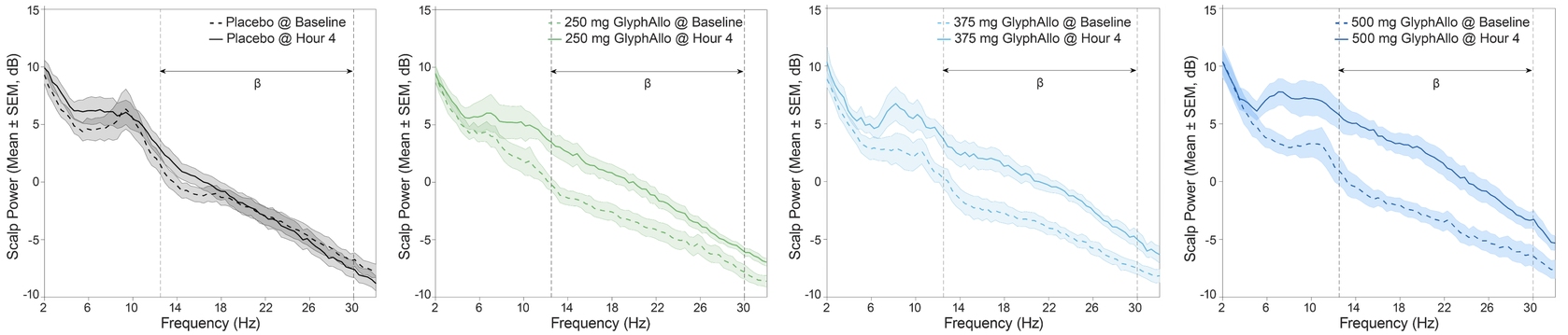
- EEG signal was evaluated in a subpopulation of 36 healthy adult volunteers enrolled in a randomized, double-blind, placebo-controlled, multiple ascending dose phase 1 trial (NCT05129865)
- Participants were randomized to receive GlyphAllo (Total N=27; 250 mg, N=9; 375 mg, N=9; 500 mg, N=9) or placebo (N=9) for 7 days
- EEG (32 leads, 10-20 system) recording sessions were approx. 15 minutes in duration (Day 1 & Day 7) under quiet, resting conditions and included periods of Eyes Open (EO) and Eyes Closed (EC)
- qEEG bands (Hz) were defined as follows: delta (δ; 1.5-6), theta (θ; 6-8.5), alpha (α; 8.5-12.5); beta (β; 12.5-30), gamma (γ; 30-40)
- Effects were quantified from the averaged scalp power spectral densities following pre-processing and artifact rejection utilizing a blind source separation-canonical correlation analysis algorithm
- Group comparisons (placebo vs. treatment) were analyzed using a two-way ANOVA with Dunnett's Test for multiple comparisons

Results

- GlyphAllo induced a significant dose-dependent increase in EEG derived α, β, and γ power compared to baseline at 4 hours post dose, with the strongest effects in β, all of which returned to baseline by 8 hours post dose
- There were no or minimal effects of GlyphAllo on EEG derived δ or θ power at 4 or 8 hours post dose
- GlyphAllo was generally well tolerated with minimal adverse effects reported; the most common adverse event was somnolence, which was mild and transient in all cases

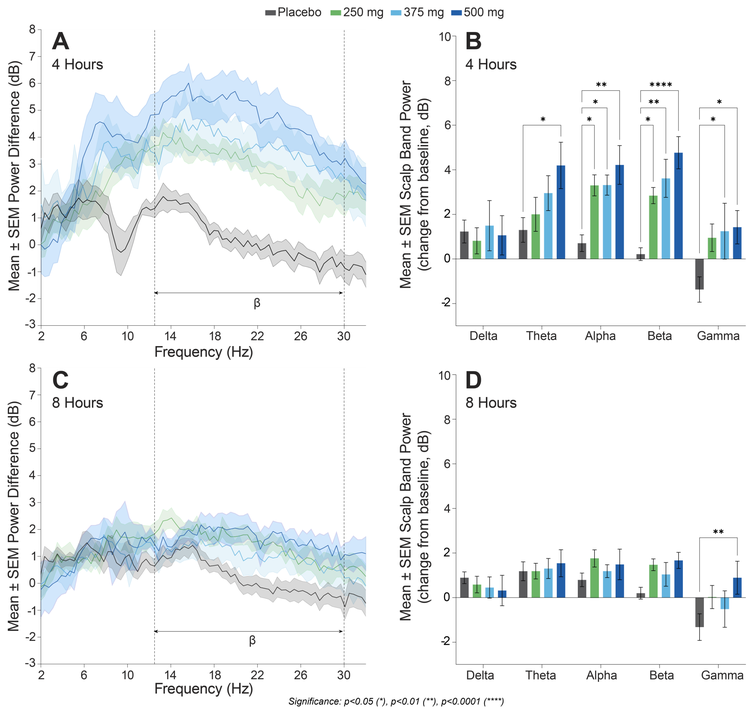
Results

Figure 1. GlyphAllo dose-dependently increases EEG derived β power at 4 hours post dose.



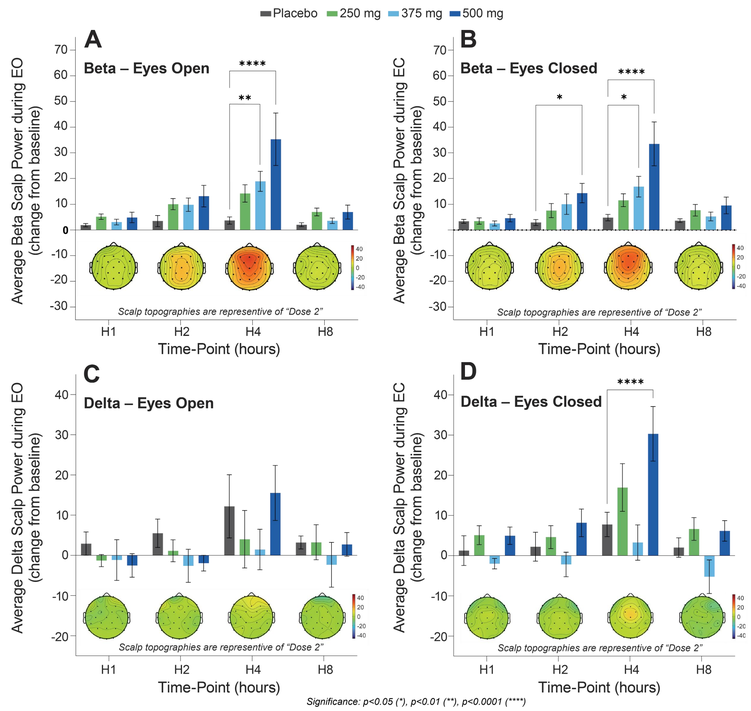
- Power spectral densities (PSD) during eyes open for baseline (pre dose, dashed line) and 4 hours (post dose, solid line)
- Effects of GlyphAllo are dose-dependent, selective to frequencies above the δ band (1.5-6 Hz), and most prominent in the β band (12-30 Hz)

Figure 2. Dose-dependent effects of GlyphAllo on qEEG with a return to baseline at 8 hours post dose.



- Mean corrected band power at baseline (B&D) calculated from the PSDs (A&C, respectively) measured as change from baseline during eyes open at 4 and 8 hours post dose
- Changes in frequencies above the δ band (0.5-4 Hz) are transient

Figure 3. Time course of β and δ band power change from baseline.



- The peak, dose-dependent increase in β power occurs at hour 4, consistent with previously presented pharmacokinetic data showing a peak increase in allopregnanolone plasma concentrations after GlyphAllo dosing in healthy volunteers

Discussion

- GlyphAllo demonstrates dose-dependent effects on EEG, most prominently on β power, consistent with previously reported effects of allopregnanolone on EEG activity[2]
- There were no or minimal effects of GlyphAllo on δ power, a band modulated by and associated with sedative doses of benzodiazepines[4] and all EEG changes after GlyphAllo administration returned to baseline between 4 and 8 hours post dose, suggesting minimal sedative effects
- The overall EEG profile differs from benzodiazepines, consistent with allopregnanolone's differential $GABA_A$ binding sites, receptor engagement, and signaling, which may drive allopregnanolone's antidepressant and/or anxiolytic activity[2]
- GlyphAllo has the potential to expand the clinical use of allopregnanolone to patients with major depressive disorder (MDD) and a phase 2b, placebo-controlled trial (BUOY-1; NCT07065240) is currently underway to evaluate the efficacy and safety of GlyphAllo in patients with MDD

Funding sources: This study was supported by Seaport Therapeutics and, previously, Seaport Therapeutics' predecessor, PureTech Health. ClinicalTrials.gov Identifier: NCT05129865.
Disclosures: DKB, TL, and MCC are employees of Seaport Therapeutics. HLR, BDH and GV are employed by Biotrial.
References: 1. Visser SA et al. J Pharmacol Exp Ther. 2003;304(1):88-101. 2. Lambert PM et al. Neuropsychopharmacology. 2023;48(2):371-379. 3. Jamie S. Simpson et al. Sci. Transl. Med.18,eadu2352(2026). Berro LF et al. Psychopharmacology (Berl). 2021;238(5):1373-1386.

Presented at the Society of Biological Psychiatry (SOBP); April 30 to May 2, 2026; New York City, New York.