A First-in-Human Phase 1 Study of SPT-300, a First-in-Class Orally Bioavailable Prodrug of the Neurosteroid Allopregnanolone That is Absorbed via the Lymphatic System

Michael C. Chen[1], James Shipley[2], Varun Garg[2], Daniel Bonner[1], Eric Elenko[2], Julie Krop[2]

[1] Seaport Therapeutics, Boston, MA, USA;
[2] PureTech Health, Boston, MA, USA;

SEAPORT THERAPEUTICS

Introduction

- Allopregnanolone, a neurosteroid $GABA_A$ positive allosteric modulator that regulates phasic and tonic GABA inhibition[1], has antidepressant and anxiolytic properties. Development as a pharmacotherapy has been limited by poor oral bioavailability due to first-pass metabolism. The Glyph™ platform shifts absorption of a drug from the liver to the gut-draining lymphatics by reversibly connecting it to a fat molecule, bypassing the liver (Fig 1) and first-pass metabolism.
- SPT-300* is a first-in-class orally bioavailable prodrug of allopregnanolone. We present results from a Phase 1, safety, tolerability, and pharmacokinetics (PK) study of single and multiple doses of SPT-300 in which pharmacodynamic (PD) markers of $GABA_A$ engagement, beta EEG power and saccadic eye velocity, known to be sensitive to GABA potentiation[2-3], are assessed.

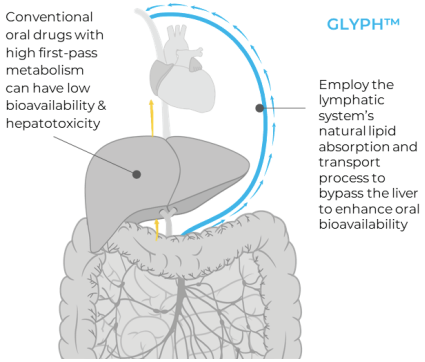

Figure 1. Glyph™ technology platform

		Part 1: SAD			Part 2: FE	Part 3: MAD
Variable	Statistics	Cohort 1 N=11	Cohort 2 N=9	Cohort 2a N=10	Cohort 3 N=9	Cohorts 4-8 N=60
Age (years) at Screening	N	11	9	10	9	60
	Mean	28.6	32	27.7	28.3	29.9
	SD	8.4	8.5	8.2	7	9
	Median	25	30	25.5	28	28
	Minimum	21	21	19	18	18
	Maximum	48	48	46	40	54
Sex n (%)	Female	4 (36.4%)	2 (22.2%)	1 (10.0%)	2 (22.2%)	24 (40.0%)
	Male	7 (63.6%)	7 (77.8%)	9 (90.0%)	7 (77.8%)	36 (60.0%)
Childbearing potential n (%)	Yes	4 (100%)	1 (50.0%)	1 (100%)	2 (100%)	23 (95.8%)
Ethnicity n (%)	Hispanic/ Latino	3 (27.3%)	1 (50.0%)	1 (10.0%)	2 (22.2%)	6 (10.0%)
Race n (%)	Asian	3 (27.3%)	1 (11.1%)	3 (30.0%)	1 (11.1%)	11 (18.3%)
	White	6 (54.5%)	8 (88.9%)	7 (70.0%)	7 (77.8%)	36 (60.0%)
	Other	2 (18.2%)	0	0	1 (11.1%)	7 (11.7%)
BMI (kg/m²) at Screening	Mean (SD)	24.81 (2.05)	23.64 (3.73)	24.99 (2.18)	26.12 (3.13)	24.18 (3.15)

Table 1. Participant disposition

Methods

- This study included double-blind single-ascending dose (SAD), multiple ascending dose (MAD) and open-label food effect (FE) parts (NCT05129865). The SAD and FE parts used crossover designs, while the MAD used sequential cohorts dosed over 7 days. PK and safety were collected throughout. EEG and saccadic eye velocity (SEV) PD endpoints were assessed in the MAD part.
- PK data were compared to published data for steady state allopregnanolone levels during 60-hour IV regimen administered for post-partum depression.

Results

- Ninety-nine participants were enrolled: SAD N=30, Food Effect N=9, MAD N=60 (Table 1).
- **SAD**: A dose-proportional increase in C_{max} and AUC of allopregnanolone was observed at all but the two highest dose cohorts (Fig 2A). T_{max} was generally 3-5 hours post-dose
- **MAD**: Minimal accumulation was observed with multiple dosing and steady state was reached by Day 2 or 3 of daily administration. T_{max} was generally observed 3-5 hours post-dose (Fig 3).
- **PD**: SPT-300 dosing increased beta EEG power vs. placebo, maximally at 4h post-dose and more notably at the highest doses tested (Fig 4). Video oculography revealed a reduction in SEV at 4h post-dose, also maximal at 4h and the highest doses tested. The eye velocity changes diminished by Day 7.

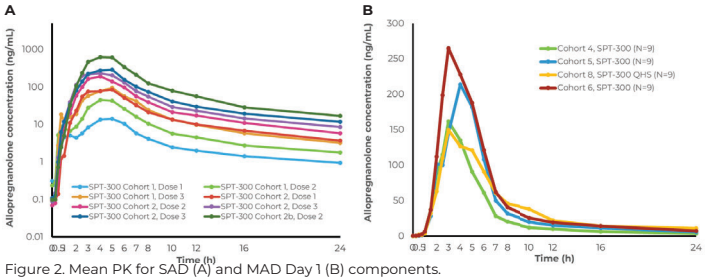

Figure 2. Mean PK for SAD (A) and MAD Day 1 (B) components.

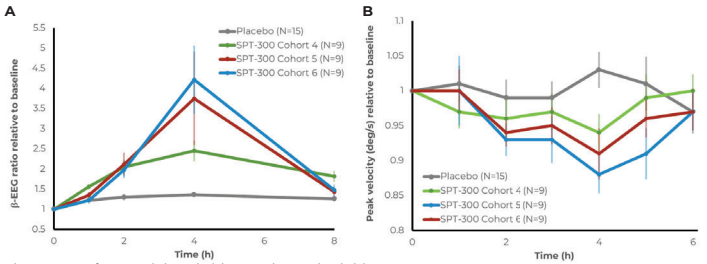

Figure 3. PD for EEG (A) and video oculography (B) in MAD part. Mean ± S.E.M.

- No treatment-related severe or serious adverse events (AEs), including clinically important hepatic, cardiac and renal AEs, were reported. The most common AE across all parts was somnolence, which was mild in all cases. A dose-dependent increase in the number of AEs was observed, but no dose limiting toxicity was reached.

Discussion

- Dosing of SPT-300 resulted in therapeutically relevant exposures of allopregnanolone ~9x greater than previously published values[4], validating the Glyph platform's ability to enhance bioavailability.
- Clinically relevant exposure and PD markers consistent with allopregnanolone-driven $GABA_A$ modulation support further exploration of SPT-300 in mood and anxiety disorders.

References:
1. Meltzer-Brody, Samantha, and Stephen J. Kanes. "Allopregnanolone in postpartum depression: Role in pathophysiology and treatment." *Neurobiology of stress* 12 (2020): 100212.
2. Christian, Edward P., et al. "EEG-β/γ spectral power elevation in rat: a translatable biomarker elicited by GABAAα2/3-positive allosteric modulators at nonsedating anxiolytic doses." *Journal of neurophysiology* 113.1 (2015): 116-131.
3. Timby, Erika, et al. "Pharmacokinetic and behavioral effects of allopregnanolone in healthy women." *Psychopharmacology* 186 (2006): 414-424.
4. U.S. Food and Drug Administration. (2018). FDA drug approval package: Zulresso (Application No. 211,371)

* SPT-300 formerly known as LYT-300