SPT-300, a First-in-Class Orally Bioavailable Prodrug of the Neurosteroid Allopregnanolone: Safety, Tolerability, and Clinical Pharmacology in Healthy Volunteers

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Introduction

- SPT-300 is a first-in-class orally bioavailable prodrug of allopregnanolone developed using the Glyph™ platform, which bypasses first-pass liver metabolism by shifting absorption through the gut-draining lymphatics.
- SPT-300 enables therapeutic exposure levels of allopregnanolone, an endogenous neurosteroid $GABA_A$ positive allosteric modulator (PAM) that regulates both phasic and tonic GABA inhibition[1] and has antidepressant and anxiolytic properties.
- Here, we present results from a Phase 1 safety, tolerability, and pharmacokinetics (PK) study and profile measures related to somnolence, the most common adverse event for $GABA_A$ PAMs.

Methods

- This study included double-blind single-ascending dose (SAD), 7-day multiple ascending dose (MAD) and open-label food effect (FE) parts (NCT05129865). SPT-300 was dosed orally, once-daily, either during the day or before bedtime.
- Safety, PK, and pharmacodynamic (PD) data were collected across all study cohorts. PD assessments included the Stanford Sleepiness Scale (SSS), quantitative EEG (qEEG)[2] and video-oculography for saccadic eye velocity (SEV)[3].

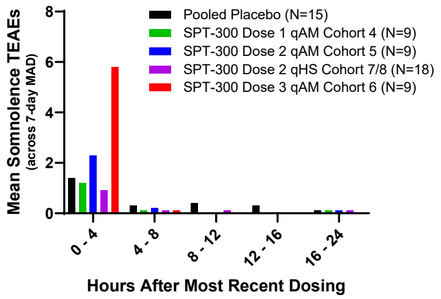
Variable	Statistics	Pooled Placebo (N=15)	Dose 1 qAM Cohort 4 (N=9)	Dose 2 qAM Cohort 5 (N=9)	Dose 2 qHS Cohorts 7/8 Pooled (N=18)	Dose 3 qAM Cohort 6 (N=9)
Age (years) at Screening	N	15	9	9	18	9
	Mean	28.6	30	32.1	29.6	30.2
	SD	8.8	5.8	8.4	10.9	9.2
	Median	26	28	31	26.5	29
	Minimum	18	21	24	19	19
	Maximum	47	39	50	54	49
Sex n (%)	Female	5 (33.3%)	2 (22.2%)	5 (55.6%)	8 (44.4%)	4 (44.4%)
	Male	10 (66.7%)	7 (77.8%)	4 (44.4%)	10 (55.6%)	5 (55.6%)
Childbearing potential n (%)	Yes	5 (100%)	2 (100%)	5 (100%)	7 (87.5%)	4 (100%)
Ethnicity n (%)	Hispanic /Latino	2 (13.3%)	1 (11.1%)	1 (11.1%)	2 (11.1%)	0
Race n (%)	Asian	2 (13.3%)	3 (33.3%)	1 (11.1%)	2 (11.1%)	3 (33.3%)
	White	12 (80.0%)	4 (44.4%)	5 (55.6%)	11 (61.1%)	4 (44.4%)
	Other	1 (6.7%)	2 (22.2%)	3 (33.3%)	5 (27.8%)	2 (22.2%)
BMI (kg/m²) at Screening	Mean (SD)	23.74 (2.95)	23.81 (3.93)	23.87 (2.76)	24.7 (3.21)	24.6 (3.21)

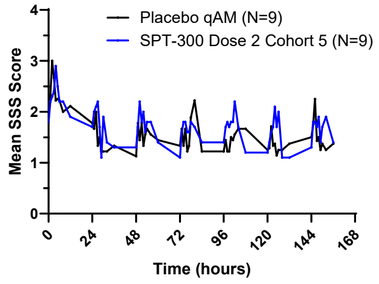
qAM = dosed daily in morning. qHS = dosed daily in evening.
Pooled placebo = pooling of placebo subjects from all cohorts (3/cohort)

Summary of MAD Treatment Emergent Adverse Events (AEs)

System Organ Class Preferred Term	Pooled Placebo (N=15) n (%) m	Dose 1 qAM Cohort 4 (N=9) n (%) m	Dose 2 qAM Cohort 5 (N=9) n (%) m	Dose 2 qHS Cohorts 7/8 Pooled (N=18) n (%) m	Dose 3 qAM Cohort 6 (N=9) n (%) m
Subjects with ≥ 1TEAE	**14 (93.3%) 58**	**9 (100%) 30**	**9 (100%) 43**	**15 (83.3%) 72**	**9 (100%) 119**
Nervous System Disorders	**10 (66.7%) 42**	**8 (88.9%) 14**	**7 (77.8%) 26**	**10 (55.6%) 40**	**9 (100%) 96**
Somnolence	10 (66.7%) 39	8 (88.9%) 13	7 (77.8%) 24	7 (38.9%) 20	9 (100%) 57
Balance disorder	0	0	0	2 (11.1%) 2	7 (77.8%) 27
Cognitive disorder	0	0	1 (11.1%) 1	2 (11.1%) 5	4 (44.4%) 5
Headache	0	1 (11.1%) 1	1 (11.1%) 1	2 (11.1%) 3	2 (22.2%) 2
Dizziness	2 (13.3%) 3	0	0	2 (11.1%) 2	1 (11.1%) 1
Lethargy	0	0	0	0	2 (22.2%) 2
General Disorders	**1 (6.7%) 1**	**0**	**1 (11.1%) 1**	**5 (27.8%) 5**	**3 (33.3%) 6**
Fatigue	1 (6.7%) 1	0	0	2 (11.1%) 2	0
Gastrointestinal Disorders	**1 (6.7%) 2**	**3 (33.3%) 4**	**1 (11.1%) 1**	**4 (22.2%) 7**	**2 (22.2%) 2**
Diarrhea	1 (6.7%) 1	1 (11.1%) 1	0	2 (11.1%) 3	0
Psychiatric Disorders	**2 (13.3%) 2**	**0**	**1 (11.1%) 1**	**3 (16.7%) 4**	**2 (22.2%) 4**
Insomnia	2 (13.3%) 2	0	0	2 (11.1%) 2	0
Euphoric mood	0	0	0	1 (5.6%) 1	2 (22.2%) 2

Includes events experienced by ≥ 2 HVs in a cohort. Excludes vascular access and skin irritation events not related to drug for brevity.
n = number of subjects in cohort with a TEAE, m = number of TEAEs.





Results

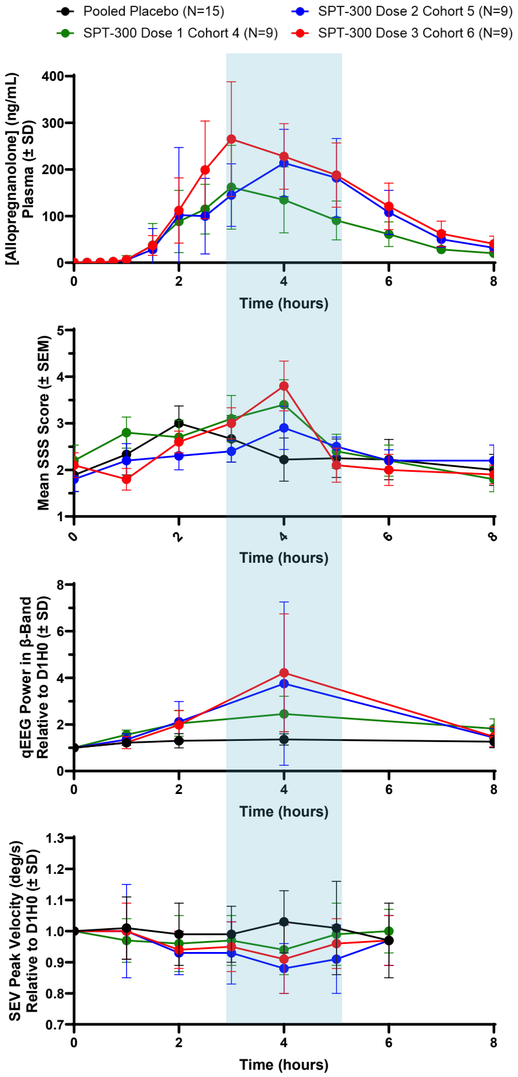
- N=99 participants were enrolled, including N=60 in the MAD.

Safety

- No treatment-related severe or serious AEs, including clinically important hepatic, cardiac and renal AEs, were reported.
- There were no observed clinically significant changes in laboratory parameters or vital signs.
- The most common AE across all parts was somnolence, which was mild and transient in all cases.
- Frequency of somnolence increased with dose and typically occurred in the first several hours following dosing.

PK/PD:

- SSS scores decreased after Day 1 and were comparable to placebo.
- Peak allopregnanolone plasma levels and PD signals were observed at 3-5 hours post-dose, corresponding to peak in:
  - increase in sleepiness (SSS)
  - increase in beta EEG power
  - deflection in saccadic eye velocity at 4h post-dose



Discussion

- SPT-300 was generally well-tolerated. AEs were dose-dependent and consistent with the pharmacology of GABA.
- Multiple well-tolerated, pharmacodynamically active doses will be included in a planned Phase 2b study in MDD (Dose 1 and Dose 2). SPT-300 will be dosed in the evening based on observed PK-PD association and adverse events.

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.