Phase I results from a Phase I/IIa clinical trial of SPL026-assisted psychedelic therapy

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BACKGROUND

Major Depressive Disorder (MDD) is a common, recurrent mental illness with a large global prevalence. The World Health Organisation (WHO) currently estimates that approximately 322 million people of all ages worldwide suffer with MDD[1]. Remission is reached in approximately 1/3 patients with SSRIs[2], demonstrating a significant unmet need.

Development Rationale

Psychedelics and Depression

- DMT shown to increase plasticity via neuritogenesis/ spinogenesis both *in vitro* and *in vivo*, which may be induced via highly activated 5HT2A signalling pathways[3]
- Ayahuasca, containing DMT as its primary psychoactive ingredient, demonstrated rapid antidepressant effects in patients with MDD/TRD[4,5]
- Imaging studies demonstrate high degree of similarity in neural network functioning for serotonergic drugs psilocybin, LSD and DMT[6]
- Proposed mechanisms of action: DMT hypothesized to act similarly to psilocybin by decreasing activity of the default mode network and increasing global connectivity
- DMT has demonstrated safety in over 160 participants in clinical trials with minimal AEs
- With a short-acting psychedelic experience, SPL026 could provide clinical flexibility with short-lived effects lasting only 20-30min

OBJECTIVES

Primary Objective:

- To assess the safety and tolerability of single intravenous (IV) doses of SPL026 in psychedelic-naïve healthy subjects

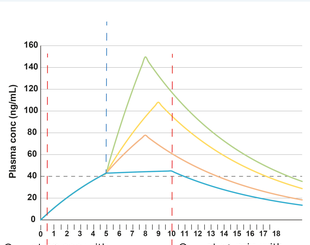
Secondary Objectives

- To assess the pharmacodynamics (PD) of single IV doses of SPL026 in psychedelic-naïve healthy subjects
- To assess the pharmacokinetics (PK) of single IV doses of SPL026 in psychedelic-naïve healthy subjects

METHODS

Key Inclusion/Exclusion Criteria:

Psychedelic-naïve healthy volunteers, age ≥ 25 years



C_{max} at 30 sec with bolus injection

C_{max} at 10 min with slow injection

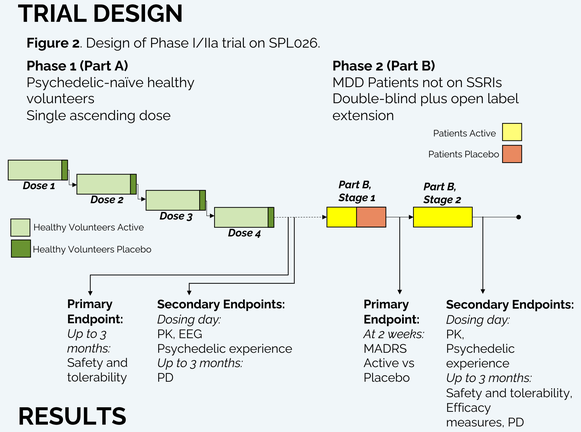
Figure 1. 2-phase injection modelled using clinical data from C. Timmerman (Imperial College London, ICL), by G. Allen, with design input from D. Erritzoe (ICL)

Table 1. Simulated trial doses based on literature PK data

Timmerman et al (2018, 2019) and Strassman et al (1994)		SPL026 Clinical Trial Part A	
Total dose by single bolus injection (mg)	Simulated C_{max} (ng/mL)	Planned total dose by single slow injection (mg)	Simulated C_{max} (ng/mL)
4.33	38.75	9.00	44.93
8.66	77.50	12.00	77.77
12.37	1110.71	17.00	108.01
17.32	155.00	21.50	149.60

TRIAL DESIGN

Figure 2. Design of Phase I/IIa trial on SPL026.



RESULTS

Table 2.

Psychedelic-naïve healthy volunteers – drug-related AEs

Placebo N=8	9 mg N=6	12 mg N=6	17 mg N=6	21.5 mg N=6
1	2	8	10	1

- No dose-relationship in drug-related adverse events, and all were mild
- There were 21 mild and 7 moderate unrelated TEAEs
- As the main tolerability measure, participants were asked: *"Do you wish you had not gone through that experience?"*
- **All healthy volunteers asked answered "No", demonstrating SPL026 was well-tolerated at doses tested**

The drug-related AEs were as follows: 7 General disorders and administration site conditions; 5 Psychiatric disorders; 3 Nervous system disorders; 2 Gastrointestinal disorders; 2 Cardiac and vascular investigations, 2 Vascular disorders; 1 Skin and subcutaneous disorders.

Pharmacokinetics

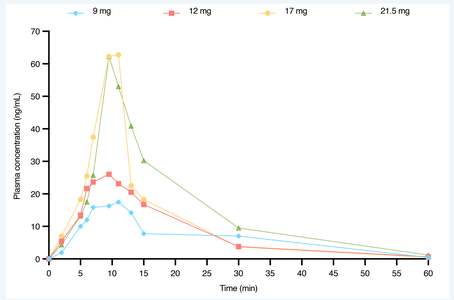


Figure 3. Mean linear PK concentrations of SPL026 at doses of 9 mg (N=5), 12 mg (N=6), 17 mg (N=5) and 21.5 mg (N=6).

Table 3.	9 mg; N=6	12 mg, N=6	17 mg; N=6	21.5 mg; N=6
		C_{max} ng/mL		
Mean	20.8	30.6	72.1	62.7
Range	5.0– 34.0	12.7 – 62.3	16.2 – 126.0	29.0 – 107.0
		AUC_{last} ng.min/mL		
Mean	349	451	842	835
Range	71 - 705	245-755	204 - 1390	477 - 1052

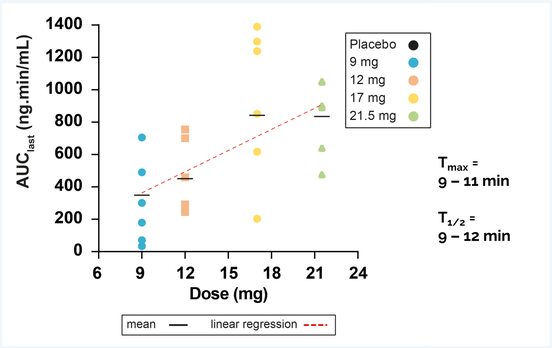


Figure 4. SPL026 dose versus AUC_{last} of SPL026 after slow injection

BMI: Exposure-response

In our flat-rate dosing strategy, no relationship was found across all dose cohorts between:

- **BMI** (R^2=0.048, p=0.327)
- **Weight** (R^2=0.009, p=0.681)
- **Age** (R^2=0.024, p=0.489)

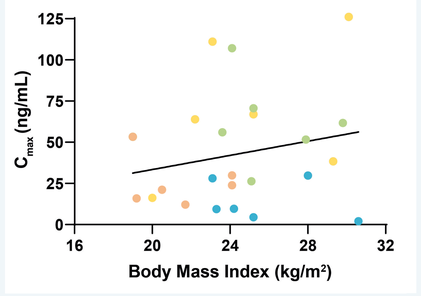


Figure 5. BMI versus C_{max} of SPL026 after slow injection

Secondary Endpoints: Pharmacodynamics

Psychedelic experience scales were completed 30 min post infusion start:

MEQ, CEQ, EBI, EDI, set of VAS, 5DASCQ, Metaphysical Qx

- A correlation was found between average scores on the Mystical Experience Questionnaire and C_{max}

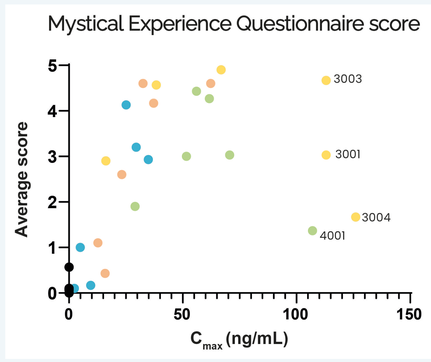


Figure 6. MEQ score versus C_{max} of SPL026 after slow injection

Intensity of Psychedelic Experience

Participants and the psychiatrist rated the intensity of the psychedelic experience on a VAS from 0-100

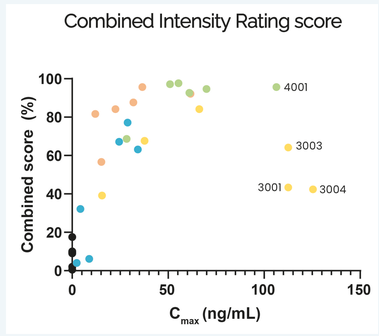


Figure 7. IRVAS score versus C_{max} of SPL026 after slow injection. The average score for participant and therapist correlated highly with C_{max}.

The pharmacodynamic scales completed at baseline and follow-ups (1 wk, 2 wk, 1 month, 3 months) included:

- WEMWBS, STAI-T, POMS, BFI, SHAPS, FS-8, MLQ, BRS, PIS, WCS, PTCS and others

Outcome measures

- Participant **wellbeing** showed **no significant decreases across timepoints** (WEMWBS)
- Participant **Trait-Anxiety** measured showed **no significant increases across all timepoints** (STAI-T)

CONCLUSIONS

- SPL026 has a good safety and tolerability profile in psychedelic-naïve healthy volunteers at all doses tested
- SPL026 is metabolized and cleared rapidly, leading to variable PK
- No rationale found for weight-adjusted dosing
- Strong exposure-response relationship
- Dose and dosing paradigm established for patients, alongside tailored therapy model

Progress in Phase IIa:

- Dosing and enrollment complete
- No drug-related SAEs reported so far
- Expecting a good safety profile
- Therapists trained at 3 sites across the UK
- Phase IIa efficacy results due early 2023

References: 1.WHO. 2017. Depression and Other Common Mental Health Disorders: Global Health Estimates. WHO/MSD/MER/2017.2; 2. Rush AJ, et al. 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 163: 1905–17; 3. Ly C, et al. 2018. Psychedelics Promote Structural and Functional Neural Plasticity. Cell Rep. 23: 3170–82; 4. Osório F, et al. 2015. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Braz J Psychiatry. 37: 13–20; 5. Palhano-Fontes F, et al. 2019. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med. 49: 655–63; 6. Timmermann C, et al. 2019. Neural correlates of the DMT experience assessed with multivariate EEG. Sci Rep. 9: 16324

Disclosures: Dr Tiffanie Benway is an employee and shareholder of Small Pharma Ltd

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