Efficacy, Safety & Tolerability of SPL026 (DMT fumarate) with Support Therapy in Patients with Major Depressive Disorder: Phase IIa Proof of Concept Study

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BACKGROUND

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

Psychedelics such as psilocybin, LSD and N,N-Dimethyltryptamine (DMT), are being widely studied for their potential as therapeutic agents. DMT is lesser known yet has clinical potential in treating mental health disorders with the advantage of eliciting a short-duration psychedelic experience. DMT is <30 mins, compared to ~8 hours with psilocybin, and up to 12 hours with LSD. Small Pharma recently completed the first blinded, randomized, placebo-controlled efficacy study exploring SPL026 with support therapy for the treatment of MDD.

OBJECTIVES

Primary Objective

To assess efficacy of a single 21.5mg intravenous (IV) dose of SPL026 in patients with moderate-severe MDD using Montgomery-Asberg Depression Rating Scale (MADRS) change in baseline at 2 weeks post-blinded dose.

Secondary Objectives

- To assess efficacy of single dose of SPL026 at 1-week post-blinded dose using MADRS
- To assess efficacy of 1 and 2 doses of SPL026 at 1 and 2 weeks, and 1, 3, 6 months post-open label dose using MADRS, Becks Depression Rating Scale (BDI) and State-Trait Anxiety Inventory-Trait scale (STAI-T)
- To assess pharmacodynamics (PD) of single IV doses of SPL026 (1 & 2 doses)
- To assess safety and tolerability of 1 & 2 IV doses of SPL026

METHODS

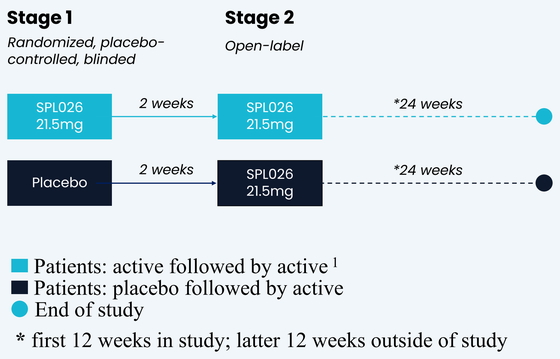

Figure 1. Phase IIa Study Design

METHODS

- Moderate/severe MDD patients (N=34)
- Patients enrolled not on antidepressant medication or willing to discontinue medication
- Phase IIa study completed Q4'22

Primary Endpoint: blinded phase

- Efficacy: MADRS change from baseline (CFB) 2-weeks post-blinded dose

Key Secondary Endpoints: open-label phase

- MADRS CFB 1-week post-blinded dose
- MADRS CFB after open label dose at W1, M1, M3 and M6[2]

Secondary Endpoints: blinded and open-label phase

- Safety and tolerability of 1 & 2 doses of SPL026
- Intensity & quality of subjective psychedelic experience measures of 1 & 2 doses of SPL026
- Efficacy (MADRS, BDI, STAI-T) of 1 vs 2 doses

Statistical analysis:

MADRS score change from baseline at 1 week (Day 8) and 2 weeks (Day 14) after the first dose of SPL026 and placebo was compared using an independent 2-sample t-test.

RESULTS

Safety & Tolerability

- Positive safety and tolerability profile observed following administration of SPL026 with no drug-related Serious Adverse Events
- All Adverse Events (AEs) deemed possibly related to treatment were mild to moderate in severity
- ~80% AEs occurred and resolved during dosing
- No clinically significant safety concerns, including no concerns with vital signs, ECG or clinical laboratory findings in any treatment group

AEs possibly related to treatment	Blinded phase (to Day 14)		Total study
	Active	Placebo	All subjects
Infusion site pain or reaction	7	3	17
Musculoskeletal and connective tissue disorder	1		2
Nausea	3		6
Headache	1		2
Anxiety	2		5
Insomnia		1	3
Restlessness Hypertesnion	1		2
Other[2]	6		10
Total mild and moderate	**21**	**4**	**47**
Total severe	**0**	**0**	**0**
Total	**23**	**4**	**47**

Table 1. Treatment-related adverse events

Efficacy – Change in MADRS over time

- Primary endpoint of study was met. See Figure 2
- Single dose of SPL026 demonstrated a statistically significant (P=0.02) and clinically relevant reduction in depressive symptom severity 2-weeks post-treatment
- Rapid onset of antidepressant effects with a significant (p=0.002) reduction in depression 1-week post-treatment
- Both 1-and 2-dose regimens demonstrated antidepressant effects out to at least 3 months (when compared to original baseline) with a similar magnitude of effect at all timepoints
- No significant difference between 1- and 2-dose regimens indicating that 1 dose of SPL026 with support therapy has rapid and durable antidepressant effects

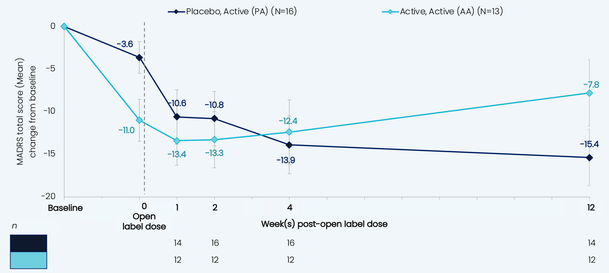

Figure 2. Effects of SPL026 *vs* placebo on change in MADRS over time

Efficacy: Response and Remission rates

- The rapid onset and durable antidepressant effect of SPL026 was also observed when the percent responders and patients in remission were analyzed (Figure 3)
- A similar magnitude of effect in terms of percent responders and for patients in remission for both dose regimens out to at least 3 months
- 50 and 42% responders at 3 months and 57 and 33% of patients still in remission at 3 months for the 1-dose and 2-dose regimens respectively

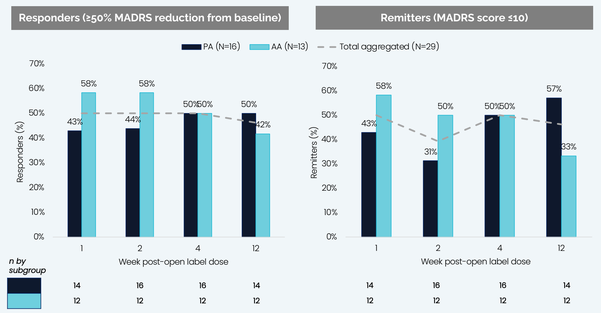

Figure 3. Response & Remission rates following 1 & 2 doses of SPL026; dashed line shows aggregate of data for both dosing regimens

Efficacy: Remission rate at 6 months

- 25 patients completed assessments at 6-months post-dose
- 64% of patients in remission at 3 months were still in remission at 6 months
- 6-month data assessed by Imperial College, London

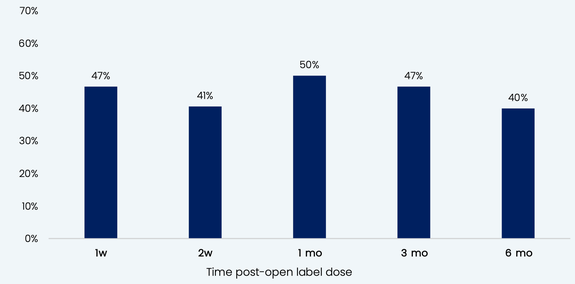

Figure 4. Remission rates over time (aggregate of data from both dosing regimens) out to 6 months following administration of SPL026 *vs* placebo

Additional Efficacy endpoints

- Self-reported BDI depression scores reflect the rapid and sustained efficacy profile demonstrated using independent rater-assessed MADRS with significant (P=0.002) decrease in depressive symptoms
- Significant (p=0.03), rapid and sustained improvements in anxiety scores observed as measured using STAI-T (SPL026 *vs* placebo)
- Rapid and sustained positive improvements in patient wellbeing demonstrated as measured using the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)

CONCLUSIONS

- SPL026 was demonstrated to have a very good safety and tolerability profile in patients with MDD; no treatment-related SAEs and all treatment-related AEs were mild to moderate
- The proof-of-concept Phase IIa study met its primary endpoint with SPL026 demonstrating a rapid and durable antidepressant effect out to 6 months post-dose when compared to placebo as assessed using the MADRS scale
- No significant difference observed between a 1- and 2-dose regimen, indicating that just one dose of SPL026 with support therapy is sufficient to elicit this durable antidepressant effect
- Patient self-reported assessments (BDI, STAI-T and WEMWBS) corroborates the MADRS findings and demonstrates the robustness of the efficacy findings in this study
- Preparations for a subsequent Phase IIb study in patients with MDD are underway

Disclosures: Dr Carol Routledge is an employee and shareholder of Small Pharma Ltd

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