SPL026 (DMT fumarate) in combination with Selective Serotonin Reuptake Inhibitors (SSRIs) for patients with Major Depressive Disorder (MDD)

Ellen H. James, Zelah Joel, Victoria Attwooll, Tiffanie A. Benway, Meghan H. Good, George Tziras, Carol Routledge, Thomas A. Macek

NYSE:CYBN
NEO:CYBN

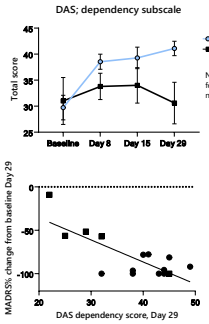
Cybin Inc, 5600-100 King St West, Toronto, ON M5X 1C9, Canada

Introduction

- Selective serotonin reuptake inhibitors (SSRIs) are the standard of care for Major Depressive Disorder (MDD).
- Clinical trials investigating psychedelics have most often enrolled participants who are not currently taking SSRIs. The reason for this is due to both SSRIs and serotonergic (or classical) psychedelics exerting their primary effects through activation of the serotonergic system.
- However, withdrawal from SSRIs can be deleterious to patients as it may be associated with significant side effects and can destabilize the disease.
- SPL026 (DMT fumarate) has shown efficacy as a treatment for MDD in participants who were not taking SSRIs. Mean difference between active and placebo at 2 weeks of -7.35 [Montgomery-Åsberg Depression Rating scale (MADRS)] (p=0.023) [Ref 1].
- Studying the combined use of SSRIs and psychedelics would help advance our understanding of their concomitant use to treat patients with MDD.

Concomitant use of SSRIs may influence PD results

- The Set subscale of the PPS was higher in the SSRI Cohort, compared to Non-SSRI (SSRI 0.81; Non-SSRI 0.69). This could imply that SSRIs are **beneficial to** participants' state of mind (**'set'**) prior to dosing, helping them to feel more prepared and open to the experience.
- Results from the MEQ, EBI and EDI suggested SPL026 evoked a **more** complete **mystical** experience, more **emotional breakthrough** and greater **ego dissolution** in the SSRI Cohort, compared to the Non-SSRI Cohort (data not shown).



- The DAS **dependency** subscale showed a large differentiation between cohorts at Day 29. Subscale scores showed a **significant correlation to change in MADRS** score at this timepoint (R^2 = 0.5863, p=0.0005), suggesting a link between depression and how dependent one is on others for one's happiness.

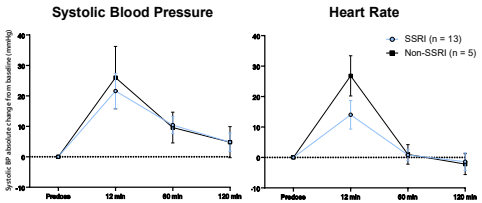
Results

SPL026 (DMT) was **well tolerated** alongside SSRIs, with the potential for **improved efficacy**

Safety

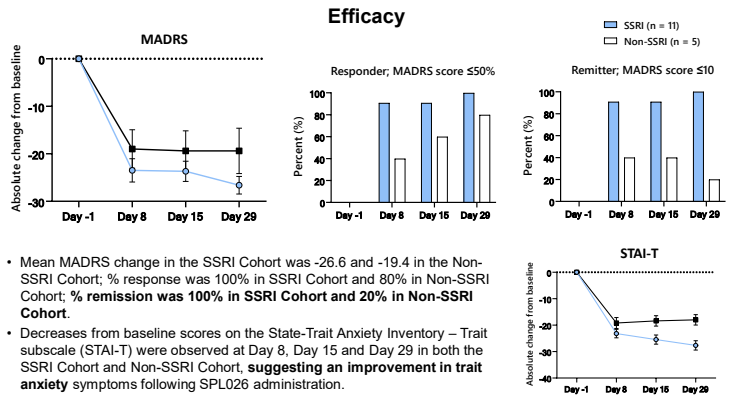
Treatment-related Adverse Events	SSRI Cohort (N=13) n (%) [e]	Non-SSRI Cohort (N=5) n (%) [e]	Overall (N=18) n (%) [e]
Any treatment-related Adverse Events (AEs)*	**5 (38.5%) [8]**	**2 (40.0%) [3]**	**7 (38.9%) [11]**
Nausea	2 (15.4%) [2]	1 (20.0%) [1]	3 (16.7%) [3]
Vomiting	2 (15.4%) [3]	0	2 (11.1%) [3]
Abnormal dreams	0	1 (20.0%) [1]	1 (5.6%) [1]
Anxiety	1 (7.7%) [1]	0	1 (5.6%) [1]
Infusion site pain	1 (7.7%) [1]	0	1 (5.6%) [1]
Infusion related reaction	1 (7.7%) [1]	0	1 (5.6%) [1]
Lethargy	0	1 (20.0%) [1]	1 (5.6%) [1]

*Psychedelic experience-related events were not recorded as AEs. n (%) [e]: No. of participants with events (percentage of participants with events) [number of events]



- There were **no drug-related serious adverse events** (SAEs); all AEs were **mild-moderate**, and the majority resolved during the dosing visit. There were no increases in suicidal ideation or behavior.
- In both cohorts **increases in heart rate and blood pressure** were observed with maximum mean increases at 12 min (around the peak; C_{max}). These increases were transient and without clinical sequelae.
- Interestingly, the **SSRI Cohort had a smaller increase** in HR than the Non-SSRI Cohort.

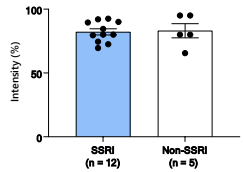
Efficacy



- Mean MADRS change in the SSRI Cohort was -26.6 and -19.4 in the Non-SSRI Cohort; % response was 100% in SSRI Cohort and 80% in Non-SSRI Cohort; **% remission was 100% in SSRI Cohort and 20% in Non-SSRI Cohort**.
- Decreases from baseline scores on the State-Trait Anxiety Inventory – Trait subscale (STAI-T) were observed at Day 8, Day 15 and Day 29 in both the SSRI Cohort and Non-SSRI Cohort, **suggesting an improvement in trait anxiety** symptoms following SPL026 administration.

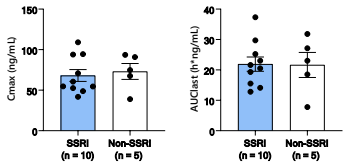
Concomitant use of SSRIs shows **no** apparent **attenuation** of the subjective intensity or pharmacokinetics of DMT

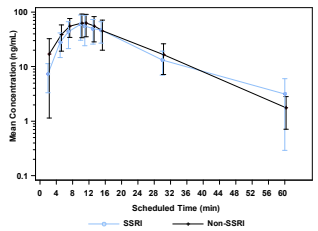
Subjective Intensity



- Participants and psychological-support monitors were asked to rate the intensity of the experience on a VAS scale (IRVAS). The combined scores were compared between SSRI and Non-SSRI cohorts with no apparent difference. This suggests the subjective **intensity of the psychedelic experience is unaffected** by concomitant SSRIs.

Pharmacokinetics

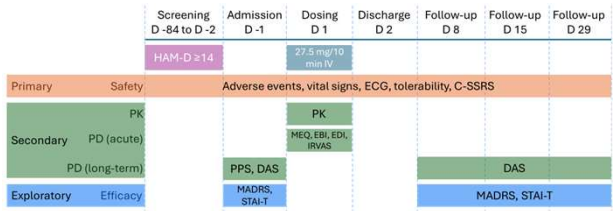




- **Overall systemic exposures of DMT were similar between the SSRI and Non-SSRI Cohorts.** Geometric mean AUC_{0-inf} was 21.7 h*ng/mL in the SSRI-Cohort (8 participants), and 19.6 h*ng/mL in the Non-SSRI-Cohort (5 participants).

Study Design

- Open-label study investigating the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of a single SPL026 intravenous dose, alone or in combination with SSRIs.
- The Test Cohort (N=13) ("SSRI Cohort") consisted of participants currently on a stable, but not fully effective, treatment of SSRIs.
- The Control Cohort (N=5) ("Non-SSRI Cohort") consisted of participants not currently using any pharmacological antidepressant treatment.



Conclusions

- This study is the first to demonstrate safety and tolerability of SPL026 (DMT) in participants taking SSRIs, supporting previous reports that SSRIs and psilocybin can be safely administered together [Ref 2 & 3].
- SPL026 (DMT) with support therapy improved depression and anxiety scores in both cohorts, possibly to a greater degree in those taking SSRIs concomitantly.
- Results suggest that patients do not need to stop taking an SSRI to undergo psychedelic treatment.
- These findings will be taken forward into our next study in participants with Generalized Anxiety Disorder administered CYB004 (a deuterated DMT analog), where participants will not need to discontinue ongoing antidepressant/anxiolytic treatment during the trial.

REFERENCES
1: https://doi.org/10.1186/ISRCTN42293056. 2: Becker et al 2022; https://doi.org/10.1002/cpt.2487. 3: Goodwin et al 2023; https://doi.org/10.1038/s41386-023-01648-7.

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