In vivo characterisation of SPL028: a deuterated derivative of *N,N*-dimethyltryptamine, developing a treatment for mental health disorders

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INTRODUCTION

N,N-dimethyltryptamine (DMT, SPL026)

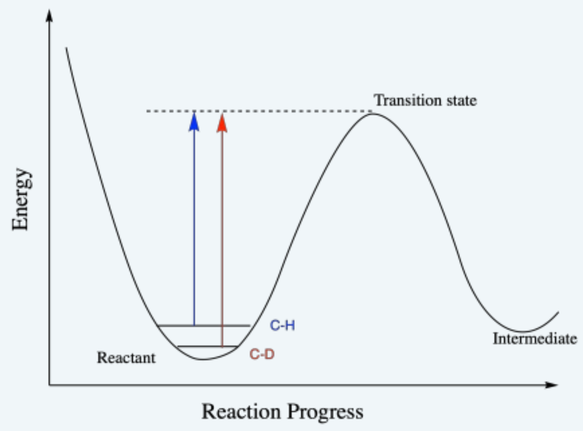
- Short acting and intense psychedelic compound
- Clinical efficacy in the treatment of major depressive disorder
- Complex receptor pharmacology
- Rapid metabolism by monoamine oxidase A (MAO-A)
- No oral bioavailability and quick clearance following systemic administration routes

Deuterated-*N,N*-dimethyltryptamine (d_2-DMT, SPL028)

Deuterated derivative of DMT, increasing C-H bond strength to inhibit metabolism

Hypothesis:

- Same quality but prolonged duration of subjective psychedelic effects of DMT
- May offer clinical advantage via more practical dosing routes and/or prolonged exposure over therapeutic concentrations



In vivo pharmacokinetics

Intravenous dosing

- Individual animals' PK profiles following IV administration were highly variable.
- Inconsistent differences between SPL028 and SPL026 profile over the dose range 0.6–6 mg/kg IV however, cassette dosing of SPL026 and SPL028(viii) IV = no differences in exposure, significant difference in half-life ($p<0.05$)

Intramuscular dosing

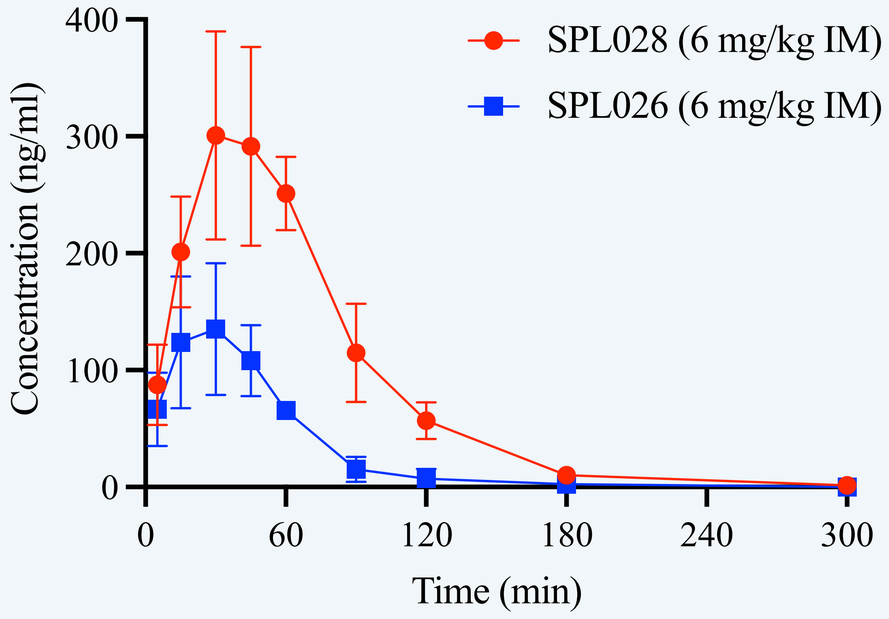


Figure 3. The PK profile of SPL028 vs SPL026 following IM administration in male and female Sprague Dawley rats (n=3/sex/group), demonstrating increased SPL028 exposure and half-life

In vivo pharmacodynamics

Ex vivo receptor occupancy

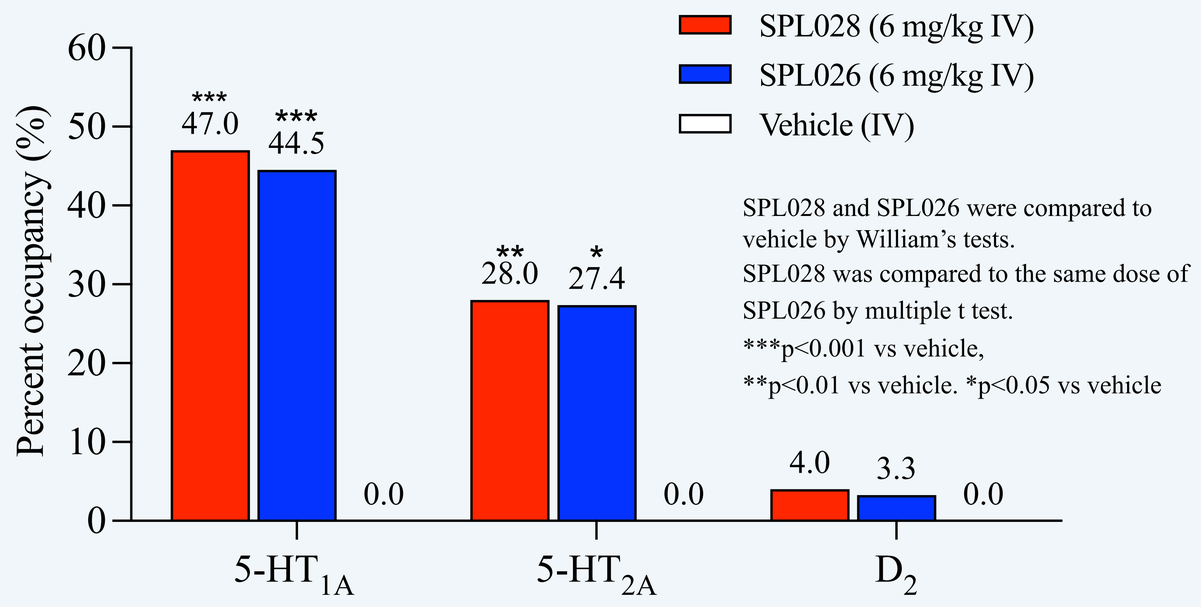
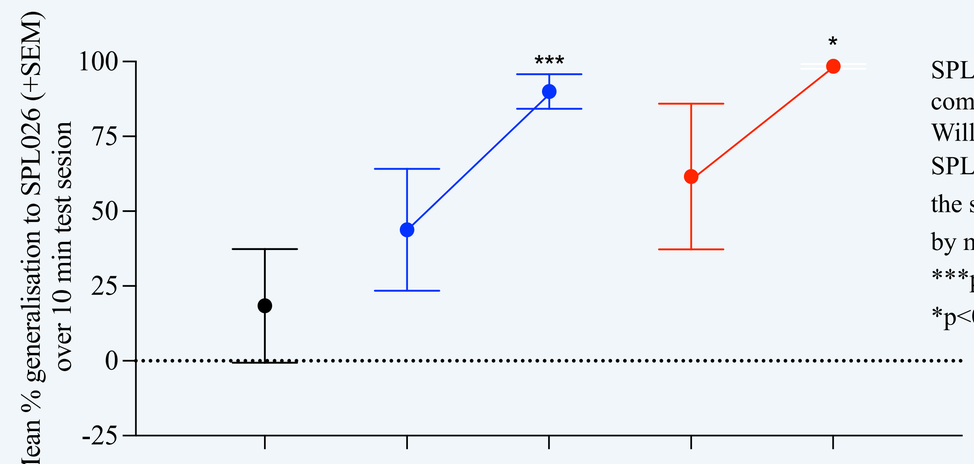


Figure 4. Ex vivo receptor occupancy of SPL028 vs SPL026 at (on-target) rat hippocampal 5-$HT_{1A,}$ rat cortical 5-HT_{2A}; and (off-target) striatal D_2 receptors in Sprague Dawley rats (n=5/group).
No differences in occupancy between SPL028 and SPL026

Drug discrimination



	Vehicle	SPL026 0.2 mg/kg	SPL026 0.6 mg/kg	SPL028 0.2 mg/kg	SPL028 0.6 mg/kg
Test period (min)	5	5	5	5	5
No. animals tested	8	8	8	8	8
No. animals disrupted	1	1	1	0	5

Figure 5. Effect on overall % generalisation response of IV doses of SPL026 and SPL028 at a dose-test interval of 5 min post dose in female lister hooded rats trained to discriminate SPL026 (3 mg/kg IP) from vehicle. SPL028 broadly generalised to SPL026 cue when tested at 5 min after dosing. There was a near identical dose-dependent effect with SPL026 and SPL028, with full generalization at the higher dose 0.6 mg/kg. This effect was lost with both compounds at the later timepoints, 30 min onwards

CONCLUSIONS

- Reduced clearance and increased half-life of SPL028 *in vivo* resulting in a prolonged PK profile and increased exposure when compared to SPL026
- The *ex vivo* receptor binding profile of SPL028 was comparable to SPL026, with the highest affinity at serotonergic receptors
- No impact on behavioural pharmacology assessed by SPL028 generalisation to SPL026 cue

Progress in Clinical studies:
A phase I study to investigate the safety, tolerability and PK of SPL028 (EudraCT No.: 2022-002618-17) administered via IV and IM began in Q1 2023

Small Pharma

Disclosures: Meghan Good is an employee and option holder of Small Pharma Ltd