2. SYNOPSIS (PART A ONLY)

Study Title: A Phase 1, Double-Blind Study Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous and Intramuscular Dosing of SPL028 (Deuterated DMT Fumarate [A Serotonergic Psychedelic]) in Healthy Participants (Part A); Followed by an Open-Label Study Investigating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Exploratory Efficacy of SPL028 in Participants with Major Depressive Disorder (Part B).	
Sponsor: Small Pharma Ltd	
Coordinating Investigator: Dr Ezanul Abd Wahab, MBBCh MRCP(UK) DPM MFPM	
Study Sites: This was a single-centre study which was conducted in Manchester, UK.	
Publication (reference): n/a	
Length of Study: Date of first participant entered: 18 January 2023 Date of last participant completed: 15 December 2023	Phase: I

Objectives:

Primary Objective:

The primary objective of the study was to evaluate the safety and tolerability of SPL028 with support therapy following intravenous (IV) infusion and intramuscular (IM) administration in healthy participants.

Secondary Objectives:

- To evaluate plasma pharmacokinetics (PK) of SPL028 following IV infusion and IM administration.
- To assess the pharmacodynamics (PD) of SPL028 following IV infusion and IM administration.
- To assess potential effects on QT interval.
- To assess blinding integrity.

Study Design:

Part A was a Phase 1, double-blind study to determine the safety, tolerability, PK and PD of IV infusion and IM dosing of SPL028 in healthy participants. Participants in Cohorts 1 and 2 took part in two Treatment Periods (TP); IV administration took place in TP 1 and IM administration took place in TP 2. Participants in Cohorts 3, 4 and 5 took part in 1 TP and SPL028 was administered via IM injection in Cohorts 3 and 5, and via IV infusion in Cohort 4.

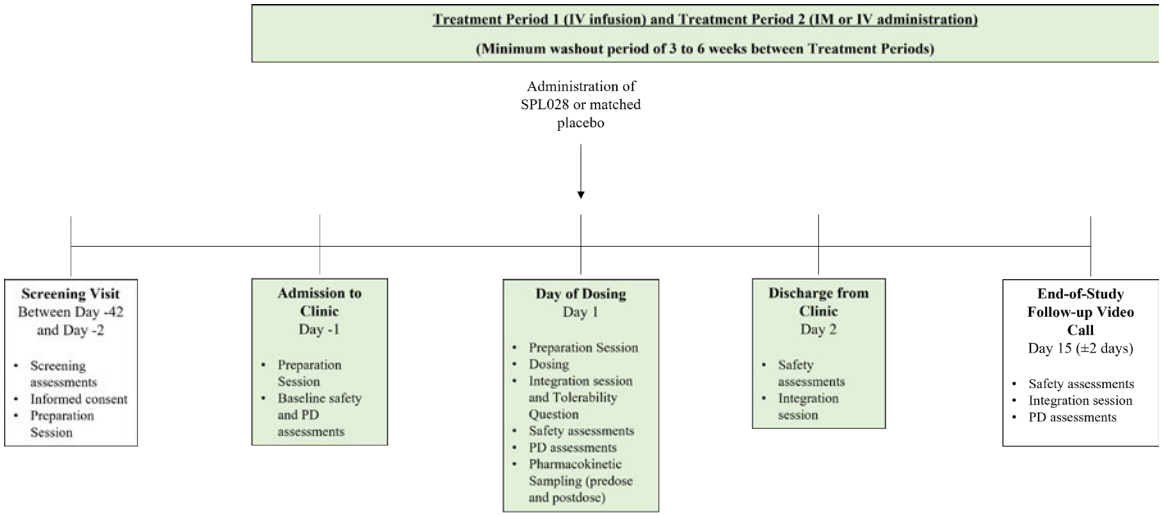

Figure 1 Study Design Cohort 1 and Cohort 2

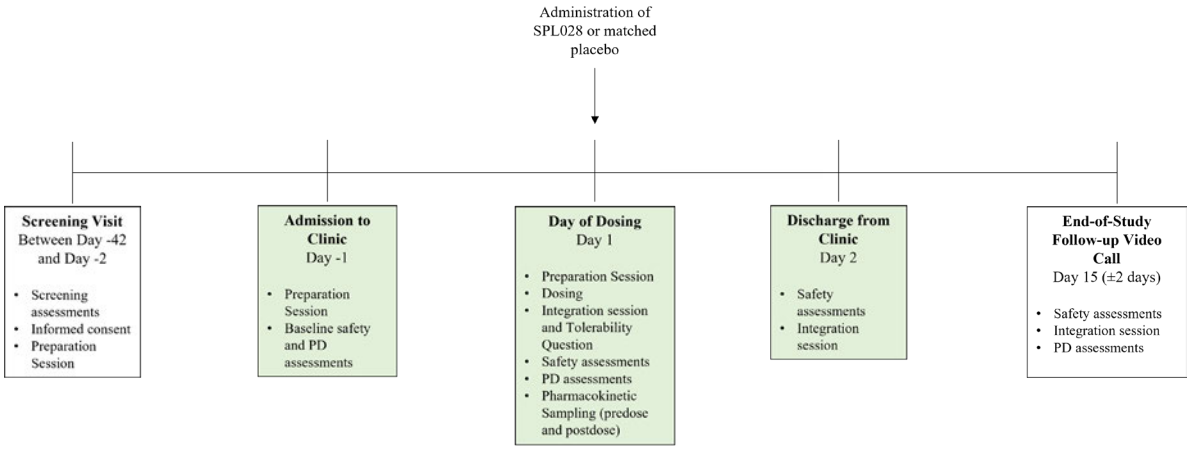

Figure 2 Study Design Cohort 3, Cohort 4 and Cohort 5

Number of Healthy Participants:

Planned: Up to 40
Enrolled: 38
Treated: 36
Completed: 36

Main Criteria for Inclusion:

Healthy participants in good general health, aged 25 to 65 years (inclusive) with a body mass index (BMI) of 18 to 33.9 kg/m^2 (inclusive).

Study Drug, Dose and Mode of Administration:

For IV infusion, the starting dose in Cohort 1 (TP1) was 9 mg SPL028, followed by 11 mg SPL028 IV in Cohort 2 and 17 mg SPL028 IV in Cohort 4. The IV infusions were administered over 10 minutes. For the IM injection, the starting dose in Cohort 1 was 7.5 mg IM SPL028, followed by 15 mg SPL028 IM in Cohort 2, 30 mg IM in Cohort 3 and 20 mg IM in Cohort 5.

Each study participant was in a separate dosing room which had been set up to provide the appropriate 'setting'. It was a calm, relaxing space where they could not see or interact with other participants for the duration of their study medication administration and safety assessment. They were provided with eye shades and headphones and were encouraged to allow themselves to focus inwards and on their internal experience. The participants remained in the room for the duration of the treatment session regardless of the intensity of the effects, until they had completed the postdose Integration session.

Duration of Treatment and Study Schedule:

The treatment duration was 1 day (Day 1). The maximum study duration was approximately 15 weeks for Cohort 1 and Cohort 2 and 8 weeks for Cohort 3, Cohort 4 and Cohort 5.

The following procedures constituted the study:
Screening Visit (within Day -42 to Day -2): Informed consent, Screening and eligibility assessments and enrolment of eligible healthy participants. A Preparation session also took place.

The following procedures took place in each treatment period:
Inpatient Period (Day -1 to Day 2):
Day -1: A Preparation session and baseline safety and PD assessments took place.
Day 1: Prior to dosing, safety assessments and a Preparation session took place. The IV infusion and IM injection were then administered. Pharmacokinetic blood sampling took place at specified timepoints before and following dosing. Pharmacodynamic assessments, an Integration session, an assessment of tolerability and safety assessments took place once the subjective psychedelic effect had ended.
Day 2: Prior to discharge, an Integration session and safety assessments took place.
End-of-Study Follow-up Video Call (Day 15 [±2 days]): An Integration session, safety and PD assessments took place. The Investigator and/or psychiatrist could have chosen to perform this visit remotely or ask the participant to attend the Clinical Research Unit (CRU) if there were any safety concerns; this was judged on a case-by-case basis.

Criteria for Evaluation:

The primary safety endpoints of the study were:

- Monitoring of adverse events (AEs), vital signs (blood pressure, heart rate and temperature), 12-lead electrocardiogram (ECG) evaluations, cannulation and injection site reactions, clinical laboratory assessments (haematology, clinical chemistry, coagulation and urinalysis) and physical examination findings. Suicidal ideation and behaviour was evaluated using Beck Scale for Suicidal Ideation (BSS). Tolerability was evaluated by reviewing the therapists' notes that documented the subjective psychedelic effects and with a tolerability assessment.

The secondary endpoints of the study were:

- The PK parameters in plasma calculated for SPL028 included maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the concentration-time curve (AUC) from zero to the last measurable concentration (AUC_{last}), AUC from zero to infinity (AUC_{inf}), AUC extrapolated as a percentage of the total ($\%AUC_{extrap}$), terminal elimination rate constant (λ_z), half-life ($t_{½}$), apparent total clearance of the drug from plasma (CL), terminal phase volume of distribution (V_z), volume of distribution at a steady state (V_{ss}) and mean residence time (MRT_{inf}).

The following PD assessments were completed in Part A of the study:

- The Psychedelic Predictor Scale ([PPS] pre-dosing only)
- Spielberger's State - Trait Anxiety Inventory – Trait Subscale ([STAI-T] completed at baseline and Day 15)
- Warwick-Edinburgh Mental Wellbeing Scale ([WEMWBS] completed at baseline and Day 15)
- Post-treatment Changes Scale ([PTCS] completed at baseline and Day 15)

The following acute subjective PD measures were completed in Part A of the study (completed postdose on Day 1):

- Mystical Experience Questionnaire (MEQ)
- Ego Dissolution Inventory (EDI)
- Emotional Breakthrough Inventory (EBI)
- Challenging Experience Questionnaire (CEQ)
- Intensity Rating Visual Analogue Scale (IRVAS [completed after Integration])
- Visual Analogue Scales (VAS)

Evaluation Methods:

Safety was assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations, clinical laboratory evaluations and cannulation site reactions; suicidal ideation and behaviour was evaluated using the BSS. Tolerability was evaluated by reviewing the therapists' notes that documented the subjective psychedelic effects and a tolerability assessment, consisting of the question 'Do you wish you had not gone through that experience?'. Blood samples were collected for assessment of PK. Pharmacodynamics were assessed with several psychological scales and questionnaires measuring the quality of the psychedelic experience and assessing study participants' psychological well-being. Exploratory efficacy was assessed with scales measuring depression and anxiety symptoms.

Statistical Methods:

Safety parameters were listed and summarised using descriptive statistics. Pharmacokinetic parameters were calculated by noncompartmental analysis. Pharmacokinetic data were listed for each participant, along with summary statistics. All PD and efficacy endpoint data were listed by cohort for each timepoint for individual participants. The endpoints had summary statistics produced by cohort and by timepoint.

Results:

Safety Results:

Intravenous Infusion

No deaths or serious adverse events (SAE) leading to withdrawal occurred in the study. SPL028 was well tolerated when administered at a dose level of 9 mg IV in Cohort 1 (TP 1) and 11 mg IV in Cohort 2 (TP 1).
In Cohort 4 (17 mg IV), 2 participants were discontinued from the treatment (infusion stopped early) due to SPL028 side effects.

[redacted]

In Cohort 1 (9 mg IV, TP 1), 7 treatment emergent adverse events (TEAEs) reported by 5 (83.3%) participants were mild in severity and 1 TEAE reported by 1 (16.7%) participant was moderate in severity.
In Cohort 2 (11 mg IV, TP 1), 1 TEAE reported by 1 (16.7%) participant was mild in severity and 2 TEAEs reported by 2 (33.3%) participants were moderate in severity.

In Cohort 4 (17 mg IV), 5 TEAEs reported by 3 (60%) participants were moderate in severity and 1 TEAE (psychomotor hyperactivity) reported by 1 (20%) participant was severe in severity.

The highest number of treatment-related TEAEs was observed in Cohort 4 (17 mg IV), with a total of 16 events reported by 4 (80%) participants, of which 1 event reported by 1 (20%) participant was severe in severity and 5 events reported by 3 (60%) participants were moderate in severity. In general, the treatment-related TEAEs observed in Cohort 4 (17 mg IV) were more severe than those reported by Cohort 1 (9 mg IV, TP1) and Cohort 2 (11 mg IV, TP1). [redacted] As coded by preferred term (PT), the most common reported treatment-related TEAE was anxiety reported by 2 (40%) participants.

In Cohort 1 (9 mg IV, TP 1), 3 treatment-related TEAEs were reported by 3 (50%) participants, all mild in severity. The most common reported SOC were gastrointestinal disorders with all 3 events falling under this category. As coded by PT, the most common reported treatment-related TEAE was nausea reported by 2 (33.3%) participants.
In Cohort 2 (11 mg IV, TP 1), Pooled Placebo Cohort 1 & 2 (IV, TP 1) and Placebo Cohort 4 (IV) all events were mild in severity, except 1 event reported by 1 (25%) participant in the pooled Placebo Cohort 1 & 2 (IV, TP 1) which was moderate in severity. All SOC (by PT) were reported by 1 participant only.

Table 1 Summary of Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Intravenous Infusion

System Organ Class Preferred Term	Cohort 1 SPL028 - IV (N = 6) n (%), [e]	Cohort 2 SPL028 - IV (N = 6) n (%), [e]	Cohort 4 SPL028 - IV (N = 5) n (%), [e]	Pooled Cohort 1 & 2 Placebo - IV (N = 4) n (%), [e]	Cohort 4 Placebo - IV (N = 2) n (%), [e]
Any TEAEs	3 (50.0), [3]	0	4 (80.0), [16]	0	1 (50.0), [1]
Gastrointestinal disorders	3 (50.0), [3]	0	1 (20.0), [1]	0	0
Nausea	2 (33.3), [2]	0	1 (20.0), [1]	0	0
Vomiting	1 (16.7), [1]	0	0	0	0
General disorders and administration site conditions	0	0	2 (40.0), [2]	0	0
Feeling cold	0	0	1 (20.0), [1]	0	0
Gait disturbance	0	0	1 (20.0), [1]	0	0
Nervous system disorders	0	0	1 (20.0), [3]	0	1 (50.0), [1]
Dizziness	0	0	0	0	1 (50.0), [1]
Dystonia	0	0	1 (20.0), [1]	0	0
Facial spasm	0	0	1 (20.0), [1]	0	0
Psychomotor hyperactivity	0	0	1 (20.0), [1]	0	0
Psychiatric disorders	0	0	3 (60.0), [10]	0	0
Abnormal dreams	0	0	1 (20.0), [1]	0	0
Adjustment disorder with anxiety	0	0	1 (20.0), [1]	0	0
Anxiety	0	0	2 (40.0), [3]	0	0
Disorientation	0	0	1 (20.0), [1]	0	0
Flashback	0	0	1 (20.0), [1]	0	0
Hallucination	0	0	1 (20.0), [1]	0	0
Paranoia	0	0	1 (20.0), [2]	0	0

Abbreviation: AE = Adverse Event; IV = Intravenous; MedDRA = Medical Dictionary for Regulatory Activities; TEAEs = Treatment Emergent Adverse Events; TP = Treatment Period.
Doses administered: Cohort 1 = 9 mg IV (TP 1); Cohort 2 =11 mg IV (TP 1); Cohort 4 = 17 mg IV.
A TEAE is an AE that was not present prior to treatment, but appeared following treatment. For Cohorts 1 & 2, any TEAE reported on the day of dosing for TP 2 was not reported as a TEAE for TP 1.
Coded using MedDRA version 25.1.

There were no significant treatment- or dose-related trends in the mean or individual participant vital signs, physical examination or 12-lead ECG parameters during the study.

There were no significant treatment- or dose-related trends in the mean or individual participant haematology, biochemistry, or urinalysis data during the study.

In Cohort 4 (17 mg IV), a drop in phosphate levels was noted following study medication administration. However, this drop was also observed in both placebo participants, and was therefore considered to be unrelated to SPL028.

SPL028 did not increase suicidal ideation or behaviour in study participants. No participant required rescue medication during the study.

Intramuscular Injection
No deaths or SAEs leading to withdrawal occurred in the study.

The highest number of TEAEs were reported in Cohort 3 (30 mg IM). In total, 15 events were reported by 5 (100%) participants. Of these, 3 events reported by 2 (40%) participants were moderate in severity and the remaining events reported by 3 (60%) participants were mild in severity.
In Cohort 5 (20 mg IM) all 11 TEAEs reported by 4 (66.7%) participants were mild in severity.
In Cohort 2 (15 mg IM; TP 2), a total of 7 TEAEs were reported by 5 (83.3%) participants. Of these, 2 events reported by 2 (33.3%) participants were moderate in severity and 3 events reported by 3 (50%) participants were mild in severity.
In Cohort 1 (7.5 mg IM; TP 2) 1 TEAE reported by 1 participant was mild in severity.

The highest number of treatment-related TEAEs was observed in Cohort 5 (20 mg IM) with 10 events reported by 4 participants (66.7%) being probably or possibly related to the SPL028, all mild in severity. In Cohort 3 (30 mg IM) a total of 9 treatment-related TEAEs was reported by 3 (60%) participants, with 2 events reported by 1 (20%) participant being moderate in severity and all remaining events being mild in severity. No treatment-related TEAEs were reported in Cohort 1 (7.5 mg IM; TP 2), in Cohort 2 (15 mg IM; TP 2) and Pooled Placebo Cohort 1 & 2 (IM, TP 1).
The most common treatment-related TEAEs by SOC were gastrointestinal disorders reported by 2 participants in Cohort 5 (20 mg IM).
In Cohort 5 (20 mg IM), Cohort 3 (30 mg IM) and Pooled Placebo Cohort 3 & 5, each treatment-related TEAE (by PT) was reported by 1 participant only.

Table 2 Summary of Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Intramuscular Injection

System Organ Class	Cohort 1	Cohort 2	Cohort 5	Cohort 3	Cohort 1 & 2	Cohort 3 & 5
Preferred Term	SPL028 - IM	SPL028 - IM	SPL028 - IM	SPL028 - IM	PP- IM	PP - IM
	(N = 4)	(N = 6)	(N = 6)	(N = 5)	(N = 4)	(N = 4)
	n (%), [e]	n (%), [e]	n (%), [e]	n (%), [e]	n (%), [e]	n (%), [e]
Any TEAEs	0	0	4 (66.7), [10]	3 (60.0), [9]	0	2 (50.0), [2]
Eye disorders	0	0	1 (16.7), [1]	1 (20.0), [1]	0	0
Photophobia	0	0	1 (16.7), [1]	0	0	0
Visual impairment	0	0	0	1 (20.0), [1]	0	0
Gastrointestinal disorders	0	0	2 (33.3), [2]	1 (20.0), [2]	0	0
Nausea	0	0	1 (16.7), [1]	1 (20.0), [2]	0	0
Vomiting	0	0	1 (16.7), [1]	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1 (25.0), [1]
Muscle twitching	0	0	0	0	0	1 (25.0), [1]
Nervous system disorders	0	0	1 (16.7), [4]	1 (20.0), [2]	0	1 (25.0), [1]

Dyskinesia	0	0	0	1 (20.0), [2]	0	0
Headache	0	0	1 (16.7), [3]	0	0	1 (25.0), [1]
Hypoaesthesia	0	0	1 (16.7), [1]	0	0	0
Psychiatric disorders	0	0	1 (16.7), [1]	3 (60.0), [4]	0	0
Abnormal dreams	0	0	0	0	0	0
Anxiety	0	0	0	1 (20.0), [1]	0	0
Confusional state	0	0	1 (16.7), [1]	0	0	0
Flashback	0	0	0	1 (20.0), [1]	0	0
Hallucination, olfactory	0	0	0	1 (20.0), [1]	0	0
Nightmare	0	0	0	1 (20.0), [1]	0	0
Renal and urinary disorders	0	0	1 (16.7), [1]	0	0	0
Urinary incontinence	0	0	1 (16.7), [1]	0	0	0
Vascular disorders	0	0	1 (16.7), [1]	0	0	0
Flushing	0	0	1 (16.7), [1]	0	0	0

Abbreviations: AE = Adverse Event; IM = Intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; PP = Pooled Placebo; TEAEs = Treatment Emergent Adverse Events; TP = Treatment Period.
Doses administered: Cohort 1 = 7.5 mg IM (TP 2); Cohort 2 =15 mg IM (TP 2); Cohort 5 = 20 mg IM; Cohort 3 = 30 mg.
A TEAE is an AE that was not present prior to treatment, but appeared following treatment. For Cohorts 1 & 2, any TEAE reported on the day of dosing for TP 2 was not reported as a TEAE for TP 1.
Coded using MedDRA version 25.1.
N = The number of participants who were randomised to the stated treatment group.
n (%), [e]: number of participants with events (percentage of participants with events) [number of events].
Percentage (%) = The n as a proportion of N.

There were no significant treatment- or dose-related trends in the mean or individual participant vital sign, physical examination or 12-lead ECG parameters during the study.

There were no significant treatment- or dose-related trends in the mean or individual subject haematology, biochemistry, or urinalysis data during the study.

The study drug was well tolerated and did not increase suicidal ideation or behaviour in study participants. No participant required rescue medication during the study.

PK Results:
Data from 35 participants were included in the PK Analysis Set.
Intravenous Infusion and Intramuscular Injection

Single dose SPL028 plasma PK parameters were determined for IV infusion doses of 9, 11 and 17 mg and IM injection doses of 7.5, 15, 20 and 30 mg.

[redacted] The IM injection had a delayed T_{max} of approximately 10 to 20 minutes compared to the IV infusion. It should be noted that the T_{max} relating to the IV infusion is subject to the end of infusion time (10 minutes), and this should be taken into account when comparing differences in parameters associated with the distribution phase (e.g. peak concentration and time) between the IV and IM dose routes.

All intravenous infusion doses had higher dose-normalised mean C_{max} values compared to 7.5, 15 and 20 mg IM doses, and 9 and 17 mg IV doses had higher dose-normalised mean C_{max} values compared to the 30 mg IM dose.

The 17 mg IV dose had the highest dose-normalised C_{max}, AUC_{last} and AUC_{inf} values compared to all other IV and IM dose cohorts. The 11 mg IV dose had a lower mean C_{max}, AUC_{last} and AUC_{inf} than the 9 mg dose, [redacted] This surprising result may be attributable to the relatively rapid PK and small samples sizes, or small differences in the time of PK sampling and individual differences in participants' physiology and blood flow.

Mean C_{max} and AUC increased in a greater than dose proportional manner across the dose range of 7.5 to 30 mg IM doses. This may be due to altered absorption kinetics, for example, more efficient, rapid, prolonged or saturated drug release from the injection site at higher doses, which could be attributed to a depot effect at the injection site. Saturated metabolic or elimination routes could also explain or contribute to the non-dose

proportional pharmacokinetics across the IM dose range, as well as for the 9 mg or 11 mg vs 17 mg IV dose range.

[redacted]

SPL028 was rapidly cleared following both IV and IM routes of administration over an approximately 5 to 6 hour timeframe (mean <0.7 ng/mL at 5 hours) and was extensively distributed throughout body tissues based on the apparent volume of distribution.

PD Results:

Intravenous Infusion

The total mean (CV%) scores on the PPS varied across cohorts, with Placebo Cohort 4 (IV) scoring the lowest, Cohort 1 (9 mg IV; TP 1) scoring the highest and Cohort 2, Cohort 5 and Pooled Placebo Cohort 1 & 2 scoring in-between. The largest between group differences were observed on the PPS "Set" subscale with Placebo Cohort 4 (IV) scoring the lowest and Cohort 1 (9 mg IV; TP 1) scoring the highest.

There were no clear treatment or dose-related trends in trait anxiety changes as measured with the STAI-T.
The baseline scores on the WEMWBS varied somewhat between cohorts. Following SPL028 administration, a slight decrease from baseline scores on the WEMEBS was observed in Cohort 2 (11 mg IV; TP 1), Cohort 4 (17 mg IV) and Pooled Placebo Cohort 1 & 2 at Day 15; and slight increase from baseline scores was observed in Cohort 1 (9 mg IV; TP 1) and Placebo Cohort 4 at Day 15. These changes were also associated with large interindividual variability suggesting that is likely that the changes from baseline reflect day-to-day fluctuation in mental well-being as assessed with the WEMWBS.

There were no clear treatment or dose-related trends in the emotional, psychological or physical well-being of participants as measured with the PTCS at Day 15.

The total mean score on the MEQ was >60% (usually considered a completed mystical experience) in Cohort 4 (17 mg IV) and Cohort 1 (9 mg IV; TP 1), suggesting that the study drug evoked a complete mystical experience in those cohorts. The total mean score on the MEQ in Cohort 2 (11 mg IV; TP 1) was >50% and was associated with large interindividual variability as measured with CV%.
The Pooled Placebo Cohort 1&2 and Placebo Cohort 4 MEQ scores were <20%.

There were no clear dose-related trends and ego dissolution as measured with the EDI. The mean score on the EDI was highest in Cohort 4 (17 mg IV). The mean scores on the EDI were similar in Cohort 1 (9 mg IV; TP 1) and Cohort 2 (11 mg IV; TP 1). The mean scores in the placebo cohorts were low, suggesting that the placebo evoked no or small ego dissolution as measured with the EDI.

There were no clear dose-related trends in emotional breakthrough as measured with the EBI.
The mean scores in Pooled Placebo Cohort 1&2 (IV; TP1) were higher than Placebo Cohort 4 (IV), suggesting that the psychedelic psychedelic-experienced cohort experienced a stronger placebo effect.

There were no clear dose-related trends and challenging experiences as measured with the CEQ. The total mean score on the CEQ was highest in Cohort 4 (17 mg IV). The mean scores on the CEQ were similar in Cohort 1 (9 mg IV; TP 1) and Cohort 2 (11 mg IV; TP 1).

There were no clear dose-related trends in the psychedelic experience, as measured with the IRVAS.
The total mean score on the IRVAS was higher in Pooled Placebo Cohort 1&2 (IV, TP 1) compared to the Placebo Cohort 4 (IV). This difference was driven by a higher "Subject" mean score in Pooled Placebo Cohort 1&2.

The mean score on the VAS items were lower in Cohort 2 (11 mg IV; TP 1) compared to Cohort 1 (9 mg IV; TP 1) and Cohort 4 (17 mg IV). There were no other clear dose-related trends on the VAS items.

The mean score on the VAS items tended to be higher in the Pooled Placebo Cohort 1&2 (IV, TP 1) compared to Cohort 4 Placebo (IV).

The lack of dose-related trends on the above cohorts is likely due to the lower plasma concentrations in the 11 mg dose (Cohort 2) compared to the 9 mg dose (Cohort 1). There were plasma exposure-related trends observed for MEQ, EDI, CEQ and IRVAS.

Intramuscular Injection
The total mean (CV%) scores on the PPS varied slightly across the cohorts, with Cohort 5 (20 mg IM) scoring the lowest, Cohort 3 (30 mg IM) scoring the highest and Cohort 1 (7.5 mg IM; TP 2), Cohort 2 (15 mg IM; TP 2), Pooled Placebo Cohort 1&2 (IM; TP 2) and Pooled Placebo Cohort 3&5 (IM) scoring in-between. No notable differences between the cohorts on any of the subscales were observed.

There were no clear treatment- or dose-related trends in trait anxiety changes as measured with the STAI-T. Some analysis groups increased between baseline and Day 15 while others decreased. However, participants in Cohort 3 (30 mg IM) reported the highest increase in trait anxiety as measured with the STAI-T.

The baseline scores on the WEMWBS varied somewhat between cohorts. Following SPL028 administration a decrease from baseline scores was observed in Cohort 1 (7.5 mg IM; TP 2), Cohort 3 (30 mg IM), Cohort 5 (20 mg IM) and Pooled Placebo Cohort 3&5 (IM) at Day 15 and an increase in Cohort 2 (15 mg IM, TP 2) and Pooled Placebo Cohort 1&2 (IM; TP 2) was observed at Day 15. These changes were also associated with large interindividual variability suggesting that is likely that the changes from baseline reflect day-to-day fluctuation in mental well-being as assessed with the WEMWBS.
There were no clear treatment- or dose-related trends in the emotional, psychological or physical well-being of participants as measured with the PTCS at Day 15.

There seemed to be a dose-related trend on the MEQ with the SPL028 evoking a more complete mystical experience with increasing dose (>60% is usually considered a completed mystical experience). Consequently, a complete mystical experience was observed in Cohort 3 (30 mg IM) and Cohort 5 (20 mg IM) but was absent in Cohort 2 (15 mg IM, TP 2) and Cohort 1 (7.5 mg IM; TP 2). In addition, the CV% values decreased with increasing dose in Cohort 5 (20 mg IM) and Cohort 3 (30 mg IM).

The total mean scores were higher in Pooled Placebo Cohort 3&5 compared to Pooled Placebo Cohort 1&2.
Of the active treatment groups, mean scores on the EDI were lowest in Cohort 1 (7.5 mg IM; TP 2) and highest in Cohort 3 (30 mg IM), with Cohort 2 (15 mg IM; TP 2) and Cohort 5 (20 mg IM) scoring in-between, suggesting that increasing SPL028 dose was associated with increased ego dissolution as measured with the EDI.

In the active cohorts, there was a potential dose-related trend in emotional breakthrough, as measured with the EBI, with higher doses evoking a higher emotional breakthrough. The mean scores in Pooled Placebo Cohort 1 & 2 (IM; TP 2) and Pooled Placebo Cohort 3 & 5 (IM) were low, suggesting that the placebo evoked no or small emotional break through as measured with EBI.

There were no clear dose-related trends in challenging experience as measured with the CEQ. However, it should be noted that Cohort 3 scored higher on all subscales. The mean scores in Pooled Placebo Cohort 1&2 (IM; TP 2) and Pooled Placebo Cohort 3&5 (IM) were low, suggesting that the placebo evoked no or small challenging experience as measured with CEQ.

The total mean score on the IRVAS was higher in Cohort 3 (30 mg IM) and Cohort 5 (20mg IM), compared to Cohort 1 (7.5 mg IM; TP2) and Cohort 2 (15 mg IM; TP2), suggesting that intensity of the subjective effects increased with dose, but it also plateaued at the higher doses. The total mean scores for Pooled Placebo Cohort 1&2 (IM; TP2) and Pooled Placebo Cohort 3&5 (IM) were comparable.

The mean score on the VAS items tended to be lower in Cohort 1 (7.5 mg IM; TP2) and Cohort 2 (15 mg IM; TP2) compared to Cohort 5 (20 mg IM) and Cohort 3 (30 mg IM). There were no other clear dose-related trends on the VAS items.
The mean score on the VAS items tended to be higher in the Pooled Placebo Cohort 1&2 (IM, TP 2) compared to Pooled Placebo Cohort 3&5 (IM).

Conclusions:

- No deaths or SAEs leading to withdrawal occurred in the study.
- SPL028 was well tolerated when administered at dose level of 9 mg IV (Cohort 1 [TP 1]), 11 mg IV (Cohort 2 [TP 1]), 7.5 mg IM (Cohort 1 [TP 2]), 15 mg IM (Cohort 2[TP 2]), and 20 mg IM (Cohort 5).
- [redacted]
- In Cohort 4 (17 mg IV), 2 participants stopped the infusion of SPL028 early due to side effects.
- Overall, higher doses of SPL028 were associated with more severe TEAEs. For the IV SPL028 administration, the highest number of treatment-related TEAEs was observed in Cohort 4 (17 mg IV). [redacted] As coded by PT the most common reported treatment-related TEAE was anxiety reported by 2 (40%) participants.
- For the IM SPL028 administration, the highest number of treatment-related TEAEs was observed in Cohort 5 (20 mg IM) with 10 events being probably or possibly related to SPL028, all events were mild in severity. The most common treatment-related TEAEs by SOC were gastrointestinal disorders with 2 events reported by 2 (33.3%) participants. Each event within the gastrointestinal disorders SOC was reported by 1 participant only. In Cohort 3 (30 mg IM) there were 9 events being probably or possibly related to SPL028, with 2 events being moderate and the remaining being mild in severity. The most common treatment-related TEAEs by SOC were psychiatric disorders. Each event within the psychiatric disorders was reported by 1 participant only.
- There were no significant treatment- or dose-related trends in the mean or individual participant vital sign, physical examination or 12-lead ECG parameters during the study.
- There were no significant treatment- or dose-related trends in the mean or individual participant haematology, biochemistry, or urinalysis data during the study, except a drop in phosphate levels following study medication administration in Cohort 4 (17 mg IV). However, this drop was also observed in both placebo participants, thus was thought to have a multifactorial explanation and to be unrelated to the SPL028.
- The study drug did not increase suicidal ideation or behaviour in study participants.
- No participant required rescue medication during the study.
- Single dose SPL028 plasma PK parameters were well characterised for IV infusion doses of 9, 11 and 17 mg and IM injections of 7.5, 15, 20 and 30 mg.
- [redacted]
- The highest tested IV (17 mg) and IM (30 mg) doses of SPL028 resulted in the highest mean C_{max} values among the doses administered. [redacted]
- SPL028 IV doses of 9 and 11 mg and IM doses of 7.5, 15 and 20 mg had mean C_{max} values that were less than half those values observed for the 17 mg IV and 30 mg IM doses [redacted].
- Somewhat greater than a dose proportional mean C_{max} was observed for the 17 mg IV dose relative to the lower IV doses, and disproportionately higher C_{max} and AUC_{last} and AUC_{inf} were observed for the 30 mg IM doses relative to the lower IM doses. However, confirmation of whether SPL028 displays non-linear pharmacokinetics at these higher doses is limited by small sample sizes and some participants who had the IV infusion stopped early and had missing PK samples.
- SPL028 has a short half-life [redacted], a high clearance rate and a large apparent volume of distribution; consistent with a high clearance drug (e.g. DMT). Mean residence time appears to be approximately 1.5-fold higher for the IM injection versus the IV infusion, likely due to the effects of the additional absorption phase associated with the IM dosing route.
- SPL028 IV half-life was approximately 3-times longer than IV DMT (Good et al., 2023), demonstrating a robust kinetic isotope effect via deuteration of the DMT α-carbon.
- SPL028 was rapidly cleared with both IV and IM routes of administration over an approximately 5 to 6 hour timeframe (mean <0.7 ng/mL at 5 hours).
- There was no clear positive or negative effect of the SPL028 on psychological well-being of the study participants as measured with the WEMWBS.
- No clear relationship between increasing dose and STAI-T scores was observed in the IV group.

- The most commonly reported change on the PTCS was on item "My ability to feel compassion" and "Ability to feel intense emotion" suggesting a potential positive effect on psychological well-being. However, due to low study participant numbers and large interindividual variability, caution should be taken when interpreting the between group differences.
- There were no clear trends in the effect of the dose of the SPL028 IV administration on participants' subjective psychedelic experiences as measured with the EDI, EBI, CEQ, IRVAS and VAS. This was a result of Cohort 2 (11 mg IV; TP 1) scoring invariably below Cohort 1 (9 mg IV; TP 1]) on all subjective psychedelic experience assessments, despite a higher SPL028 dose.
- Dose-response trends were observed of SPL028 IM administration on participants' subjective psychedelic experiences as measured with the MEQ, EDI and IRVAS and VAS.
- Potential dose-response trends were observed in the effect of the SPL028 IM administration on participants' subjective psychedelic experiences as measured with EBI and CEQ, was observed.
- The higher doses of the SPL028 (Cohort 4 [17 mg IV], Cohort 5 [20 mg IM] and Cohort 3 [30 mg IM]) and the lowest IV dose (Cohort 1 [9 mg IV (TP 1)]) evoked a complete mystical experience (as measured by total average score ≥60%).

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