2. SYNOPSIS

Study Title: An Open-Label Study Investigating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Exploratory Efficacy of Intravenous Dosing of SPL026 Drug Product (DMT Fumarate [A Serotonergic Psychedelic]) Alone or in Combination with Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder.

Sponsor: Small Pharma Ltd

Coordinating Investigator: Dr Neel Bhatt, MBChB MRCGP FHEA

Study Sites: This was a multi-centre study which was conducted at 2 study sites in the UK (Liverpool and Manchester).

Publication (reference): n/a

Length of Study:	Phase: Ib
Date of first participant entered: 15 November 2022 Date of last participant completed: 03 August 2023	

Objectives:

Primary Objective:

The primary objective of the study was to evaluate the safety and tolerability of a single intravenous (IV) administration (infusion over 10 minutes) of SPL026 DP with therapy in major depressive disorder (MDD) participants who were taking a selective serotonin reuptake inhibitor (SSRI) at the time of the study that was ineffective in fully relieving their depression (Test Cohort), compared to a single IV administration of SPL026 DP with therapy in MDD participants who were not taking any pharmacological treatment for their depression at the time of the study (Control Cohort).

Secondary Objectives:

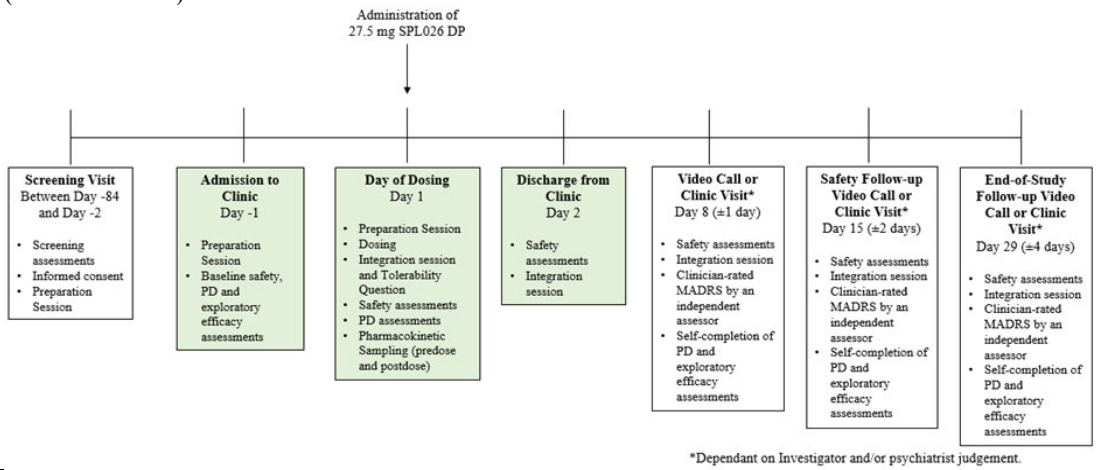
- To evaluate plasma pharmacokinetics (PK) of a single IV administration of SPL026 DP in the Test Cohort compared to the Control Cohort.
- To assess the pharmacodynamics (PD) of a single IV administration of SPL026 DP in the Test Cohort compared to the Control Cohort.

Exploratory Objective:

The exploratory objective of the study was to assess the efficacy of SPL026 DP in treating MDD symptoms in the Test Cohort compared to the Control Cohort.

Study Design:

This was a Phase Ib, open-label study to determine the safety, tolerability, PK profile, PD and exploratory efficacy of a single IV dose of SPL026 DP in participants with MDD who were taking an SSRI that was ineffective in fully relieving their depression (Test Cohort), compared to a single IV dose of SPL026 DP with therapy in participants with MDD who were not taking any pharmacological treatment for their depression (Control Cohort).



Number of Participants with MDD:

Planned: Up to 24
Enrolled: 19
Treated: 18
Completed: 17

Diagnosis and Main Criteria for Inclusion:

Participants had a diagnosis of mild to severe MDD, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Additionally, participants with MDD were in good general health, aged ≥18 years with a body mass index (BMI) of 18 to 33.9 kg/m^2 (inclusive). Participants must have tried at least one approved method of treatment for their depression.

Participants in the Test Cohort were taking a stable dose of an unspecified single SSRI alone and not in combination with any other psychiatric medications, for at least 6 weeks prior to Screening with no intention of making any changes.

Participants in the Control Cohort were not receiving any pharmacological treatment for MDD within 6 months of dosing.

Study Drug, Dose and Mode of Administration:

A single dose of SPL026 DP (27.5 mg) administered as a continuous 10-minute IV infusion via a cannula (the infusion rate was 1.1 mL/min over 10 minutes giving a total administered volume of 11 mL).

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 the study drug 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 at least 1 hour post-infusion start time.

Duration of Treatment and Study Schedule:

The treatment duration was 1 day (Day 1). The maximum study duration was approximately 17 weeks.

The following procedures constituted the study:

Pre-Screening Call (within 6 months of dosing): A psychiatrist and/or therapist assessed participant suitability and severity of depression.

Screening Visit (within Day -84 to Day -2): Informed consent, Screening and eligibility assessments and enrolment of eligible participants with MDD. A Preparation session also took place.

Inpatient Period (Day -1 to Day 2):

Day -1: A Preparation session and baseline safety, PD and efficacy assessments took place.

Day 1: Prior to dosing, safety assessments and a Preparation session took place. Participants with MDD were administered 27.5 mg SPL026 DP as a continuous 10-minute IV infusion via a cannula. PK blood sampling took place before, throughout and after the subjective psychedelic effect. PD 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, safety and PD assessments took place.

Safety Follow-up Video Call (Day 8 [±1 day]): An independent assessor completed the Montgomery-Åsberg Depression Rating Scale (MADRS) via a video call and an Integration session, PD, safety and efficacy assessments also took place. The Investigator and/or psychiatrist could have chosen to perform this visit remotely or ask the participant to attend the CRU if there were any safety concerns; this was judged on a case-by-case basis.

Safety Follow-up Video Call (Day 15 [±2 days]): An independent assessor completed the MADRS via a video call. An Integration session, PD, safety and efficacy assessments were performed. The Investigator and/or psychiatrist could have chosen to perform this visit remotely or ask the participant with MDD to attend the clinical research unit (CRU) if there were any safety concerns; this was judged on a case-by-case basis.

End-of-Study Follow-up Video Call (Day 29 [±4 days]): An independent assessor completed the MADRS via a video call. An Integration session, PD, safety and efficacy assessments took place. The Investigator and/or psychiatrist could have chosen to perform this visit remotely or ask the participant with MDD to attend the 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, clinical laboratory assessments (haematology, clinical chemistry, coagulation and urinalysis), cannulation site reactions and physical examination findings.

Suicidal ideation and behaviour evaluated using the Columbia Suicide Severity Rating Scale (C-SSRS). Tolerability was evaluated by reviewing the therapists' notes that document the subjective psychedelic effects and with a tolerability assessment.

The secondary endpoints of the study were:

- The PK parameters in plasma calculated for SPL026 DP 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_{∞}), 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}).

<u>The secondary PD endpoints completed immediately after dosing were:</u>

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

<u>The secondary PD endpoints completed by study participants before dosing and at home were:</u>

- The Psychedelic Predictor Scale ([PPS] completed once before dosing only)
- Dysfunctional Attitude Scale (DAS)
- Ruminative Responses Scale (RRS)
- Social Connectedness Scale - Revised (SCS-R)
- Psychological Insight Scale (PIS)
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)
- Post-treatment Changes Scale (PTCS)

The exploratory efficacy endpoints of the study were:

- MADRS
- Beck Depression Inventory II (BDI-II)
- Spielberger's State-Trait Anxiety Inventory Trait Subscale (STAI-T)

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 C-SSRS. 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 was listed for each participant, along with summary statistics. All PD and efficacy endpoint data was listed by cohort for each timepoint for individual participant. The endpoints had summary statistics produced by cohort and by timepoint.

Results:

<u>Safety Results:</u>

Data from 18 participants were included in the Safety Analysis Set

No deaths, serious adverse events (SAE)s or treatment emergent adverse events (TEAEs) leading to withdrawal occurred in the study.

Single doses of SPL026 DP in combination with SSRI treatment (Test Cohort) and alone (Control Cohort) appeared to be safe and well tolerated.

Overall, 15 (83.3%) participants reported 35 TEAEs across both cohorts.
Treatment-emergent AEs appeared to be more frequently reported in participants in the Test Cohort; of the 35 TEAEs reported, 27 were reported by 12 (92.3%) participants in the Test Cohort and 8 were reported by 3 (60.0%) participants in the Control Cohort.

Of the 35 TEAEs reported, 17 reported by 9 (50.0%) participants were mild in severity and 11 events reported by 6 (33.3%) participants were moderate; four of these events were considered to be either possibly or probably related the study treatment (3 events reported by 1 [7.7%] participant following dosing in the Test Cohort [1 event of nausea and 2 events of vomiting] were considered to be possibly related to the study treatment and 1 event reported by 1 [20.0%] participant following dosing in the Control Cohort [nausea] was considered to be probably related to the study treatment).

The percentage of participants who experienced events that were considered to either be possibly or probably related to the study treatment were comparable between the cohorts (3 reported by 2 [40.0%] participants in the Control Cohort and 8 reported by 5 [38.5%] participants in the Test Cohort).

The most commonly reported TEAEs were within the nervous system disorders and gastrointestinal disorders SOCs.
Within these SOCs, the most common TEAEs (by preferred term [PT]) were headache (reported by 6 [33.3%] participants) and nausea (reported by 4 [22.2%] participants), and all other TEAEs (except vomiting, infusion site pain, gastroenteritis, and dysmenorrhoea, each reported by 2 participants), were reported by a single participant overall.

Table 1: Summary of Treatment Emergent Adverse Events

	Test Cohort (N=13) n (%) [e]	**Control Cohort (N=5) n (%) [e]**	**Overall (N=18) n (%) [e]**
Any TEAE	12 (92.3%) [27]	3 (60.0%) [8]	15 (83.3%) [35]
Any Serious TEAE	0	0	0
Any TEAE Leading to Discontinuation of Treatment	0	0	0
Study Medication-Related TEAE	0	0	0
Serious TEAE	0	0	0
Any Life-Threatening Serious TEAEs	0	0	0
TEAE Leading to Death	0	0	0
Severity			
Mild	8 (61.5%) [16]	1 (20.0%) [1]	9 (50.0%) [17]
Moderate	4 (30.8%) [7]	2 (40.0%) [4]	6 (33.3%) [11]
Severe	0	0	0
Causality			
Not Related	5 (38.5%) [9]	2 (40.0%) [2]	7 (38.9%) [11]
Unlikely Related	9 (69.2%) [10]	1 (20.0%) [3]	10 (55.6%) [13]
Possibly Related	2 (15.4%) [4]	2 (40.0%) [2]	4 (22.2%) [6]
Probably Related	4 (30.8%) [4]	1 (20.0%) [1]	5 (27.8%) [5]
Related [a]	5 (38.5%) [8]	2 (40.0%) [3]	7 (38.9%) [11]
Unrelated [b]	10 (76.9%) [19]	2 (40.0%) [5]	12 (66.7%) [24]

Abbreviations: AE – Adverse Event; N – The number of participants who were enrolled to the stated cohort; TEAE – Treatment-Emergent Adverse Event.
n (%) [e]: number of participants with events (percentage of participants with events) [number of events].
A TEAE is an AE that was not present prior to treatment, but appeared following treatment.

Table 2: Summary Of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Treatment

System Organ Class Preferred Term	**Test Cohort (N=13) n (%) [e]**	**Control Cohort (N=5) n (%) [e]**	**Overall (N=18) n (%) [e]**
Any TEAEs	12 (92.3%) [27]	3 (60.0%) [8]	15 (83.3%) [35]
Nervous system disorders	7 (53.8%) [9]	1 (20.0%) [2]	8 (44.4%) [11]
Headache	6 (46.2%) [8]	0	6 (33.3%) [8]
Dizziness	1 (7.7%) [1]	0	1 (5.6%) [1]
Lethargy	0	1 (20.0%) [2]	1 (5.6%) [2]
Gastrointestinal disorders	4 (30.8%) [6]	1 (20.0%) [2]	5 (27.8%) [8]
Nausea	3 (23.1%) [3]	1 (20.0%) [2]	4 (22.2%) [5]
Vomiting	2 (15.4%) [3]	0	2 (11.1%) [3]
General Disorders and Administration Site Conditions	2 (15.4%) [2]	1 (20.0%) [1]	3 (16.7%) [3]
Infusion site pain	1 (7.7%) [1]	1 (20.0%) [1]	2 (11.1%) [2]
Vessel puncture site haematoma	1 (7.7%) [1]	0	1 (5.6%) [1]
Infections and infestations	3 (23.1%) [3]	0	3 (16.7%) [3]
Gastroenteritis	2 (15.4%) [2]	0	2 (11.1%) [2]
COVID-19	1 (7.7%) [1]	0	1 (5.6%) [1]

System Organ Class Preferred Term	Test Cohort (N=13) n (%) [e]	Control Cohort (N=5) n (%) [e]	Overall (N=18) n (%) [e]
Psychiatric disorders	2 (15.4%) [2]	**1 (20.0%) [1]**	3 (16.7%) [3]
Abnormal dreams	0	1 (20.0%) [1]	1 (5.6%) [1]
Anxiety	1 (7.7%) [1]	0	1 (5.6%) [1]
Insomnia	1 (7.7%) [1]	0	1 (5.6%) [1]
Reproductive system and breast disorders	1 (7.7%) [1]	1 (20.0%) [1]	2 (11.1%) [2]
Dysmenorrhoea	1 (7.7%) [1]	1 (20.0%) [1]	2 (11.1%) [2]
Skin and subcutaneous tissue disorders	2 (15.4%) [2]	0	2 (11.1%) [2]
Skin reaction	1 (7.7%) [1]	0	1 (5.6%) [1]
Urticaria	1 (7.7%) [1]	0	1 (5.6%) [1]
Immune system disorders	0	1 (20.0%) [1]	1 (5.6%) [1]
Hypersensitivity	0	1 (20.0%) [1]	1 (5.6%) [1]
Injury, poisoning and procedural complications	1 (7.7%) [1]	0	1 (5.6%) [1]
Infusion related reaction	1 (7.7%) [1]	0	1 (5.6%) [1]
Musculoskeletal and connective tissue disorders	1 (7.7%) [1]	0	1 (5.6%) [1]
Back pain	1 (7.7%) [1]	0	1 (5.6%) [1]

Abbreviations: AE = Adverse Event; N = The number of participants who were enrolled to the stated cohort; TEAE = Treatment-Emergent Adverse Event.
n (%) [e]: number of participants with events (percentage of participants with events) [number of events].
A TEAE is an AE that was not present prior to treatment, but appeared following treatment.

There were notable decreases in mean percentage change from baseline in the following clinical haematology parameters: basophils, eosinophils, lymphocytes and monocytes. There were also notable increases in the mean percentage change from baseline in leukocyte and neutrophil parameters. None of these findings were deemed clinically significant.

A notable mean percentage decrease from baseline in phosphate was observed in the Control Cohort. However, they returned to the normal range within 120 minutes and were not deemed clinically significant. The phosphate levels in the Test Cohort were comparable to baseline.

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.

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. All participants responded 'No' to the tolerability question ('Do you wish you had not gone through that experience?') suggesting that the study drug was well tolerated.

PK Results:
Data from 16 participants were included in the PK Analysis Set.

DMT plasma concentrations following administration of SPL026 were detectable at 2 minutes after the start of infusion for most participants.

Median t_{max} was 10.98 minutes (range 9.96 to 13.26, which extended to 9.96 to 60.6, when including 1 anomalous profile) and 10.14 minutes (range 7.86 to 10.98) after 27.5 mg SPL026 administration in Test and Control Cohorts, respectively.

[redacted]

Overall systemic exposures were similar between the Test and Control Cohorts. Geometric mean AUC_{last} (11 participants) and AUC_{∞} (8 participants) were 19.4 h*ng/mL (1,164 min*ng/mL) and 21.7 h*ng/mL (1,302 min*ng/mL) for the Test Cohort, respectively. In the Control cohort (5 participants), geometric mean AUC_{last} and AUC_{∞} were 19.5 h*ng/mL (1,170 min*ng/mL) and 19.6 h*ng/mL (1,176 min*ng/mL), respectively.

[redacted]

Arithmetic mean CL, V_z and V_{ss} were 22.0 L/min, 590 L and 403 L, respectively in the Test Cohort (8 participants) and were within a similar range in the Control Cohort (5 participants) at 26.9 L/min, 410 L, 353 L. These data were in line with the expected range as seen in previous clinical trials with DMT.
Overall variability in PK in this study was moderate-to-high. This may in part be explained by inherent subject to subject metabolism of DMT, a small sample size and/or minor deviations in the sampling collection times.

Table 3: Summary of DMT Plasma Pharmacokinetic Parameters in Participants with MDD: PK Population

Parameter	Treatment	n	Geom. Mean	95% CI (Lower, Upper)	SD (logs)	%CV_b
[redacted]						
AUC_{last} (h*ng/mL)	Test (N=13)	11	19.4	(15.0, 25.3)	0.389	40.4
	Control (N=5)	5	19.5	(9.85, 38.8)	0.552	59.7
AUC_{∞} (h*ng/mL)	Test (N=13)	8	21.7	(16.6, 28.4)	0.319	32.8
	Control (N=5)	5	19.6	(9.87, 38.9)	0.552	59.7
λ_z (/h)	Test (N=13)	8	2.18	(1.53, 3.12)	0.426	44.6
	Control (N=5)	5	3.56	(2.27, 5.58)	0.361	37.4
[redacted]						
CL (L/h)	Test (N=13)	8	1266	(970, 1654)	0.319	32.8
	Control (N=5)	5	1403	(707, 2785)	0.552	59.7
V_z (L)	Test (N=13)	8	580	(489, 686)	0.202	20.4
	Control (N=5)	5	394	(263, 590)	0.325	33.4
V_{ss} (L)	Test (N=13)	8	393	(323, 479)	0.237	24
	Control (N=5)	5	336	(215, 524)	0.358	37
MRT_{inf} (h)	Test (N=13)	8	0.311	(0.248, 0.389)	0.269	27.4
	Control (N=5)	5	0.239	(0.165, 0.347)	0.3	30.7

Abbreviations: %CV_b = between-subject coefficient of variation, λ_z = terminal rate constant, AUC = area under the plasma concentration=time curve, AUC_{∞} = AUC extrapolated to infinity, AUC_{last} = AUC up to the last measurable concentration, CL = total clearance from plasma after administration, C_{max} = maximum plasma concentration, IV = intravenous; MRT_{inf} = mean residence time, PK = pharmacokinetic, SD = standard deviation, $t_{½}$ = terminal elimination half-life, V_{ss} = apparent volume of distribution at steady state, V_z = apparent volume of distribution after administration.
N = The number of participants who were enrolled to the stated cohort.
n = The number of participants who were enrolled to the stated cohort and were included in mean calculation.
Participant 1004 and Participant 1005 (Test Cohort) parameters derived from λ_z and AUC_{∞} from could not be derived due to poor estimation of λ_z ($R2 < 0.8$).

PD Results:
Data from 17 participants were included in the PD Analysis Set.

The total mean scores for the PPS were higher in the Test Cohort compared to Control Cohort, suggesting a greater preparedness for the psychedelic experience in the Test Cohort.
The difference in the total mean scores for the PPS was mainly due to the difference in the "set" subscale. The mean scores for "setting", "rapport" and "clear intentions" subscales were comparable between both cohorts.

The total mean scores for the MEQ were moderately higher in the Test Cohort compared to the Control Cohort, suggesting that the study drug evoked a more complete mystical experience in the Test Cohort.

The mean scores for the EDI were higher in the Test Cohort compared to the Control Cohort, suggesting that the study drug evoked greater ego dissolution in the Test Cohort.

The mean scores for the EBI were moderately higher in Test Cohort compared to the Control Cohort, suggesting that the study drug evoked a psychedelic experience with moderately more emotional breakthrough in the Test Cohort.

The total mean scores for the CEQ were moderately lower in the Test Cohort compared to the Control Cohort, suggesting that the study drug evoked a moderately lower psychedelic-occasioned challenging experience in the Test Cohort.

The total mean scores for the IRVAS were slightly lower in the Test Cohort compared to the Control Cohort, suggesting that the study drug evoked a slightly lower intensity psychedelic experience in the Test Cohort.

The mean scores for the itemised VAS were comparable between the Test Cohort and Control Cohort, suggesting that the study drug evoked a similar experience in both cohorts, except for the "experience more real" (item VAS05), where the Test Cohort scored higher compared to the Control Cohort.

The mean baseline scores for the RRS were comparable between the Test Cohort and Control Cohort. A decrease from mean baseline RRS scores was observed at Day 29 in both cohorts, suggesting a reduction in ruminative thinking following study drug administration.

The mean baseline scores for the SCS-R were comparable between the Test Cohort and Control Cohort. Similar increases from baseline scores were observed in both cohorts at Day 15 and Day 29, suggesting higher levels of social connectedness following study drug administration.

The mean baseline scores for the PIS were higher in the Test Cohort compared to the Control Cohort, suggesting higher levels of psychological insight in the Test Cohort prior to study drug administration. Increases from baseline scores were observed in both cohorts at Day 15 and Day 29.
The increases from baseline scores were greater at Day 29 compared to Day 15, suggesting a prolonged effect of the study drug.

The mean baseline scores for the WEMWBS were comparable between the Test Cohort and Control Cohort. Increases from baseline scores were observed in both cohorts at Day 15 and Day 29.
In the Test Cohort the increase from baseline score was greater at Day 29 compared to Day 15 suggesting a prolonged effect of the study drug.
In the Control Cohort the increase from baseline score remained comparable at Day 15 and Day 29, suggesting maintenance of effect.

The mean baseline scores for the DAS were comparable between the Test Cohort and Control Cohort. Increases from baseline scores were observed in both cohorts at Day 8, Day 15 and Day 29, suggesting a reduction in dysfunctional attitudes following study drug administration.
In the Test Cohort the increase from baseline score was greater at each consecutive visit, suggesting a prolonged effect of the study drug.
In the Control Cohort the increase from baseline score remained comparable at each consecutive visit, suggesting maintenance of effect.
However, the range of scores on the DAS was similar in the Test Cohort and Control Cohort suggesting an overlap.

An increase in positive affect and psychological wellbeing following study drug administration was observed at Day 15 and Day 29 as measured with the PTCS items in both the Test Cohort and Control Cohort. In addition, no change in physiological symptoms, measured with the PTCS, following study drug administration was observed at Day 15 and Day 29 in both the Test Cohort and Control Cohort, suggesting good tolerability of the study drug over time with none to small changes in physical symptoms.

Efficacy Results
Data from 17 participants were included in the Efficacy Analysis Set.

The mean baseline scores for the MADRS were lower in the Test Cohort compared to the Control Cohort (28.8 and 35.4, respectively). Decreases from baseline scores were observed in both cohorts at Day 8, Day 15 and Day 29 following study drug administration, suggesting reduction in depression symptoms following study drug administration. The differences between the Test Cohort and Control Cohort are more pronounced when comparing mean percentage change from baseline values at Day 8, Day 15 and Day 29, which takes into account the different baseline scores.

Decreases from baseline scores in the Test Cohort were greater at Day 29 compared to Day 15 and Day 8 suggesting a prolonged effect of the study drug.
Decreases from baselines scores in the Control Cohort remained at similar levels at Day 8, Day 15 and Day 29 suggesting an initial improvement followed by maintenance of effect.
Decreases from mean baseline scores were greater in the Test Cohort compared to the Control Cohort at Day 8, Day 15 and Day 29, particularly at Day 29 where the difference between the two cohorts was marked.

Table 4: Summary Statistics for the Montgomery-Åsberg Depression Rating Scale

MADRS Total Score	**Observed Value**						
Treatment / **Visit**	**n**	**Mean**	**SD**	**CV%**	**Median**	**Min**	**Max**
Test (N=13)							
Baseline	12	28.8	6.37	22.08	30	13	36
Day 8	12	6.7	8.85	132.68	2	0	27
Day 15	12	6	8.08	134.65	3.5	0	27
Day 29 (EOS)	12	3	3.91	130.27	1	0	11
Control (N=5)							
Baseline	5	35.4	2.61	7.37	35	33	39
Day 8	5	16.4	7.8	47.55	21	7	24
Day 15	5	16	8.28	51.73	18	7	26
Day 29 (EOS)	5	16	10.7	66.88	17	0	30

MADRS Total Score	**Change from Baseline**							
Treatment / **Visit**	**n**	**Mean**	**SD**	**CV%**	**Median**	**Min**	**Max**	**Mean%**
Test (N=13)								
Day 8	12	-22.2	9.1	-41.07	-24	-35	-7	-78.1
Day 15	12	-22.8	7.41	-32.44	-24.5	-31	-9	-81.2
Day 29 (EOS)	12	-25.8	6.49	-25.13	-26.5	-36	-13	-90.2
Control (N=5)								
Day 8	5	-19	9.06	-47.66	-16	-32	-9	-53.1
Day 15	5	-19.4	9.5	-48.98	-19	-31	-7	-54.2
Day 29 (EOS)	5	-19.4	10.74	-55.35	-20	-33	-3	-54.8

Baseline: The last observation prior to the first dose of study treatment.
Abbreviations: CV = Coefficient of Variation, EOS = End of Study, MADRS = Montgomery-Åsberg Depression Rating Scale, Max = Maximum, Min = Minimum, SD = Standard Deviation.
N = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort including participants with major protocol deviations.
n = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort excluding participants with major protocol deviations.

The mean baseline scores for the BDI were lower in the Test Cohort compared to the Control Cohort. Decreases from baseline scores were observed in both cohorts at Day 15 and Day 29, suggesting lower depression symptoms following study drug administration.
Decreases from baseline scores in both cohorts were greater at Day 29 compared to Day 15, suggesting a prolonged effect of study drug.
Decreases from mean baseline scores were greater in the Test Cohort compared to the Control Cohort at Day 15 and Day 29.

Table 5: Summary Statistic for the Beck Depression Inventory II

BDI - Total Score	**Observed Value**						
Treatment / **Visit**	**n**	**Mean**	**SD**	**CV%**	**Median**	**Min**	**Max**
Test (N = 13)							
Baseline	12	30	9.62	32.07	31	14	46

BDI - Total Score	Observed Value						
Treatment / Visit	n	Mean	SD	CV%	Median	Min	Max
Day 15	12	5.1	7.98	157	3	0	29
Day 29 (EOS)	12	3.1	3.7	120.1	1.5	0	11
Control (N = 5)							
Baseline	5	36	6.16	17.12	37	27	42
Day 15	5	16.8	5.36	31.89	17	8	22
Day 29 (EOS)	5	14.8	10.47	70.77	13	2	31

BDI - Total Score	Change from Baseline							
Treatment / Visit	n	Mean	SD	CV%	Median	Min	Max	Mean%
Test (N = 13)								
Day 15	12	-25	10.07	-40.4	-25	-41	-8	-83.6
Day 29 (EOS)	12	-27	10.09	-37.5	-26	-46	-7	-88.4
Control (N = 5)								
Day 15	5	-19	5.12	-26.7	-20	-25	-11	-53.7
Day 29 (EOS)	5	-21	11.23	-53	-25	-29	-2	-59

Baseline: The last observation prior to the first dose of study treatment.
Abbreviations: BDI = Beck Depression Inventory II, CV = Coefficient of Variation, EOS = End of Study, Max = Maximum, Min = Minimum, SD = Standard Deviation.
N = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort including participants with major protocol deviations.
n = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort excluding participants with major protocol deviations.

Mean baseline scores for the STAI-T were lower in the Test Cohort compared to the Control Cohort. Decreases from baseline scores were observed in both cohorts at Day 8, Day 15 and Day 29 following study drug administration, suggesting a reduction in trait anxiety following study drug administration.
Decreases from baseline scores in the Test Cohort were greater at Day 29 compared to Day 15 and Day 8 suggesting a prolonged effect of study drug.
Decreases from baselines scores in the Control Cohort remained at similar levels at Day 8, Day 15 and Day 29 suggesting maintenance of effect.
Decreases from mean baseline scores were greater in the Test Cohort compared to the Control Cohort at Day 8, Day 15 and Day 29.

Table 6: Summary Statistics for the Spielberger's State-Trait Anxiety Inventory – Trait Subscale

STAI - Total Score	Observed Value						
Treatment / Visit	n	Mean	SD	CV%	Median	Min	Max
Test (N = 13)							
Baseline	12	60.9	7.56	12.41	61	48	71
Day 8	12	39.8	11.19	28.16	39	26	66
Day 15	12	37.3	10.68	28.61	37	22	62
Day 29 (EOS)	12	35.2	7.38	21	34	23	45
Control (N = 5)							
Baseline	5	65.6	6.58	10.03	69	58	72
Day 8	5	46.4	8.88	19.13	44	38	60
Day 15	5	47.2	7.85	16.64	46	39	58
Day 29 (EOS)	5	47.6	9.84	20.67	49	32	59

STAI - Total Score	Change from Baseline							
Treatment / Visit	n	Mean	SD	CV%	Median	Min	Max	Mean%
Test (N = 13)								
Day 8	12	-21	13.89	-65.6	-24	-41	1	-33.6
Day 15	12	-24	13.73	-58.2	-28	-44	-3	-37.5
Day 29 (EOS)	12	-26	11.62	-45.1	-29	-43	-5	-41
Control (N = 5)								
Day 8	5	-19	9.83	-51.2	-20	-32	-9	-28.9
Day 15	5	-18	9.56	-51.9	-17	-30	-7	-27.6
Day 29 (EOS)	5	-18	10.37	-57.6	-22	-26	0	-27.2

Baseline: The last observation prior to the first dose of study treatment.
Abbreviations: CV = Coefficient of Variation, EOS = End of Study, Max = Maximum, Min = Minimum, SD = Standard Deviation, STAI = Spielberger's State-Trait Anxiety Inventory.
N = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort including participants with major protocol deviations.
n = The number of participants with all evaluable data for that analysis who were enrolled to the stated cohort excluding participants with major protocol deviations.

Conclusions

- No deaths or SAEs were reported during this study and no participants were discontinued due to a TEAE.
- Single doses of SPL026 DP in combination with SSRI treatment (Test Cohort) and alone (Control Cohort) appeared to be safe and well tolerated.
- Overall, 15 (83.3%) participants reported 35 TEAEs across both cohorts.
- Of these, 11 TEAEs reported by 7 participants were deemed treatment-related. The most commonly reported treatment-related TEAEs were within the gastrointestinal disorders SOC.
- Within this SOC, the most common TEAEs (by PT) were nausea (3 [16.7%] participants) and vomiting (2 [11.1%] participants), all other treatment-related TEAEs, were reported by a single participant overall.
- Clinical laboratory evaluation showed non-clinically significant mean percentage changes from baseline in several parameters including basophils, eosinophils, lymphocytes, monocytes, leukocytes and neutrophils following study drug administration in Test Cohort and Control Cohort.
- A decrease in mean percentage change from baseline in phosphate was present in the Control Cohort, only.
- Although some of the clinical laboratory evaluations were outside the appropriate reference ranges, all findings were considered to be transient, clinically non-significant and occurred at isolated timepoints only.
- There were no significant treatment-related trends in vital sign values, physical findings and ECG parameters.
- DMT plasma concentrations following administration of SPL026 were detectable at 2 minutes after the start of infusion for most participants. Median t_{max} was 10.98 minutes (range 9.96 to 13.26, which extended to 9.96 to 60.6, including Participant 1011's anomalous profile) and 10.14 minutes (range 7.86 to 10.98) after 27.5 mg SPL026 administration in Test and Control Cohorts, respectively.
- There was a high level of individual variability in C_{max} within the Test Cohort, which was similar to variability seen in previous clinical trials of DMT.
- Overall, with consideration of variability and unbalanced and small sample sizes, systemic exposure (C_{max} and AUC) was comparable between both cohorts.
- [redacted]
- Overall variability in PK in this study was moderate-to-high. This may in part be explained by inherent subject to subject metabolism of DMT, a small sample size and/or minor deviations in the sampling collection times.
- Prior to study drug administration participants in the Test Cohort demonstrated a higher preparedness for psychedelic experience as assessed with the PPS.
- The Test Cohort scored higher on the MEQ, EBI and EDI, whereas the Control Cohort scored

higher on the CEQ following study drug administration, suggesting that the study drug evoked somewhat different psychedelic experiences as measured with these assessments.

- The Test Cohort and Control Cohort scored similarly on the VAS, and the Test Cohort scored slightly lower on the IRVAS following study drug administration, suggesting a similar but slightly lower intensity of the psychedelic experience in the Test Cohort when compared to the Control Cohort.
- Following study drug administration an improvement in psychological and social wellbeing was observed in Test Cohort and Control Cohort, which appeared to be maintained out to Day 29.
- Decreases from baseline score on the RRS were observed on Day 29 and increases from baseline scores on the DAS were observed at Day 8, Day 15 and Day 29 in the Test Cohort and Control Cohort, suggesting a reduction in ruminative thinking and improvement in dysfunctional attitudes following study drug administration, in both cohorts. Increases from baseline scores on the PIS, WEMBWS, PTCS and SCS-R were observed at Day 15 and Day 29 in both the Test Cohort and Control Cohort, suggesting higher levels of psychological wellbeing and social connectedness following study drug administration.
- The efficacy results suggest that SPL026 DP decreased depression symptoms in both the Test Cohort and Control Cohort, which appeared to be maintained out to Day 29.
- Decreases from baseline scores in the Test Cohort and Control Cohort were observed on the BDI at Day 15 (5.1 and 16.8, respectively) and Day 29 (3.1 and 14.8, respectively), suggesting reduction in depression symptoms following study drug administration.
- Changes from baseline in MADRS scores were more similar between the Test Cohort and Control Cohort at Day 8 (-22.2 and -19, respectively) and Day 15 (-22.8 and 19.4, respectively). At Day 29 there was a slightly greater difference between the Test Cohort and the Control Cohort (-25.8 and -19.4, respectively).
- Decreases from baseline in the Test Cohort and Control Cohort were observed on STAI-T at Day 8 (39.8 and 46.4, respectively), Day 15 (37.3 and 47.2, respectively) and Day 29 (35.2 and 47.6, respectively), suggesting reduction in trait anxiety following study drug administration.
- However, the trend in changes in the efficacy assessments demonstrated between group difference over time.
- Specifically, in the Test Cohort a decrease in depressive and anxiety symptoms was observed at each consecutive visit, i.e. clinical symptoms scores were lower at Day 29 assessments compared to Day 15 assessments and (MADRS and STAI-T only) Day 8 assessments, suggesting a prolonged effect on depressive symptoms over time when SPL026 DP was added to existing SSRI treatment.
- In the Control Cohort, this trend was absent, i.e. the symptoms scores remained at similar levels at the Day 29, Day 15 and Day 8 assessments, suggesting an initial improvement followed by maintenance of improvement in depressive symptoms over time. However, conclusions must be taken with caution due to low study participant numbers, unbalanced group sizes and difference in baseline characteristics.

Date of the Report: 20 March 2024