Synopsis

Sponsor: Small Pharma Ltd	
Name of finished product: SPL026	**Name of active ingredient:** N,N-dimethyltryptamine (DMT) fumarate
Title: A double-blind, randomised, placebo-controlled study of intravenous doses of SPL026 (DMT fumarate), a serotonergic psychedelic, in healthy subjects (Part A) and patients with major depressive disorder (Part B)	
Investigator(s): Dr David Erritzoe (Imperial College London), Dr Malcolm Boyce (HMR), Dr Fabian Devlin (MAC; Part B only).	
Trial centre(s): HMR, Cumberland Avenue, Park Royal, London NW10 7EW; MAC, 11 Tiger Court, Kings Business Park, Kings Drive, Prescot, Merseyside, L34 1BH (Part B only); Imperial College London Hammersmith Campus, Du Cane Road, London W12 0NN.	
Publication(s): Good M, Joel Z, Benway T, et al. Pharmacokinetics of N,N-dimethyltryptamine in Humans. *European Journal of Drug Metabolism and Pharmacokinetics*. 2023;48(3):311-327.	
Trial period: 08 February 2021–21 December 2022	**Phase of Development:** 1
Date of the report: 29 June 2023	

Objectives

Primary objectives

Part A: To assess the safety and tolerability of single intravenous (IV) doses of SPL026 in psychedelic-naïve healthy subjects.

Part B: To assess the efficacy of single IV doses of SPL026 versus placebo in major depressive disorder (MDD) patients.

Secondary objectives

Part A: To assess the pharmacodynamics (PD) of single IV doses of SPL026 in psychedelic-naïve healthy subjects.

To assess the pharmacokinetics (PK) of single IV doses of SPL026 in psychedelic-naïve healthy subjects.

Part B: To assess the safety and tolerability of single IV doses of SPL026 in MDD patients.

To assess the PK of single IV doses of SPL026 in MDD patients.

To assess the PD of 1 or 2 IV doses of SPL026 in in MDD patients.

To compare the PD of 1 dose of SPL026 given 2 weeks after placebo with 2 doses of SPL026 given 2 weeks apart, in MDD patients.

To compare the efficacy of 1 dose of SPL026, given as either the first or second dose, versus 2 doses given 2 weeks apart, in MDD patients.

To compare the efficacy of 1 dose of SPL026 given 2 weeks after placebo with 2 doses of SPL026 given 2 weeks apart, in MDD patients.

Exploratory objectives

Part A: To assess the PD of SPL026 in psychedelic-naïve healthy subjects given single IV doses.

To assess the PK of SPL026 metabolites in psychedelic-naïve healthy subjects given single IV doses (optional, reported separately).

Part B: To assess the PD of SPL026 in MDD patients given 1 or 2 IV doses.

Methods

This trial was in 2 parts, as follows.

- Part A was a phase 1, double-blind, randomised, placebo-controlled, parallel group, dose-escalation trial to investigate the safety, tolerability, PD, and PK of single IV doses of SPL026 in psychedelic-naïve healthy participants.
- Part B was a phase 2a evaluation of the efficacy, safety, tolerability, PD, and PK of SPL026, given as 1 or 2 single IV doses in participants with MDD.

Part A

In Part A, 32 healthy participants were enrolled in 4 groups (Groups 1–4) of 8 participants each. In each group, 6 participants received a single dose of SPL026, and 2 participants received a single dose of placebo, by IV infusion. The infusion was given in 2 phases:

- the first phase was given over 5 min and was intended, at the starting dose, to bring the participants to the verge or early stages of a psychedelic experience;
- the second phase was given over 5 min, with the intention to either maintain or further intensify the psychedelic effects attained in the first phase, achieving a complete psychedelic experience.

The planned and actual doses and dose regimens of SPL026 are in Table S1. There were no changes to the planned doses, but duration of Phase 2 IV infusions was adjusted in Groups 2–4. Group 5 was optional and did not take place.

Because N,N-dimethyltryptamine (DMT) has been studied previously in healthy psychedelic-experienced participants, this was not a first in human (FIH) trial. However, at the time of first approvals of this study by the Medicines and Healthcare products Regulatory Agency (MHRA) and research ethics committee (REC), the published literature did not give full details of the safety and tolerability findings from those trials, and DMT had not

previously been studied in healthy psychedelic-naïve participants. Part A of this study was therefore designed taking into consideration the guidance on strategies to identify and mitigate risks for FIH and early clinical trials with investigation medicinal products (IMPs), issued by the European Medicines Agency (EMA). Therefore, each new ascending dose level was staggered: 2 sentinel participants(1 randomised to active and 1 to placebo) were dosed first, and the remaining participants in the group were dosed (5 randomised to active and 1 to placebo) at least 48 h later, provided that the safety and tolerability in the sentinels (up to and including Day 2 procedures) were acceptable.

Table S1: Planned and actual doses and dose regimens in Part A (healthy participants)

Group	Planned total dose of SPL026*	Planned duration of IV infusion	Actual total dose of SPL026	Actual duration of IV infusion	Number of participants‡
1	9 mg	Phase 1: 6 mg over 5 min Phase 2: 3 mg over 5 min	9 mg	Phase 1: 6 mg over 5 min Phase 2: 3 mg over 5 min	8
2	12 mg	Phase 1: 6 mg over 5 min Phase 2: 6 mg over 3 min	12 mg	Phase 1: 6 mg over 5 min Phase 2: 6 mg over 5 min	8
3	17 mg	Phase 1: 6 mg over 5 min Phase 2: 11 mg over 4 min	17 mg	Phase 1: 6 mg over 5 min Phase 2: 11 mg over 5 min	8
4	21.5 mg	Phase 1: 6 mg over 5 min Phase 2: 15.5 mg over 3 min	21.5 mg	Phase 1: 6 mg over 5 min Phase 2: 15.5 mg over 5 min	8
5†	20 mg	Phase 1: 10 mg over 3 min Phase 2: 10 mg over 3 min	–	–	–

Doses were administered as a continuous infusion in 2 phases (2 syringes and 2 syringe pumps joined via a 3-way tap into a single cannula), as indicated in the table. Doses did not exceed 21.5 mg SPL026 over a total infusion duration of 6–11 min.
Doses in Part A could be altered based on emerging data .
* Dose refers to free base DMT.
‡ Including 2 participants in each group who received placebo.
† Group 5 was optional and did not take place

Part B

34 participants with MDD were enrolled in Part B. Participants received up to 2 doses of trial medication by IV infusion in 2 stages, as follows.

- **Stage 1**: participants were randomised (1:1; double blind, parallel-group fashion) to receive a single dose of SPL026 or placebo.

- **Stage 2**: participants received a dose of SPL026 (either their first or second, depending on whether they received active treatment or placebo in Stage 1) at 2 weeks after dosing in Stage 1. If the participant declined a second dose or was discontinued from dosing by the study psychiatrist for safety reasons, they would enter follow-up (Visit 4) after their first dose in Stage 1.

Therefore, 3 dosing regimens were possible in Part B:

- a dose of SPL026, followed 2 weeks later by a second dose of SPL026;
- placebo, followed 2 weeks later by a dose of SPL026;
- a dose of SPL026 or placebo and no second dose.

Dosing in Part B did not start until dosing in Part A was completed, and a dose level and infusion regimen had been tested at which a mean average of evaluable participants on active treatment achieved ≥ 60% of the maximum possible score on the Mystical Experience Questionnaire (MEQ). The dose and infusion regimen of SPL026 tested in Part B was selected after review by the Safety Review Group (SRG) of the safety, tolerability, PK and PD data from all dose levels tested in Part A.

The dose selected for Part B was 21.5 mg SPL026 (as in Part A Group 4), by IV infusion over 10 min, given in 2 phases as 6 mg over 5 min, and 15.5 mg over 5 min. The dose administered in Part B did not exceed the highest dose that was found to be safe and well tolerated in Part A. Sentinels were therefore not required, but no more than 1 participant was dosed per day per dosing room.

All study parts

Following the end of the infusion, the subjective psychedelic effects of SPL026 were expected to resolve rapidly (within 20 min). Psychometric scales (Table S3; with the exception of the intensity rating visual analogue scale [IRVAS] which was done after integration [see Table S2]) were administered to determine the quality of the participant's psychedelic experience. Once those were completed, the therapist and psychiatrist began the integration session [Table S2]). During that interview the psychiatrist asked questions to determine the details of the participant's subjective psychedelic experience. Overall tolerability of the experience was initially determined using the IRVAS (Part A, Groups 1 and 2), then formally assessed using a question during the postdose integration interview (Part A, Groups 3 and 4, and Part B; these changes were implemented in amendments to the protocol during the trial). The definitive question asked of the participants to assess tolerability was: *Do you wish you had not gone through that experience?* Participants also completed scales at baseline and remotely throughout the study follow-up period.

Screening and study duration

Part A

In Part A, healthy participants were screened during the 3 weeks before their dose of trial medication. In addition to screening assessments, participants had individual psychiatric interviews with the study psychiatrist and a preparation session with both the study

psychiatrist and study therapist. If screening took place > 2 weeks before dosing, participants had a 'refresher call' (telephone or videocall) with the study team during the 1–2 weeks before dosing.

Participants were resident on the ward from the day before their dose (Day –1) until the morning after dosing (Day 2). Participants had follow-up assessments by telephone or video call on Days 8 (± 1 day), 15 (± 1 day), 30 (± 2 days), and 90 (± 5 days).

Part B

Visit 1 (screening)*:* participants were pre-screened during the 6 months before their first dose of trial medication. Eligibility to proceed to screening was assessed by the study psychiatrist or study therapist via correspondence, telephone, and or/video calls. Eligible participants were screened during the 3 months before their first dose of trial medication. In addition to screening assessments, participants had an individual psychiatric interview with the study psychiatrist and a preparation session with both the study psychiatrist and study therapist. Participants had at least 2 'refresher calls' before admission to the ward for their first dose.

Visit 2 (Stage 1 dose): participants were resident on the ward from the day before their dose (Day –1) until the morning after dosing (Day 2). They had follow-up assessments by telephone or video call on Day 8.

Visit 3 (Stage 1 assessment and Stage 2 dose): participants attended the ward 13 days after their Stage 1 dose (Day 14). They underwent Montgomery–Åsberg Depression Rating Scale (MADRS) assessment by an independent assessor (who was blinded and not present at dosing or integration), and a psychiatrist completed a psychological assessment and discussed their Stage 1 experience with them. Based on those assessments and previous conversations with the participant, the psychiatrist determined if the participant could continue into Stage 2.

Eligible participants who agreed to proceed to Stage 2 received a dose of SPL026 on the morning of Day 15 and remained resident on the ward until the following morning (Day 16). Participants who did not proceed to Stage 2 were discharged on Day 14 or 15, having completed their predose and selected follow-up procedures. All participants had follow-up assessments by telephone or video call on Day 22 (1 week after the second dose, if applicable).

Visit 4 and final follow-up: participants who received a Stage 2 dose at Visit 3 returned to the ward 14 days after that dose (Day 29) for follow-up assessments (they could request to have those assessments via video call). Participants who did not have a Stage 2 dose had their Day 29 follow-up assessments via video call.

All participants had further follow-up assessments by video call at 1 month (Day 45 ± 2 days), and 3 months (Day 105 ± 2 days) after the Visit 3 dosing day or equivalent (Day 15). Participants could have an optional follow-up assessment at 6 months after visit 3, for exploratory purposes.

Study procedures

Definitions of study procedures are given in Table S2.

Table S2: Study procedure definitions

Term	Definition
Pre-screening	Correspondence, telephone and/or video calls to determine a volunteer's suitability for the trial. Consent to be contacted about the trial, and for the study psychiatrist to contact a participant's GP, were obtained.
Screening day	An outpatient visit held during the screening period, including giving informed consent, standard screening procedures, group or individual *preparation sessions*, and the *psychiatric interview*.
Preparation session	Held on the screening day and the day before dosing. Volunteers received advice on what to expect and how to respond to the psychedelic experience. Volunteers were also familiarised with the setting and study staff.
Dosing room	The clinical dosing room was set up and decorated according to best practice principles for psychedelic studies, including soft lighting, soft furnishings, and nature pictures. Each dosing room had a dedicated therapist team (either 2 therapists, or 1 psychiatrist and 1 therapist). Additional personnel present included clinical staff supervising dosing and PK sampling.
Psychiatric interview	Held on the screening day. Volunteers were assessed for their suitability to participate in the trial in a structured psychiatric interview.
Final preparation session (Part B)	Held on the day of dosing. Participants were advised on how to benefit from the psychedelic experience. The study therapist suggested a symbolic or metaphorical interpretation of the experience to be used as a guide.
Integration session	An ongoing interaction with the study therapist, beginning immediately upon cessation of the psychedelic experience in the participant. The participant was encouraged to discuss their experience with the study therapist. The session took the form of an interview in the first instance and was continued on an ad hoc basis (comprising several activities described in the study procedures manual) until the participant was discharged from the ward. Participants were also given the opportunity to draw their experience. The psychiatrist and/or therapist used the first postdose integration session to assess the tolerability of the psychedelic experience.
Subjective experience evaluation	Participants completed psychometric scales (Table S3) before the first interview of the postdose integration session with the exception of the intensity rating visual analogue scale, which was done by the participant and psychiatrist or therapist after the postdose integration session.

Additional detail is available in the study procedures manual.

Number of participants

Planned: up to 76 participants, excluding replacements (≤ 40 healthy, psychedelic-naïve participants in Part A, and 28–36 participants with MDD in Part B)

Actual: 32 in Part A, and 34 in Part B

Diagnosis and main criteria for inclusion

Normotensive male or female, aged ≥ 25 years (Part A) or ≥ 18 years (Part B), deemed healthy on the basis of a clinical history, physical examination, electrocardiogram (ECG), vital signs, laboratory tests of blood and urine, Mini-International Neuropsychiatric Interview (MINI) and Beck Scale for Suicidal Ideation (BSS); with veins deemed to be suitable for cannulation (IV infusion and blood sampling); willing to follow the contraception requirements of the trial; willing to refrain from psychedelic drug use (excluding the study

drug) during the trial and for ≥ 3 months afterwards; willing to be contacted by email and video call, and had online access; and gave fully informed written consent.

Part A only: psychedelic-naïve, ie had never taken a serotonergic psychedelic drug, in any form.

Part B only: participants with MDD who were otherwise healthy; had tried at least 2 standard of care MDD treatment options, to which they did not respond sufficiently; willing to discontinue antidepressant medication before and during the study; no psychedelic drug use during the 6 months before dosing.

Test and reference products, dose, mode of administration and batch numbers

Healthy participants in Part A received a single dose of SPL026 or placebo, given by IV infusion. Doses were administered as a 2-phase IV infusion through a venous cannula over 10 min. In Part A, all doses were administered by a registered nurse, in the presence of at least 1 therapist and 1 psychiatrist.

Participants with MDD in Part B received a single dose of SPL026 or placebo in Stage 1 and a single dose of SPL026 in Stage 2. The dose and infusion regimen for participants in Part B were decided based on the outcome of Part A. Doses were administered as a 2-phase IV infusion through a venous cannula over 10 min. All doses were administered by a registered nurse, in the presence of at least 1 therapist. A psychiatrist was in close attendance but not necessarily present in the dosing room for the duration of dosing.

The drug product was presented as a clear, colourless to pale yellow solution, in 10 mL clear glass vials containing 2.5 mg/mL (as free base) SPL026 in 10 mL aqueous sterile solution (batch number [redacted]. The placebo solution consisted of the same ingredients as the SPL026 drug product formulation, minus the active ingredient (batch number [redacted]); the ratio of those ingredients was slightly different to ensure the same pH and osmolality. The placebo and active treatments for each group were similar in appearance, with very slight differences in colour. The HMR Pharmacy transferred SPL026 drug product and placebo directly to syringes ready for administration. For each participant's dose, the syringe was filled to the correct volume and then covered with tape to obscure any difference in colour between the active drug and placebo solutions.

The initial shelf life of both SPL026 solution and placebo solution was 4 months, when stored in the clinical trial packaging, at 2–8°C. There were several extensions to the shelf-life of both the SPL026 solution and SPL026 placebo solution used in this study; at the time of writing, the most recent extension was to October 2022.

Duration of treatment

In Part A, each healthy participant received a single dose of SPL026 or placebo.

In Part B, participants with MDD received up to 2 single doses of SPL026: a single dose of SPL026 or placebo in Stage 1, and a single dose of SPL026 in Stage 2. 5 participants did not receive a dose in Stage 2 (4 received SPL026 and 1 received placebo in Stage 1).

Criteria for evaluation and endpoints

Safety and tolerability: Laboratory assessments (routine haematology, clinical chemistry, coagulation and urinalysis), physical examinations, 12-lead ECG, vital signs (blood pressure, pulse rate, and body temperature) were done before, during, and frequently after dosing until (final) discharge from the clinical unit. Adverse events (AEs) were recorded from screening until the participant's last follow-up assessment. Tolerability assessments were completed during the postdose integration interview. The BSS was done at screening and frequently during the study, and scores were received at follow-up.

Efficacy: Participants with MDD in Part B were evaluated with the MADRS, Beck Depression Inventory II (BDI-II), and Spielberger's State-Trait Anxiety Inventory TRAIT subscale (STAI-T) at baseline, after each dosing, and at multiple timepoints up to Day 105 (see Table S3).

Pharmacodynamics: Psychometric scales to assess the quality of a participant's psychedelic experience and outcomes were applied before and at regular intervals (up to 90 days in Part A, and up to 105 days in Part B) after dosing (see Table S3). Electroencephalograms (EEGs) were recorded in healthy participants in Part A from up to 90 min before and until 4 h after dosing (with a pause for participant integration).

Table S3: Psychometric scale, depression rating scale, and questionnaire endpoints

Assessment	Part A endpoint	Part B endpoint
Safety measures		
Beck Scale for Suicidal Ideation (BSS)	Primary	Secondary
Outcome measures (Efficacy, Part B only)		
Montgomery–Åsberg Depression Rating Scale (MADRS) (2 weeks after the first dose)	N/A	Primary
MADRS (1 week after the first dose; 1 and 2 weeks after the second dose)	N/A	Secondary
Beck Depression Inventory II	N/A	Secondary
Spielberger's State-Trait Anxiety Inventory TRAIT subscale (STAI-T)	N/A	Secondary
Outcome measures (PD)		
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	Secondary	Secondary
STAI-T	Secondary	N/A
The Brief Experiential Avoidance Questionnaire (BEAQ)	Secondary	Secondary
Profile of Mood States (POMS)	Secondary	Secondary

Assessment	Part A endpoint	Part B endpoint
Openness enriched 64-item Big Five Inventory (BFI)	Secondary	Secondary
The Gratitude Questionnaire Six-Item Form (GQ-6)	Secondary	Secondary
Snaith Hamilton Anhedonia Pleasure Scale (SHAPS)	Secondary	Secondary
Flourishing Scale (FS-8)	Secondary	Secondary
Life Orientation Test (LOT)	Secondary	Secondary
Meaning in Life Questionnaire (MLQ)	Secondary	Secondary
Brief Resilience Scale (BRS)	Secondary	Secondary
Dysfunctional Attitude Scale (DAS)	Secondary	Secondary
Ruminative Responses Scale (RRS)	N/A	Secondary
Barrett Impulsivity Scale (BIS)	Secondary	Secondary
Social Connectedness Scale (SCS)	Secondary	Secondary
Comprehensive assessment of Acceptance and Commitment (CompACT) Scale	Secondary	Secondary
Work and Social Adjustment Scale (WSAS)	N/A	Secondary
Metaphysical Beliefs Scale (MBS)	Exploratory	Exploratory
Watts Connectedness Scale (WCS)	Exploratory	Exploratory
Psychological Insight Scale	Exploratory	Exploratory
Post-treatment Changes Scale (PTCS)	Exploratory	Exploratory
Predictor measures		
The Psychedelic Predictor Scale (PPS)	Exploratory	Exploratory
Subjective experience evaluation (acute effects)		
Mystical Experience Questionnaire (MEQ)	Secondary	Secondary
The Ego Dissolution Inventory (EDI)	Secondary	Secondary
Emotional Breakthrough Inventory (EBI)	Secondary	Secondary
Challenging Experience Questionnaire (CEQ)	Secondary	Secondary
5 Dimension Altered States of Consciousness Questionnaire (5D-ASCQ)	Exploratory	Exploratory
Exploratory visual analogue scales (VAS) (includes participant-led and physician-led Intensity Rating VAS [IRVAS])	Exploratory	Exploratory

Assessment	Part A endpoint	Part B endpoint
Metaphysical Experience Questionnaire	Exploratory	Exploratory

Pharmacokinetics: In Part A, blood samples for assay of DMT (and its metabolites, reported separately) after dosing with SPL026 were taken before, during, and frequently up to 4 h after the start of the infusion. The following PK parameters were derived: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, λ_z, $t_{½}$, CL, V_z, V_{ss} and MRT_{inf}.

In Part B, blood samples for assay of DMT after dosing with SPL026 were taken before infusion, immediately before the end of infusion, and 60 min after the start of infusion. PK parameters were not derived, owing to an insufficient number of PK sample collection timepoints.

Statistical methods

Since Part A of this trial was exploratory, no formal sample size determination was appropriate.

For Part B, determination of sample size was done using an analysis of the sample sizes required to detect a difference between active treatment and placebo in mean change from baseline of MADRS at Day 7[1]. The calculation was based on a 2-sided 2-sample equal-variance t-test conducted at the 5% level of significance and a 1:1 allocation ratio. Based on that analysis, a participant sample size of 28–36 was selected, giving 80–90% power to detect a mean difference of 12.5 in the MADRS score (change from baseline) at Day 14. That difference has been observed in previous studies of related IMPs in similar patient populations.

Safety and tolerability data: Safety and tolerability data were not subjected to formal statistical analysis. All data were summarised using descriptive statistics.

Efficacy data (Part B only): Efficacy data (MADRS, BDI-II, and STAI-T) were summarised using descriptive statistics. MADRS score change from baseline at 1 week (Day 8) and 2 weeks (Day 14) after the first IMP dose were compared between participants who received SPL026 and those who received placebo, using an independent 2-sample t-test. A mixed model for repeated measures (MMRM) was used to compare changes from baseline MADRS score after the first and second dose of SPL026, as described in the statistical analysis plan.

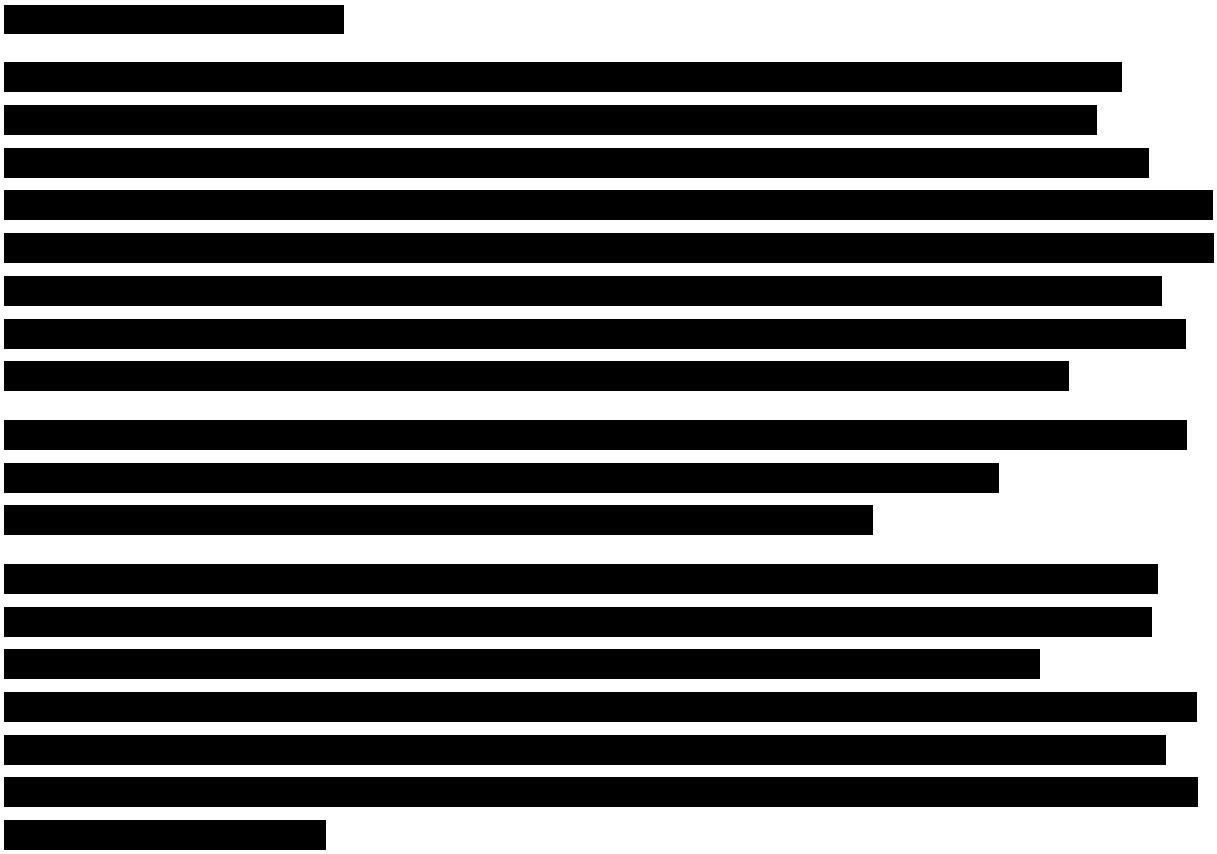
Pharmacodynamic data: PD data were summarised using descriptive statistics. WEMWBS and STAI-T were assessed by analysis of variance (ANOVA) to aid dose selection for Part B.

Pharmacokinetic data: PK concentration and parameters were summarised using descriptive statistics. Dose proportionality of the PK of DMT from SPL026 in plasma was assessed using the power model. For the dose-dependent parameters AUC_{last}, AUC_{inf}, and C_{max}, dose

[1] Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, et al. 2019. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med. 49: 655–63

proportionality was concluded if the 90% confidence interval of the slope (log PK parameter versus log dose) included 1.0.

Results



Safety and tolerability

Part A

Overall, single IV doses of 9–21.5 mg SPL026 were safe and well-tolerated in psychedelic-naïve healthy men and women. There were no deaths, non-fatal serious AEs, other significant AEs, or AEs leading to participant withdrawal. All treatment-emergent adverse events (TEAEs) were mild or moderate in severity (Table S4). There were no clinically significant physical examination findings, laboratory variables, or ECGs.

Table S4: Overall summary of healthy participants with treatment-emergent adverse events (Part A)

	Placebo (N=8)	SPL026				All participants (N=32)
		9 mg (N=6)	12 mg (N=6)	17 mg (N=6)	21.5 mg (N=6)	
Participants with	n (%) [number of TEAEs]					
Any TEAE	6 (75.0) [9]	5 (83.3) [9]	5 (83.3) [12]	5 (83.3) [14]	4 (66.7) [6]	25 (78.1) [50]
Any serious TEAE	0	0	0	0	0	0
Any drug-related TEAE	1 (12.5) [1]	2 (33.3) [2]	4 (66.7) [8]	5 (83.3) [10]	1 (16.7) [1]	13 (40.6) [22]

	Placebo (N=8)	SPL026				All participants (N=32)
		9 mg (N=6)	12 mg (N=6)	17 mg (N=6)	21.5 mg (N=6)	
Participants with	n (%) [number of TEAEs]					
Any TEAE leading to withdrawal	0	0	0	0	0	0
Any TEAE with mild as worst severity	4 (50.0)	3 (50.0)	4 (66.7)	4 (66.7)	4 (66.7)	19 (59.4)
Any TEAE with moderate as worst severity	2 (25.0)	2 (33.3)	1 (16.7)	1 (16.7)	0	6 (18.8)
Any TEAE with severe as worst severity	0	0	0	0	0	0

N: total number of participants; n: number of participants with a TEAE; TEAE: treatment-emergent adverse event.

78.1% of healthy participants had at least 1 treatment-emergent AE (50 TEAEs in total) in similar proportions after SPL026 (79.2% across all dose levels) and placebo (75.0%). Of those, 40.6% of participants had at least 1 TEAE considered by the investigator to be at least possibly related to treatment, in a higher proportion of participants who received SPL026 (50.0%) than those who received placebo (12.5%).

The most frequently reported system organ class of TEAE considered possibly related to treatment, recorded in 21.9% of participants , was general disorders and administration site conditions, all of which were related to the site of dosing or blood sampling. The most common was mild infusion site pain, recorded in 9.4% of participants and lasting up to 2 min.

There was some evidence of a dose-related effect on TEAE incidence: possibly drug-related TEAEs were recorded in a lower proportion of participants after 9 mg SPL026 (33.3%) than after 12 mg (66.7%) or 17 mg (83.3%). This trend was not seen after 21.5 mg SPL026, in which a similar proportion of participants had drug-related TEAEs (16.7%) as after placebo (12.5%). Because of this finding from the highest dose, and owing to the small sample size, a conclusion of a dose-related effect should be made with caution.

DMT has been previously shown to cause safety effects such as increases in heart rate and blood pressure, headache, and nausea. As such, the instances of possibly drug-related headache and dizziness (in single participants after 17 mg), and increased heart rate (in 2 participantsin after 17 mg), as well as dose-related changes from baseline in systolic and diastolic blood pressure, can be considered expected after SPL026 dosing. The psychiatric disorder TEAEs recorded during the study – including possibly drug-related cases of sleep disorder, euphoric mood, and anxiety – may also be considered expected given the known psychological effects of DMT. Of note, it remains unknown whether the changes in blood pressure and pulse rate that occur after DMT dosing are a direct (physiological) or indirect (psychological) effect.

All healthy participants in Part A tolerated the psychedelic experience, and none said they wished they had not gone through it. Generally, participants said they would consider or be happy to repeat the experience, and many said they would accept a higher dose. Those who did not want to repeat the experience did not regret having it.

Part B

Overall, 1 and 2 single IV doses of 21.5 mg SPL026 were safe and well-tolerated in male and female participants with MDD. There were no deaths or AEs leading to withdrawal from treatment.

1 participant had a non-fatal SAE (a severe forearm fracture caused by a road traffic accident), and 1 participant had an 'otherwise significant' TEAE (viral infection, for which the participant missed her scheduled SPL026 Stage 2 dose, consequently leading to her self-withdrawing from the study). Both AEs were deemed unlikely to be related to treatment by the investigator, and as such of no impact to the outcome of the trial.

The SAE was considered by the investigator to be severe. All other TEAEs in the study were mild or moderate in severity (Table S5). There were no clinically significant physical examination findings, laboratory variables, or ECGs.

Table S5: Overall summary of participants with MDD with treatment-emergent adverse events (Part B)

	Sequence 1		**Sequence 2**		**All participants**
	Stage 1	**Stage 2**	**Stage 1**	**Stage 2**	
	Placebo	**21.5 mg SPL026 after placebo**	**21.5 mg SPL026**	**21.5 mg SPL026 after active**	
Participants with	**(N=17)**	**(N=16)**	**(N=17)**	**(N=13)**	**(N=34)**
	n (%) [number of TEAEs]				
Any TEAE	11 (64.7) [17]	14 (87.5) [38]	16 (94.1) [30]	6 (46.2) [9]	33 (97.1) [94]
Any serious TEAE	0	0	0	1 (7.7) [1]	1 (2.9) [1]
Any drug-related TEAE	4 (23.5) [4]	10 (62.5) [19]	11 (64.7) [21]	3 (23.1) [3]	25 (73.5) [47]
Any drug-related serious TEAE	0	0	0	0	0
Any TEAE leading to withdrawal	0	0	0	0	0
Any TEAE with mild as worst severity	7 (41.2)	5 (31.3)	13 (76.5)	2 (15.4)	16 (47.1)
Any TEAE with moderate as worst severity	4 (23.5)	9 (56.3)	3 (17.6)	3 (23.1)	16 (47.1)
Any TEAE with severe as worst severity	0	0	0	1 (7.7)	1 (2.9)

N: total number of participants; n: number of participants with a TEAE; TEAE: treatment-emergent adverse event.

97.1% of participants with MDD had at least 1 TEAE during the study across both treatment sequences (94 TEAEs in total). Of those, 73.5% of participants had 47 TEAEs considered by the investigator to be possibly related to the study treatment (hereafter referred to as 'drug-

related AEs'). Drug-related TEAEs were reported in a higher proportion of participants after (first) SPL026 dosing (62.5% [Stage 2] and 64.7% [Stage 1]) than after placebo (23.5%), findings indicative of a clear SPL026-related increase in TEAE incidence. Of note, drug-related AEs were recorded in a similar proportion of participants who received a second dose of SPL026 in Stage 2 (23.1%) to those who received placebo.

As observed in Part A, the most frequently reported SOC of drug-related TEAE, recorded in 47.1% of participants with MDD, was general disorders and administration site conditions, all of which were related to the site of dosing or blood sampling; mild injection-site pain and tenderness was variously recorded in ≤ 3 participants. Again, the most common TEAE was mild or moderate infusion site pain, recorded in 44.1% of participants and lasting up to 2 h (except for 1 participant in which it lasted 13 days). Additionally, instances of drug-related headache and nausea, as well as transiently increased pulse rate and blood pressure measurements of PCI recorded in participants with MDD can be considered expected owing to the known effects of DMT. As in Part A, the cardiovascular findings had no clear physiological or psychological cause – they did not correlate with DMT PK or subjective effects, nor with a participants' 'preparedness' (or lack of such) for the dosing experience, as measured by the psychedelic predictor scale.

Drug-related psychiatric disorder TEAEs – including those related to anxiety, insomnia, restlessness, depression, emotional distress, and hallucination – were more prevalent in participants with MDD than healthy participants. As in Part A, these TEAEs may be considered expected given the known psychological effects of DMT, but can also be attributed to participants' individual severity of disease and other associated medical conditions. In those who reported anxiety (14.7% of participants overall; of onset 10 min to 74 days postdose), the TEAE either resolved quickly (within 3 min) or was longer lasting (≤ 83 days). [redacted] Overall, there were no BSS findings considered important or concerning by the investigator.

All participants in Part B tolerated the psychedelic experience, though 1 participant regretted taking a second dose of SPL026. No other participant said they wished they had not undergone the dosing experience.

Efficacy

Part A

Efficacy was not assessed in Part A.

Part B

SPL026 efficacy was assessed using MADRS, BDI-II, and STAI-T.

Mean MADRS scores, including changes from baseline, are summarised in Table S6.

Analysis (t-test) of MADRS difference from placebo in change from baseline after Stage 1 dosing is in Table S7.

Table S6: Summary of Montgomery-Åsberg Depression Rating Scale after single IV doses of 21.5 mg SPL026 in participants with major depressive disorder (Part B)

Treatment	Planned relative time	Mean (SD)	Change from baseline (SD)	% change from baseline (SD)
Placebo (N=17)	Day –1	25.5 (7.25)	–	–
	Day 8*	23.6 (8.29)	–1.9 (6.04)	–6.0 (26.65)
	Day 14	21.9 (10.71)	–3.6 (7.67)	–15.8 (34.52)
21.5 mg SPL026 (Stage 2 after placebo[a]) (N=16)	Day 22†	14.4 (11.72)	–10.6 (12.03)	–40.6 (45.63)
	Day 29	14.4 (10.93)	–10.8 (12.77)	–36.7 (45.86)
	Day 45	11.9 (9.94)	–13.3 (12.93)	–46.9 (46.08)
	Day 105†	9.6 (8.05)	–15.4 (12.21)	–53.7 (43.41)
21.5 mg SPL026 (Stage 1) (N=17)	Day –1	26.3 (6.14)	–	–
	Day 8*	13.3 (10.36)	–12.7 (10.38)	–48.2 (36.33)
	Day 14	15.3 (10.20)	–11.0 (10.11)	–41.0 (35.67)
21.5 mg SPL026 (Stage 2 after active[b]) (N=13)	Day 22ǂ	11.1 (8.53)	–13.4 (9.89)	–52.2 (40.22)
	Day 29ǂ	11.2 (9.49)	–13.3 (11.57)	–50.7 (43.23)
	Day 45ǂ	12.1 (10.29)	–12.4 (13.13)	–45.4 (46.75)
	Day 105ǂ	16.7 (12.26)	–7.8 (13.63)	–28.2 (51.82)

IV: intravenous; N: total number of participants; PD: pharmacodynamic; SD: standard deviation.
[a]: after receiving placebo in Stage 1; [b]: after receiving 21.5 mg SPL026 in Stage 1
* n=16; † n=14; ǂ n=12.

Table S7: Summary of analysis of change from baseline MADRS scores (t-test) after single IV doses of placebo and 21.5 mg SPL026 (Stage 1 dosing) in participants with major depressive disorder (Part B)

	Means		SPL026 – Placebo		P-value
	Placebo	21.5 mg SPL026	Mean	95% CI	
1 week after first dose	–1.938	–12.688	–10.750	(–16.947, –4.553)	0.002
2 weeks after first dose	–3.647	–11.000	–7.353	(–13.624, –1.082)	0.023

CI: confidence interval; IV: intravenous; MADRS: Montgomery Åsberg Depression Rating Scale.

Table S8: Summary of participants with ≥ 50% reduction from baseline of Montgomery-Åsberg Depression Rating Scale scores after 1 or 2 single IV doses of 21.5 mg SPL026 in participants with major depressive disorder (Part B)

Treatment	Total MADRS score ≥ 50% decrease				
	Responder at Day 22	Responder at Day 29	Responder at Day 22 and/or Day 29	Responder at Day 22 and/or Day 29 and Day 45	Responder at Day 22 and/or Day 29, Day 45, and Day 105
	n / m (%)				
21.5 mg SPL026 (Stage 2 after placebo[a]) (N=16)	6 / 14 (42.9)	7 / 16 (43.8)	8 / 16 (50.0)	6 / 16 (37.5)	4 / 14 (28.6)
21.5 mg SPL026 (Stage 2 after active[b]) (N=13)	7 / 12 (58.3)	7 / 12 (58.3)	8 / 12 (66.7)	6 / 12 (50.0)	4 / 12 (33.3)
All participants in Stage 2[*] (N=29)	13 / 26 (50.0)	14 / 28 (50.0)	16 / 28 (57.1)	12 / 28 (42.9)	8 / 26 (30.8)

IV: intravenous; N: total number of participants; n: number of participants; m: number of participants with observations; MADRS: Montgomery Åsberg Depression Rating Scale.
[*] all participants, excluding 4 participants who received SPL026 in Stage 1 and no dose in Stage 2.
[a]: after receiving placebo in Stage 1; [b]: after receiving 21.5 mg SPL026 in Stage 1.

Statistical analysis of MADRS data revealed SPL026 dosing resulted in significantly greater improvements (≤ 48.2% reduction) in participants' depression than placebo at 1 and 2 weeks postdose in Stage 1 ($p \leq 0.023$; Table S7). Additional MADRS analyses comparing 1 versus 2 doses of SPL026 did not reveal conclusive differences (see above). However, some findings, although not statistically confirmed, did suggest 2 successive doses result in a greater improvement than only one (though effects were not always sustained throughout the follow-up period). For example, the proportion of participants designated a 'responder' (≥ 50% decrease in MADRS) in the 2 weeks after Stage 2 dosing was higher after a second SPL026 dose (≤ 58.3%) than after a first dose (following placebo at Stage 1; ≤ 50.0%); and proportions decreased as later timepoints (Days 45 and 105) were included in the analysis (Table S8). The increased number of responders following Stage 2 dosing may be attributed to participants who did not respond to dosing in Stage 1 but did respond in Stage 2, rather than an additive effect of 2 successive doses of SPL026. Further investigation of successive SPL026 dosing may be warranted in the target population.

There was also further evidence of an SPL026-related improvement in participants' depression and anxiety, as measured by BDI-II and STAI-T, respectively. However, these 2 measures were not tested for statistical significance, and so conclusions about such trends should be made with caution.

Pharmacodynamics

Part A

In healthy volunteers, most PD measures used in the study (Table S3) recorded high levels of between-participant variability, making it difficult to draw firm conclusions about the effects of SPL026 dosing. The inherently subjective nature of the various scales and questionnaires used is likely to have contributed to that variability. Furthermore, the population investigated (volunteers who had to be of robust mental and physical health to be eligible for the study) were by definition unlikely to record notable changes in PD outcome measures. Conversely, psychedelic-naïve participants, without any frame of reference, may have also overestimated their responses to the dosing experience. In the event notable changes from baseline were recorded, those could also be attributable to the effect of the psychedelic-assisted therapy experience that enabled individuals to think more carefully about their wellbeing during the trial. Overall, as expected from the intense psychedelic experiences induced by SPL026 (when given with psychological support), there were clear effects on participants' conscious and emotional states when compared with placebo. However, whether those can be said to result in long-lasting improvements in mental wellbeing in this population is unclear for the above reasons.

There was some evidence of an exposure-response relationship, with some correlation between C_{max} and participant scores on psychometric scales and questionnaires. Notable examples included increased IRVAS, MEQ, EDI, and the participants' 'richness of experience' as recorded by exploratory VAS during the psychedelic state. Those trends are likely to require confirmation in a larger sample size.

Because the response to the psychedelic state is so subjective, and seemingly dependent on a participant's personality, psychological mindset, and openness to the experience, the impressions of study therapy team are necessary in understanding the therapeutic potential of SPL026. In their opinion, although all participants were psychedelic-naïve, they varied widely in the aforementioned factors. Some came to the study looking for a mystical experience, and were open and inquisitive, whereas others were more reserved and resistant to the psychedelic state. Consequently, those who were more open were more likely to have an emotional breakthrough experience, and those who were more resistant were more likely to have a challenging experience. Despite the high variation among participants, and the limitations of the small sample size, the therapy team concluded that the 21.5 mg dose was most likely to be effective in participants with MDD. The 21.5 mg dose, and the intense psychedelic state it induces, would better help those participants overcome the cognitive rigidity typical of their condition to allow the most therapeutic benefit. Additionally, participants with MDD were expected to have more psychological resistance to the experience owing to their condition, and would therefore be more likely to require a higher dose.

Using the analysis of the safety, tolerability, PD, PK, and therapy team assessment, 21.5 mg SPL026 was subsequently investigated in participants in Part B of this study.

Part B

In participants with MDD, most PD measures used in the study (Table S3) recorded high levels of between-participant variability, as was seen in healthy volunteers in Part A. Again, this is likely to arise from the subjective nature of the scales and questionnaires. Additionally, baseline scores in many PD measures were more likely to vary in the MDD participant population owing to the differences in individuals' severity of disease. Those observations notwithstanding, notable SPL026-related changes from baseline were recorded in most PD outcome and subjective experience measures, with clear effects on participants' conscious and emotional states (improvements in wellbeing, anxiety, experiential avoidance, anhedonia, rumination, etc) when compared with placebo. There was often little to suggest that 2 doses of SPL026 with supporting therapy resulted in further change in PD outcome measures, but more so in some subjective experiential evaluations (MEQ, EDI, EBI, etc; in which variability was lower in certain treatment sequences). Furthermore, 'complete mystical experiences' were more common in participants who received 2 doses of SPL026. Additionally, more notable post-treatment changes were reported by participants who received SPL026 in Stage 2 after placebo than after 2 successive SPL026 doses, further indicating a potential increased tolerance after 2 SPL026 doses compared with 1 dose.

Overall, participants with MDD felt well prepared for their DMT experience, with those who received 2 SPL026 doses demonstrating greater preparedness after having already experienced it once before. Prior exposure to the psychedelic-assisted therapy experience may also have affected the DMT experience of those who received a second dose. Generally, the DMT experience was more challenging for participants with MDD than for healthy volunteers, largely unchanged by the number of doses received.

Pharmacokinetics

Part A

Selected PK parameters of DMT after dosing with SPL026 are summarised in Table S9.

Table S9: Summary of DMT plasma pharmacokinetic parameters after single IV doses of 9–21.5 mg SPL026 in healthy participants (Part A): PK parameter population

PK parameters		SPL026			
		9 mg (N=5*)	**12 mg (N=6)**	**17 mg (N=5*)**	**21.5 mg (N=6)**
C_{max} (ng/mL)	Mean[a]	20.8	30.6	72.1	62.7
	SD (%CVb)	12.9 (62.1)	18.1 (59.2)	47.1 (65.3)	25.8 (41.2)
	Geo mean[b] (Geo %CVb)	16.5 (100.7)	26.6 (63.8)	56.8 (102.2)	58.2 (44.8)
	Median	25.1	27.9	66.9	58.9
	Range	4.99–34.9	12.7–62.3	16.2–126	29.0–107
T_{max} (min)	Median	9.60	10.5	9.75	9.72
	Range	7.00–11.0	6.03–11.2	9.70–11.3	9.70–11.0

PK parameters		SPL026			
		9 mg (N=5*)	**12 mg (N=6)**	**17 mg (N=5*)**	**21.5 mg (N=6)**
AUC_{last} (min·ng/mL)	Mean[a]	349	451	842	835
	SD (%CVb)	253 (72.4)	229 (50.7)	453 (53.8)	231 (27.7)
	Geo mean[b] (Geo %CVb)	265 (112.1)	405 (54.1)	704 (87.5)	804 (32.1)
	Range	70.7–705	245–755	204–1298	477–1052
AUC_{inf} (min·ng/mL)	Mean[a]	352	455	710	837
	SD (%CVb)	252 (71.6)	229 (50.4)	552 (77.8)	231 (27.6)
	Geo mean[b] (Geo %CVb)	270 (108.0)	409 (53.5)	552[c] (116.1)	806 (32.1)
	Range	75.0–707	249–763	207–1302	478–1054
$t_{½}$ (min)	Mean[a]	12.1	9.50	9.14[c]	12.1
	SD (%CVb)	4.74 (39.3)	4.02 (42.4)	7.22 (79.0)	5.16 (42.6)
	Geo mean[b] (Geo %CVb)	11.2 (46.5)	8.9 (38.9)	7.4 (94.9)	11.2 (47.6)
	Range	5.75–18.3	6.00–17.0	3.52–17.3	6.29–20.3
CL (L/min)	Mean[a]	46.0	32.4	40.8[c]	27.9
	SD (%CVb)	43.6 (94.8)	14.6 (45.1)	36.3 (89.1)	9.65 (34.6)
	Geo mean[b] (Geo %CVb)	33.3 (108.0)	29.3 (53.5)	30.8 (116.1)	26.7 (32.1)
	Range	12.7–120	15.7–48.2	13.1–81.9	20.4–45.0

%CVb = between-participant coefficient of variation; AUC = area under the plasma concentration–time curve; AUC_{inf} = AUC extrapolated to infinity; AUC_{last} = AUC up to the last measurable concentration; C_{max} = maximum (peak) plasma concentration; CL = total clearance from plasma after administration; N = total number of participants ; n = number of participants included in mean value; SD = standard deviation; T_{max} = time of C_{max} relative to the start of infusion; $t_{½}$ = terminal elimination half-life.
* Participants were excluded from the PK concentration and parameter populations owing to dosing errors. As a result, the elimination phase was unclear for 2 participants owing to missing PK samples at 11–30 min.
[a] arithmetic mean; [b] geometric mean; [c] n=3.

In Part A, DMT plasma concentrations after administration of SPL026 were detectable at the first PK sampling timepoint (2 min) after dosing started in all PK analysis population participants. As expected, median T_{max} occurred around the end of the infusion across dosing groups (9.6–10.5 min after dosing started). However, individual T_{max} ranged 6.03–11.3 min, with 3 participants having T_{max} < 9 min (2 after 9 mg and 1 after 12 mg SPL026). This suggests that, in some participants, plasma elimination of DMT (from clearance and tissue distribution) transiently exceeded the infusion rate during the second infusion phase (0.6 mg/min and 1.2 mg/min in the 9 mg and 12 mg SPL026 dosing regimens, respectively).

Systemic exposure, as indicated by C_{max}, AUC_{last} and AUC_{inf} parameters, increased with dose in a dose-proportional manner as determined by the power model: the log (parameter vs dose) slopes for AUC_{last}, AUC_{inf}, and C_{max} were 1.35, 1.24, and 1.58, respectively. Owing to missing AUC_{inf} data in the 17 mg dose group, a sensitivity analysis of the power model omitting data from those participants was conducted. Results of this analysis were: 1.29 (AUC_{last}), 1.28 (AUC_{inf}) and 1.47 (C_{max}). The 90% CI of the slope for each analysis encompassed 1.0, consistent with dose proportionality. However, as 90% CI were wide, this conclusion should be interpreted with caution.

Overall, systemic exposure increased with dose. However, the highest mean C_{max} and AUC_{last}, and the highest variation in those parameters, were recorded in the 17 mg dose group. During the 2–11 min after the start of infusion, the highest mean plasma concentrations were recorded in the 17 mg group compared to the other dose levels. However, during the 13–240 min after the start of infusion, the highest mean plasma concentrations were recorded in the 21.5 mg group. Median DMT plasma concentrations were highest in the 21.5 mg SPL026 group at all timepoints except for at 2, 10 and 11 min, when they were highest in either the 12 mg group (2 min) or the 17 mg group (10 and 11 min). Median C_{max} was similar in the 9 mg and 12 mg groups (25.1 and 27.9 ng/mL, respectively), but increased with dose after 17 mg (66.9 ng/mL) and 21.5 mg SPL026 (58.9 ng/mL). During 2–11 min postdose, 2 participants after 17 mg SPL026 had higher plasma concentrations than other participants in Part A, which likely accounts for the higher median C_{max} in that group. NB. those same participants had missing samples at 13 and 15 min postdose, which may explain why mean plasma concentrations during 13–240 min postdose were conversely lower after 17 mg than 21.5 mg.

Between-participant variation (%CVb) in C_{max} and AUC was moderate to high in all groups.

Elimination of DMT was similar across dosing groups, with a rapid decline in plasma concentration over 3–5 min from the end of infusion, though individual semi-logarithmic plots were variable. Plasma DMT was very low (< 2.5 ng/mL) in all participants by 60 min after the start of infusion across all groups, and was BLQ in all but 1 participant by 240 min.

Arithmetic mean $t_{½}$ was similar across dosing groups (9.1–12.1 min); $t_{½}$ was moderately (and similarly) variable after 9, 12, and 21.5 mg (%CVb 39.3–42.6), and highly variable after 17 mg (%CVb 79.0, n=3 owing to missing data). Visual inspection of individual λ regression lines showed that estimation of λ_Z was poor in many participants. However, variability in PK in this study may in part be explained by the fast elimination of SPL026 by all participants, with the longest individual $t_{½}$ being only 20.3 min. This was expected based on previous investigations of DMT. Owing to the rapid rate of decline in DMT plasma concentration during the distribution/early elimination phase, small time deviations in PK sampling may have contributed to the variability seen in this study.

In summary, these results show that plasma concentrations of DMT increased with dose of SPL026 when given as IV infusion, despite the notable overlap in individual PK profiles across dose levels. Overall, there was evidence for a dose-dependent increase in systemic exposure. However, there was moderate-to-high variability between participants, in part owing to the small sample size and sampling difficulties in several participants. Rapid elimination of DMT from plasma, exacerbated by small deviations in PK sampling timepoints, may have also increased between-participant variability. Hence, an increased sample size would be beneficial to confirm the relationship between dose and PK profile.

Mean plasma concentrations of the DMT metabolite IAA (measured by Pharmaron UK Ltd) were higher than those of DMT, which was also observed in other published studies. The concentrations of IAA and DMT seen in plasma are determined by the clearance and the volume of distribution of SPL026. A lower volume of distribution or clearance of IAA than

of DMT could explain the higher postdose plasma concentrations of IAA compared with SPL026: with a lower volume of distribution, IAA would to a lesser extent than DMT reside in other tissues; and with a lower clearance, it would reside in plasma for a longer period after DMT metabolism. Although plasma concentrations of IAA following SPL026 dosing were higher than endogenous levels measured predose, lifetime exposure to IAA through ingestion and tryptophan catabolism would greatly exceed the post-SPL026 dose concentrations seen in participants from this study.

Part B

DMT plasma concentrations were detectable immediately before the end of SPL026 infusion in all participants with MDD; arithmetic means were: [redacted]ng/mL in participants dosed in Stage 2 after receiving placebo in Stage 1; [redacted]ng/mL in participants dosed in Stage 1; [redacted]ng/mL in participants dosed in Stage 2 after receiving SPL026 in Stage 1. Mean DMT plasma concentrations in participants with MDD were lower than in healthy participants in Part A of this study at the equivalent timepoint. Additionally, DMT plasma concentrations were seemingly lower in participants with MDD who received SPL026 in Stage 2 than in those dosed in Stage 1 ([redacted]ng/mL) and after a second dose in Stage 2. However, between-variability was moderate to high across treatment sequences, 6–11 participants had missing PK blood samples (not included if taken outside the time deviation window), and several participants had notably low plasma concentrations on at least one SPL026 dosing occasion. Hence, the above observations should be made with caution.

Elimination of DMT was similar to that recorded in healthy volunteers at the equivalent dose and timepoint. Plasma DMT remained quantifiable (ranging 0.1–5.6 ng/mL) in all but 1 participant at 60 min after the start of SPL026 infusion across all treatment sequences (healthy volunteers at the equivalent dose and timepoint, mean 1.19 ng/mL).

Conclusions

Part A

Safety and tolerability

- Single IV doses of 9–21.5 mg SPL026 (given with psychological support) were safe and well-tolerated in psychedelic-naïve healthy participants. There were no deaths, non-fatal SAEs, other significant AEs, or AEs leading to participant withdrawal. All TEAEs were *mild* or moderate in severity. All TEAEs resolved, and all TEAEs considered to be possibly related to the study drug resolved within 2 days.
- There was some evidence of a dose-related effect on TEAE incidence. Infusion site pain was the most common possibly drug-related TEAE.
- Other reported SPL026-related safety findings in healthy participants, including cardiovascular and psychological effects, may be considered expected based on the known action of DMT.
- There were no clinically significant physical examination findings, laboratory variables, vital signs, or ECGs after SPL026 dosing in healthy participants during the study.

- All healthy participants tolerated the psychedelic experience induced by SPL026, when given with psychological support.

Pharmacodynamics

- Owing to the psychedelic experience induced by 9–21.5 mg SPL026 IV, there were clear effects on participants' conscious and emotional states when compared with placebo.
- There was some evidence of an exposure-response relationship, with some correlation between C_{max} and scores on psychometric scales and questionnaires. Notable examples included increased IRVAS, MEQ, EDI, and the participants' 'richness of experience' during the psychedelic state. Those trends are likely to require confirmation in a larger sample size.
- The high between-participant variability in acute effects scales may in part be explained by variability in systemic exposure to SPL026 seen in individual-participant PK profiles.
- Follow-up outcome measure scales were broadly similar to those at baseline, likely because of the robust psychological states of the population investigated. Hence, no firm conclusions regarding long-term improvements in mental wellbeing could be made.
- In the opinion of the therapy team – and using the analysis of the safety, tolerability, PD, PK – doses of 21.5 mg SPL026 were the most likely to provide an intense psychedelic experience in an individual. Therefore, that dose level was considered most likely to be of therapeutic benefit in the target population of MDD patients.

Pharmacokinetics

- DMT plasma concentrations following administration of SPL026 were detectable at 2 min after the start of infusion, when given as single doses of 9–21.5 mg given as a 10-min IV infusion. Median T_{max} was 9.6, 10.5, 9.75 and 9.72 min after 9, 12, 17, and 21.5 mg SPL026, respectively. Individual T_{max} ranged 6.03–11.3 min, with 3 participants having $T_{max} < 9$ min (2 after 9 mg, and 1 after 12 mg SPL026).
- Overall, there was evidence for a dose-dependent increase in systemic exposure of DMT after SPL026 dosing. Although there was a notable overlap between dose levels in individual PK profiles, mean C_{max} and AUC increased with dose and were generally equal to or greater than dose-proportional. Between-participant variation was moderate to high across all groups. Results of statistical analysis were consistent with dose proportionality although trending towards supra-proportionality; however, wide 90% CI make those results inconclusive.
- Arithmetic mean $t_{½}$ was similar across dosing groups (9.1–12.1 min), but estimation of λ_Z was unreliable in many participants. Although estimation of $t_{½}$ is not likely to be precise, elimination was fast in all participants (individual $t_{½}$ ranged 3.52–20.3 min), as expected based on data from previous investigations of DMT.
- Overall variability in PK in this study was moderate-to-high. This may in part be explained by the fast elimination of DMT by all participants, with the longest individual $t_{½}$ being only 20.3 min. Other factors affecting variability included small sample size, sampling difficulties in several participants, and small time deviations in PK sampling.

- Dosing errors affected the PK in 2 participants in Part A: those were not included in the summary analysis.

Part B

Safety and tolerability

- 1 and 2 single IV doses of 21.5 mg SPL026 (given with supportive therapy) were safe and well tolerated in participants with MDD. There were no deaths or AEs leading to participant withdrawal. 1 participant had a non-fatal SAE (severe forearm fracture), and another had an 'otherwise significant' AE (moderate viral infection), but neither were deemed likely to be related to treatment. All but 2 TEAEs (restlessness and pseudohallucination) were resolved by study end.
- There was evidence of a SPL026-related effect on TEAE incidence.
- Infusion site pain was the most common possibly drug-related TEAE. Drug-related psychiatric disorders (eg anxiety) were more prevalent in participants with MDD than healthy participants, which may be expected owing to the participant population and their associated medical conditions.
- Other reported SPL026-related safety findings in participants with MDD, including cardiovascular and psychological effects, may be considered expected based on the known action of DMT.
- There were no clinically significant physical examination findings, laboratory variables, vital signs, or ECGs after SPL026 dosing in participants with MDD during the study.
- All participants with MDD tolerated the psychedelic experience induced by SPL026, when given with supportive therapy.

Efficacy

- Statistical analysis of MADRS data revealed SPL026 dosing, with supportive therapy, resulted in significantly greater improvements in participants' depression than placebo at 1 and 2 weeks postdose in Stage 1.
- Efficacy findings suggested no difference in the improvement in participants depression and anxiety from 1 dose compared with 2 doses of SPL026 given 2 weeks apart. High between-participant variability recorded in the study, and the inherent subjectivity of the DMT experience, may mean further investigation of such trends is warranted.

Pharmacodynamics

- Owing to the psychedelic experience induced by 21.5 mg SPL026 IV, there were clear effects on participants' conscious and emotional states when compared with placebo. Between-participant variability was high, likely because of the subjective nature of many PD scales and questionnaires.
- There was little to suggest that successive SPL026 doses resulted in further change in PD outcome measures, but more so in some subjective experiential evaluations (MEQ, EDI, EBI); 'complete mystical experiences' (via MEQ) were more common after successive SPL026 doses.

- Generally, the DMT experience was more challenging for participants with MDD than for healthy participants.

Pharmacokinetics

- DMT plasma concentrations in participants with MDD (Part B) were generally lower (mean plasma concentrations ranging [redacted] ng/mL [min– max ranging [redacted] ng/mL] immediately before termination of infusion) than those in healthy participants (Part A) who received the same dose (21.5 mg SPL026) at the equivalent timepoint (mean plasma concentration 62.20 ng/mL [min–max ranging 26.3–107 ng/mL]). Subsequent elimination (60 min postdose) was similar in both populations.