2 Synopsis

Sponsor: Small Pharma	
Name of finished product: SPL026 drug product	**Name of active ingredient:** N,N-dimethyltryptamine (DMT) fumarate
Title: An open-label, cross-over study of intramuscular (IM) and intravenous (IV) doses of SPL026 drug product (DMT fumarate [a serotonergic psychedelic]), in healthy, psychedelic-experienced participants and participants with little to no psychedelic experience	
Investigator: Dr Adeep Puri	
Trial centre: HMR, Cumberland Avenue, Park Royal, London NW10 7EW	
Publication(s): None at the time of this report.	
Trial period: 13 December 2022–07 April 2023	Phase of Development: 1
Date of the report: 12 January 2024	

Objectives

Primary objective

Parts A and B: To assess the safety and tolerability of single doses of SPL026 drug product (DP) given by IM injection in healthy participants.

Secondary objectives

Parts A and B To assess the pharmacokinetics (PK) of single IM and IV doses of SPL026 in healthy participants.

To assess the pharmacodynamics (PD) of single IM and IV doses of SPL026 in healthy participants.

NB. IV doses optional in Part B.

Part A To assess the safety and tolerability of single IV doses of SPL026 in psychedelic-experienced healthy participants.

To compare the safety and tolerability of single IV and IM doses of SPL026 in psychedelic-experienced healthy participants.

To compare the PK of single IV and IM doses of SPL026 in psychedelic-experienced healthy participants.

To compare the PD of single IV and IM doses of SPL026 in psychedelic-experienced healthy participants.

Part B (optional) To assess the safety and tolerability of single IV doses of SPL026 in psychedelic-experienced healthy participants.

Methods

This was a Phase 1, open-label study to investigate the safety, tolerability, PD, and PK of SPL026 DP. The study was in 2 parts, as follows.

- Part A was a crossover group study in psychedelic-experienced healthy participants who received a single IM dose of SPL026 followed by a single IV dose 2–3 weeks later.
- Part B was a study in healthy participants with little to no psychedelic experience. Participants could receive a single IM or IV dose of SPL026; the dose and route of administration was determined based on emerging results from Part A. In the event, 1 group received a single IM dose of SPL026.

Part A

In Part A, 6 psychedelic-experienced healthy participants were enrolled in a single group (Group A1), as planned. Participants received a single dose of SPL026 (DMT fumarate) on 2 occasions: once by IM injection into the ventrogluteal muscle (Session 1), and a second time about 2–3 weeks later by IV infusion (Session 2).

The planned and actual doses of SPL026 are in Table S1.

Table S1: Planned and actual doses in Part A

Session	Route	Planned dose*	Actual dose*	
1	IM	[redacted] SPL026 given as an IM injection	Participants 1001 and 1002	[redacted] SPL026 IM
			Participants 1003–1006	[redacted] SPL026 IM
2	IV	27.5 mg SPL026 given as a single IV infusion over 10 min	27.5 mg SPL026 given as a single infusion over 10 min	

IM = intramuscular; IV = intravenous. IM doses were administered into the ventrogluteal muscle.
* Dose refers to free base DMT.
The planned Session 1 IM dose for Participants 1003–1006 could be changed based on emerging data. Doses were modelled to achieve the same plasma concentrations as selected doses in the CT026_001 study.

Since only 1 participant was dosed per day for the entire study, the first participant (at each dose level) acted as a sentinel for the remaining participants in their group. Provided the investigator considered the safety and tolerability in the sentinel participant to have been acceptable, the remaining participants in that group were dosed at least 23 h later. All participants were dosed at least 24 h apart.

Part B

In Part B, enrolment of up to 24 healthy participants with little to no psychedelic experience was planned in up to 3 cohorts (Groups B1–B3). Group B1 was to receive a single dose of SPL026 DP by IM injection into the ventrogluteal muscle in one study session. Additional dose levels, given via IM injection or IV infusion, may have been explored in 2 optional

groups (Cohorts B2 and B3), as described in protocol. In the event, only Group B1 was enrolled and dosed.

Dosing in Part B did not start until dosing in Part A was complete. Doses in Part B were selected after review by the safety review group (SRG) of all the available results from Part A. The dose selected for Part B Group B1 was [redacted] SPL026 IM.

The sponsor intended that the dose selected for Part B should be one that induced a psychedelic experience deemed to be clinically relevant for the future target patient population. However, a higher IM dose than used in Part A could only be selected in Part B if the SRG deemed the Part A IM dose to be safe and tolerable, and the plasma concentrations of SPL026 were predicted to remain below the limits stated in the protocol.

Because the IM dose chosen in Part B was higher than that tested in Part A, dosing was staggered such that 1 sentinel participant was dosed first. All participants were dosed at least 24 h apart.

All study parts

Administration of SPL026 elicits a psychedelic experience in participants that lasts about 25 min following IV administration [redacted]. Following the end of the psychedelic experience elicited by SPL026, psychometric scales* were administered to determine the quality of the participant's psychedelic experience. Once those were completed, the therapy team began the integration session (Table S2). During that integration interview the therapy team asked questions to determine the details of the participant's subjective psychedelic experience including the tolerability of the psychedelic experience. The definitive question asked of the participants to assess tolerability was: 'Do you wish you had not gone through that experience?'. Participants also completed psychometric scales at baseline and remotely at follow-up.

* see Table S3; with the exception of the intensity rating visual analogue scale (IRVAS) which was done after integration (see Table S2).

Study visits

Participants were screened during the 4 weeks before their first dose of trial medication. In addition to screening assessments, participants had an individual psychiatric interview (including the Mini-International Neuropsychiatric Interview [MINI] screen) with the study psychiatrist, and a preparation session with the therapy team (Table S2).

Participants had 2 study sessions (Part A) or 1 study session (Part B).

In each session, participants were resident on the ward from Day –1 (the day before dosing) until the day of dosing (Day 1), or until the day after dosing (Day 2) if the therapy team (comprised of at least 1 therapist who could also have been a qualified psychiatrist), clinical team, or study participant requested an additional night on the ward. Participants had refresher preparation sessions on Day –1 and predose on Day 1.

Participants had a telephone assessment at 7 days (± 1 day) after dosing, at which they reported any adverse events (AEs) since discharge from the ward. They had a follow-up assessment via video call at about 14 days (± 2 days) after their (final) dose.

The end of the trial was defined as the final follow-up visit by the last participant.

Study procedures

Definitions of study procedures are given in Table S2.

Table S2: Study procedure definitions

Term	Definition
Screening day	An outpatient visit held during the screening period to include giving informed consent, standard screening procedures, group or individual *preparation sessions*, and the *psychiatric interview*.
Preparation sessions	Held on the screening day, the day before dosing (Day –1) and dosing day (Day 1 [predose]). Participants received advice on what to expect and how to respond to the psychedelic experience. Participants 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 therapy team (of at least 1 therapist). Additional personnel present included clinical staff supervising dosing and pharmacokinetic sampling.
Psychiatric interview	Held on the screening day. Participants were assessed for their suitability to participate in the trial in a structured psychiatric interview.
Integration session	An ongoing interaction with the therapy team began upon cessation of the psychedelic experience in the participant on Day 1. The participant was encouraged to discuss their experience with the study therapy team. The session took the form of an interview in the first instance. Participants had a second integration session on the afternoon of Day 2. The therapy team used the first postdose integration session to assess the participant's tolerability of the psychedelic experience.
Subjective experience evaluation	Participants completed psychometric scales before the first interview of the postdose integration session with the exception of the intensity rating visual analogue scale (IRVAS), which was done by participant and psychiatrist or therapist after the first postdose integration session.

Subjective phenomena induced by SPL026 DP during the psychedelic experience were captured during postdose integration sessions and using PD scales and questionnaires (see Table S3).

Number of participants

Planned: ≤ 30 healthy participants, excluding replacements (≤ 6 psychedelic-experienced participants [Part A], and ≤ 24 participants with little to no psychedelic experience [Part B]).

Actual: 14 (6 in Part A, and 8 in Part B)

Diagnosis and main criteria for inclusion

Normotensive men and women, aged 25–65 years, with a body mass index 18.0–33.9 kg/m^2, who were deemed healthy on the basis of a medical history, physical examination, electrocardiogram (ECG), and clinical laboratory evaluations, 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 until follow-up; willing to be contacted by email and video call, and had online access; and gave fully informed written consent.

Part A only: psychedelic experienced (defined as having at least 2 previous experiences with breakthrough after taking serotonergic psychedelic drugs); no psychedelic drug use within 6 weeks before dosing.

Part B only: little to no psychedelic experience (defined as having never taken serotonergic psychedelic drugs, or only taken sub-breakthrough doses < 5 times); no psychedelic drug use within 6 months before dosing.

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

Each participant in Part A received 2 single doses of SPL026: an IM dose into the ventrogluteal muscle and an IV dose administered as a single IV infusion over 10 min.

Each participant in Part B Group B1 received a single IM dose of SPL026 into the ventrogluteal muscle.

All doses were administered by a registered nurse who remained in the dosing room until the psychedelic experience was complete. Dosing was done in the presence of at least 1 therapist; a psychiatrist and/or physician was in close attendance but not necessarily present in the dosing room for the duration of dosing. Another trained clinical staff member was present to observe dosing and collect blood samples.

SPL026 drug product was presented for use in the trial as follows.

- SPL026 IM 25 drug product was a clear, colourless to pale brown solution in 5 mL clear glass vials (containing 25 mg/mL [as free base] SPL026 in 5 mL of an aqueous sterile solution)
- SPL026 IV 2.5 drug product was 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 of an aqueous sterile solution).

The initial shelf life of both SPL026 IM 25 and SPL026 IV 2.5 was 12 months, when stored in the clinical trial packaging at 2–8°C. There were no extensions to the shelf-life. However, the shelf-life of SPL026 IV 2.5 (which was also used in study CT026_001) was extended several times before use in the present study; the latest extension was to October 2023.

Duration of treatment

In Part A, each participant received 2 single doses of SPL026: by IM injection in Session 1, and by IV infusion in Session 2.

In Part B, each participant received a single dose of SPL026 by IM injection.

Criteria for evaluation and endpoints

Safety and tolerability: Laboratory assessments (routine haematology, clinical chemistry, coagulation, and urinalysis), physical examination, 12-lead ECG, vital signs (pulse rate, blood

pressure, and body temperature) were done before, during, and frequently after dosing until (final) discharge from the clinical unit. BSS was done at screening, baseline, and at follow-up. Adverse events (AEs) were recorded from screening until the participant's last follow-up assessment. Tolerability assessments were completed during the (first) postdose integration interview.

Pharmacokinetics: blood samples to assay plasma concentrations of DMT and (optionally) its metabolites were taken before, during, and frequently up to 2 h after the start of IV infusion and up to 4 h after the IM dose had been administered. The following PK parameters were derived: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, λ_z, $t_{½}$ and MRT_{inf}; CL, V_z, and V_{ss} (IV dosing only); CL/F and V_Z/F (IM dosing only).

Pharmacodynamics: Psychometric scales to assess the intensity and quality of a participant's psychedelic experience and outcomes were applied before (baseline) and after dosing (postdose on Day 1 and at follow-up; see Table S3).

Continuous Holter ECG recording was done before and after dosing.

Table S3: Psychometric scale and questionnaire endpoints

Assessment	Part A and B endpoints
Safety measures	
Beck Scale for Suicidal Ideation (BSS)	Primary (intramuscular [IM] doses) and secondary (intravenous [IV] doses)
Predictive measures	
The Psychedelic Predictor Scale	Secondary
Outcome measures (pharmacodynamics [PD])	
The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	Secondary
Spielberger's State-Trait Anxiety Inventory, Trait subscale (STAI-T)	Secondary
Post-treatment Changes Scale (PTCS)	Secondary
Subjective experience evaluation (acute effects)	
Mystical Experience Questionnaire (MEQ)	Secondary
The Ego Dissolution Inventory (EDI)	Secondary
Emotional Breakthrough Inventory (EBI)	Secondary
Challenging Experience Questionnaire (CEQ)	Secondary
Exploratory visual analogue scales (VAS) participant	Secondary
Intensity rating VAS (includes participant-led and physician-led)	Secondary

Statistical methods

The trial was hypothesis generating, so no formal calculation of sample size was appropriate.

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

Pharmacokinetic data: PK concentration and parameters were summarised using descriptive statistics.

Pharmacodynamic data: PD data were summarised using descriptive statistics.

Results

Safety and tolerability

Overall, single doses of [redacted] SPL026 IM, and single doses of 27.5 mg SPL026 IV, were safe and well-tolerated in healthy participants. There were no deaths, non-fatal serious AEs (SAEs), other significant AEs, or AEs leading to participant withdrawal from treatment. All treatment emergent AEs (TEAEs) were mild or moderate in severity (Table S4). There were no clinically significant physical examination findings, laboratory variables, vital signs, or ECGs, or positive findings on the shortened BSS.

57.1% of participants had at least 1 TEAE (19 TEAEs in total). Of those, 50.0% of participants had at least 1 TEAE considered by the investigator to be possibly drug-related (hereafter referred to as 'drug-related'). Drug-related AEs were recorded in similar proportions across dosing groups and routes of administration (with the exception of [redacted] SPL026 IM, after which no participant had a TEAE). In Part A, the most frequently reported system organ class (SOC) of drug-related AE (recorded in 33.3% and 50.0% of participants after IM and IV dosing, respectively) was general disorders and administration site conditions; all drug-related AEs were single instances per preferred term (PT) and related to the site of dosing. In Part B, the most frequently reported SOC of drug-related AE was psychiatric disorders, comprising single instances of hypnopompic hallucination and sleep disorder in the same participant.

In part owing to the small sample size, there was little conclusive evidence of a dose- or mode of administration-related effect on TEAE incidence: no participants had drug-related AEs after [redacted] SPL026 IM, compared with 50% after [redacted] SPL026 IM (2 AEs) and 27.5 mg SPL026 IV (4 AEs), and 37.5% after [redacted] SPL026 IM (5 AEs).

DMT has been previously shown to cause cardiovascular effects. During this study, some raised blood pressure and heart rates of potential clinical importance (PCI) were reported, though none was deemed clinically significant by the investigator. As such, those can be considered expected after SPL026 dosing. Additionally, psychiatric disorder TEAEs recorded during the study – including drug-related abnormal dreams, hypnopompic hallucination, and sleep disorder – may also be considered expected given the known psychological effects of DMT. Lastly, TEAEs of anticipatory anxiety, although not deemed drug-related, could be considered foreseeable given participants' expectations of a psychedelic experience (although largely participants were considered well prepared).

All participants tolerated the psychedelic experience, and no participant who was asked said they wished they had not gone through it. It was observed that participants who had both IM and IV doses felt that their experience after the IV dose was more intense or challenging than the IM dose, though acute endpoint results were similar between participants who received 27.5 mg SPL026 IV and [redacted] SPL026 IM. How participants felt may in part be because of the rapid rise in plasma DMT to T_{max} and C_{max} that occurred after IV dosing; however, it may also be a result of the low IM dose tested in Part A.

Table S4: Overall summary of participants with treatment-emergent adverse events

	Part A				Part B	All participants
	[redacted] SPL026 IM (N=2)	[redacted] SPL026 IM (N=4)	[redacted] SPL026 IM (N=6)	27.5 mg SPL026 IV (N=6)	[redacted] SPL026 IM (N=8)	(N=14)
Participants with	n (%) [number of TEAEs]					
Any TEAE	0	4 (100.0) [7]	4 (66.7) [7]	3 (50.0) [7]	3 (37.5) [5]	8 (57.1) [19]
Any serious TEAE	0	0	0	0	0	0
Any drug-related TEAE	0	2 (50.0) [2]	2 (33.3) [2]	3 (50.0) [4]	3 (37.5) [5]	7 (50.0) [11]
Any drug-related serious TEAE	0	0	0	0	0	0
Any TEAE with mild as worst severity	0	3 (75.0)	3 (50.0)	2 (33.3)	2 (25.0)	5 (35.7)
Any TEAE with moderate as worst severity	0	1 (25.0)	1 (16.7)	1 (16.7)	1 (12.5)	3 (21.4)
Any TEAE with severe as worst severity	0	0	0	0	0	0
Any TEAE leading to withdrawal	0	0	0	0	0	0

N = total number of participants; n = number of participants with a TEAE; TEAE = treatment-emergent adverse event; IV = intravenous; IM = intramuscular.

Pharmacokinetics

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

Table S5: Summary of plasma pharmacokinetic parameters after single IM or IV doses of [redacted] SPL026 in healthy participants

PK parameters		SPL026			
		[redacted] IM SPL026 (N=2)	[redacted] IM SPL026 (N=4)	27.5 mg IV SPL026 (N=6)	[redacted] IM SPL026 (N=8)
C_{max} (ng/mL)	Mean[a]	[redacted]	[redacted]	82.2	[redacted]
	SD (%CVb)	[redacted]	[redacted]	52.3 (63.6)	[redacted]
	Geo mean[b] (%CVb)	[redacted]	[redacted]	68.8 (76.0)	[redacted]
	Median	[redacted]	[redacted]	69.5	[redacted]
	Range	[redacted]	[redacted]	24.9–171.0	[redacted]
T_{max} (min)	Median	[redacted]	[redacted]	10.0	[redacted]
	Range	[redacted]	[redacted]	9.87–10.7	[redacted]
AUC_{last} (min·ng/mL)	Mean[a]	[redacted]	[redacted]	1,081	[redacted]
	SD (%CVb)	[redacted]	[redacted]	669 (61.9)	[redacted]
	Geo mean[b] (%CVb)	[redacted]	[redacted]	896 (78.3)	[redacted]
	Median	[redacted]	[redacted]	967	[redacted]
	Range	[redacted]	[redacted]	384–1,883	[redacted]
$t_{½}$ (min)	Mean[b]	[redacted]	[redacted]	13.0	[redacted]
	SD (%CV_b)	[redacted]	[redacted]	5.60 (42.9)	[redacted]
	Geo mean[b] (Geo %CVb)	[redacted]	[redacted]	12.0 (49.1)	[redacted]
	Range	[redacted]	[redacted]	5.78–20.9	[redacted]
CL or CL/F* (L/min)	Mean[b]	[redacted]	[redacted]	36.8	[redacted]
	SD (%CV_b)	[redacted]	[redacted]	23.2 (63.1)	[redacted]
	Geo mean[b] (Geo %CVb)	[redacted]	[redacted]	30.5 (77.5)	[redacted]
	Range	[redacted]	[redacted]	14.6–70.2	[redacted]

PK parameters		SPL026			
		[redacted] IM SPL026 (N=2)	[redacted] IM SPL026 (N=4)	27.5 mg IV SPL026 (N=6)	[redacted] IM SPL026 (N=8)
V_z or V_z/F* (L)	Mean[b]	[redacted]	[redacted]	582	[redacted]
	SD (%CV_b)	[redacted]	[redacted]	279 (48.0)	[redacted]
	Geo mean[b] (Geo %CVb)	[redacted]	[redacted]	528 (51.8)	[redacted]
	Range	[redacted]	[redacted]	270–935	[redacted]
MRT_{inf} (min)	Mean[b]	[redacted]	[redacted]	10.4	[redacted]
	SD (%CV_b)	[redacted]	[redacted]	3.78 (36.2)	[redacted]
	Geo mean[b] (Geo %CVb)	[redacted]	[redacted]	9.92 (35.7)	[redacted]
	Range	[redacted]	[redacted]	6.73–15.3	[redacted]

N = number of participants receiving treatment; SD = standard deviation; %CV_b = between-subject coefficient of variation; AUC_{last} = AUC from time 0 to the last measurable timepoint; AUC_{inf} = AUC from time 0 to infinity (extrapolated); C_{max} = maximum observed plasma concentration; t_{max} = time relative to dosing at which C_{max} was observed; λ_Z = terminal elimination rate constant; $t_{½}$ = terminal elimination half-life; CL = total clearance from plasma after IV administration; V_z = apparent volume of distribution after IV administration; V_{ss} = apparent volume of distribution at steady state; CL/F = systemic clearance relative to absolute bioavailability; MRT_{inf} = mean residence time extrapolated to infinity; IV = intravenous; IM = intramuscular.
[a] geometric mean; [b] arithmetic mean; * CL/F and V_z/F for IM doses; CL and V_z for IV doses.

IM dosing

[redacted]

IV dosing

DMT plasma concentrations after 27.5 mg SPL026 IV were detectable at the first PK sampling timepoint (2 min after dosing start) in all participants. As expected, median T_{max} occurred around the end of the infusion (10.0 min after dosing started) in all participants.

After 27.5 mg SPL026 IV, geometric mean C_{max}, AUC_{last} and AUC_{inf} were 68.8 ng/mL, 1,081 min·ng/mL and 1,085 min·ng/mL, respectively. [redacted]

After 27.5 mg SPL026 IV, DMT elimination also showed some evidence of biphasic elimination. Arithmetic mean $t_{½}$ (13.0 min; individual range 5.8–20.9 min) [redacted], and estimation of λ_Z was adequate in all participants.

Overall, SPL026 PK after IV dosing – primarily C_{max}, AUC, and $t_{½}$, but also MRT_{inf}, clearance and volume of distribution – were within expectations based on the results of study CT026_001, in which healthy participants received near-equivalent doses (21.5 mg) via the same route of administration.

Overall conclusions

[redacted] However, the small sample sizes investigated, moderate to high variability between participants, and the rapid elimination of DMT by all participants (which may have exacerbated between-participant variability) mean such conclusions should be made with caution.

Pharmacodynamics

Between-participant variability recorded in many PD measures, combined with the small sample sizes involved, make it difficult to draw firm conclusions about the effects of SPL026 with regard to route of administration.

The populations investigated (volunteers who had to be of robust mental and physical health to be eligible for the study) were not expected to record notable changes in PD outcome measures – consequently, there were few detectable changes in participant wellbeing (WEMWBS) and the impact of SPL026 on participants' anxiety (STAI-T) was ultimately inconclusive. Participants with little to no psychedelic experience (Part B), without any frame of reference, may have overestimated their responses to the dosing experience. Conversely, psychedelic-experienced participants (Part A) may have minimised their experiences in the present study compared with previous psychedelic experiences. In any case, responses to psychedelic experiences are known to be highly subjective, and as such likely to yield highly

variable results in qualitative measures. Notable changes from baseline may also be attributable to the psychedelic-assisted therapy experience that enabled individuals to think more carefully about their wellbeing during the trial.

As expected from the psychedelic experience induced by SPL026, there were clear effects on participants' conscious and emotional states following IM or IV doses. Although MEQ and EDI varied with dose and mode of administration, 27.5 mg IV appeared to yield similar results to [redacted] IM in both measures when certain outlying participants were disregarded. For example, 'complete mystical experiences' (as determined by the MEQ) were recorded in a similar number of participants at each dose level. Also, there was some evidence to suggest that the psychedelic experience was of the greatest quality or intensity when induced by IV infusion (primarily), or by the highest IM doses (to a lesser extent).

Participants felt well prepared for their DMT experience, with no clear difference between participants with psychedelic experience and those with little to none. Most participants did not find the psychedelic experience challenging. The few notable post-treatment changes were positive in nature.

There was little evidence to suggest a correlation between C_{max} and combined IRVAS. Although all participants in Part A had notably higher C_{max} and combined IRVAS score after their IV dose compared with their IM dose, there was no clear evidence of any correlation in participants who received only [redacted] SPL026 IM in Part B. Additionally, it isn't possible to determine a correlation between C_{max} and PTCS, as score changes of +3 were reported by only 2 participants who had notably different C_{max} values.

Conclusions

Safety and tolerability

- Single doses of [redacted] SPL026 IM and 27.5 mg IV were safe and well-tolerated in 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.
- There was little evidence of a dose-or mode of administration-related effect on TEAE incidence. The most common drug-related TEAEs were related to the site of dosing (after IM injection) or psychiatric disorders (single instances of hypnopompic hallucination and sleep disorder; after IV infusion).
- 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, or positive findings on the shortened BSS, after IM or IV SPL026 dosing in healthy participants.
- All participants tolerated the psychedelic experience induced by SPL026 given with psychological support.

Pharmacokinetics

- DMT plasma concentrations were detectable at [redacted] (IM doses) and 2 min (IV) after the start of dosing. Median T_{max} was [redacted] 10.0 min (end of infusion; range 9.87–10.7 min) after 27.5 mg IV.
- [redacted] IV exposure was broadly as expected given previous experience in healthy participants using the same mode of administration.
- [redacted] Estimation of λ_Z was adequate in all participants, with $R^2 > 0.88$ in all participants. [redacted] Decline in DMT plasma concentration was faster from the peak until about 60 min postdose than afterwards, suggestive of biphasic elimination.

Pharmacodynamics

- Between-participant variability was high in most PD measures, likely influenced by the small sample sizes investigated and the inherently subjective nature of the psychedelic experience.
- There were few reliable findings in outcome measure scales, likely because of the robust psychological states of the population investigated.
- There were clear effects on participants' conscious and emotional states following dosing with either SPL026 IM or IV. Most measures varied with dose and mode of administration. However, there was some evidence that MEQ and EDI findings were similar after 27.5 mg IV and [redacted] IM; 'complete mystical experiences' were reported by similar numbers of participants after each dose level.
- Generally, participants were well prepared for their psychedelic experience, and most did not find it challenging. The few notable post-treatment changes recorded were positive in nature.