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Safety, blood levels and effects of N,N-dimethyltryptamine [DMT (SPL026)] in healthy participants that have taken psychedelic substances before (Part A) and in healthy participants with little to no psychedelic experience (Part B)

Submission date	Recruitment status	[_] Prospectively registered
19/01/2024	No longer recruiting	[_] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
26/02/2024	Completed	[X] Results
Last Edited	Condition category	[_] Individual participant data
20/03/2024	Other	

Plain English summary of protocol

Background and study aims

This is a study of N, N-dimethyltryptamine (DMT) – a psychedelic substance that occurs naturally in many plants and animals. Psychedelic substances, also known as hallucinogens, act on the brain causing temporary changes to perception, sensations, and emotions, which can be intense. DMT is best known for being the main psychedelic substance in ayahuasca (a hallucinogenic brew that has been used for centuries in religious ceremonies in some South American countries). This study is testing DMT (the study medicine, also known as SPL026, which has been manufactured for this study) as an experimental treatment for mental health conditions, including Major Depressive Disorder (MDD). This study has two parts, to find out the effects and blood levels of DMT in healthy volunteers that have taken psychedelic substances before (Part A) and in healthy volunteers with little to no psychedelic experience (Part B).

The aim is to answer these questions:

1. Are single doses of DMT safe and well tolerated when given by injection into a muscle and slow injection into a vein?
2. How much DMT gets into the bloodstream, and how long does the body take to get rid of it when given by injection into a muscle and slow injection into a vein?
3. What are the effects of DMT, when given by injection into a muscle or slow injection into a vein, on mood, feelings, and thoughts?

Who can participate?

Part A: healthy volunteers aged 25 to 65 years who have had at least two previous 'breakthrough' experiences (a 'breakthrough' experience is defined as an immersive and intense experience in which almost all connection to the real world is lost) with serotonergic psychedelic drugs, including DMT, LSD, psilocybin ('magic mushrooms'), or another psychedelic

Part B: healthy volunteers aged 25 to 65 years with little to no psychedelic experience, i.e., have never taken a serotonergic psychedelic drug, or have only taken sub-breakthrough doses of a serotonergic psychedelic drug, in any form, less than five times.

What does the study involve?
Part A:
The participant will take up to about 5 weeks to finish the study. During the 4 weeks before starting the study, they will undergo screening to determine suitability. If deemed suitable, the participant will be one of up to 6 volunteers in a single cohort in Part A. There will be 2 study sessions, approximately 2–3 weeks apart. In each session, the participant will stay on the ward for up to 3 days and 2 nights. After leaving the ward on Day 1 (the day of receiving the dose), a video call will be scheduled for the next day (Day 2). In the first study session (Session 1), the participant will receive a dose of up to 25 mg of DMT injected into a muscle on the side of the buttocks near the hip (ventrogluteal muscle). The experience is expected to last about 1 hour. In Session 1, the first 2 volunteers dosed will receive 20 mg of DMT, and based on their results, the dose for the remaining 4 volunteers in the cohort will be determined (either increased to 25 mg or decreased to 15 mg). Before receiving the DMT dose, the participant will be informed of the dose and asked for consent. In the second study session (Session 2), the participant will receive a 27.5 mg dose of DMT by slow injection into a vein in the arm over a period of 10 minutes. The experience is expected to last around 20 minutes. Doses will be administered in a quiet, private room on the ward, with a registered nurse, therapist, and another trained clinical team member present during dosing and the psychedelic experience. Before dosing, the participant will be shown the ward and dosing room, meet the study staff, and receive advice on what to expect from the psychedelic experience. A follow-up video call will be conducted about 2 weeks after the final dose.

Part B:
The participant will take up to about 2 weeks to finish the study. During the 4 weeks before starting the study, they will undergo screening to determine suitability. If deemed suitable, the participant will be one of up to 8 volunteers in a single cohort in Part B. There will be 1 study session, where the participant will stay on the ward for up to 3 days and 2 nights. After leaving the ward on Day 1 (the day of receiving the dose), a video call will be scheduled for the next day (Day 2). The dose of DMT (administered by injection into a muscle on the side of the buttocks near the hip [ventrogluteal muscle]) will be given in a quiet, private room on the ward. A registered nurse, therapist, and another trained clinical team member will be present during dosing and the psychedelic experience. Before dosing, the participant will be shown the ward and dosing room, meet the study staff, and receive advice on what to expect from the psychedelic experience. A follow-up video call will be conducted about 2 weeks after the final dose.

What are the possible risks and benefits of participating?
The participant will receive a dose of DMT that is likely to induce a psychedelic experience or 'trip,' lasting about 1 hour when administered by injection into a muscle and approximately 20 minutes when injected into a vein. Potential experiences may include visual imagery or hallucinations, a sense of detachment from thoughts or feelings, changes in time and space perception, out-of-body experiences, disorientation, confusion, anxiety, and intense emotions such as happiness or grief. Unpleasant images, sounds, and the reliving of painful memories may also occur. In published research on psychedelic treatments for depression, challenging emotions and upsetting content during the 'trip' are considered therapeutically beneficial, leading to valuable insights. The participant will be supported by expert therapist(s) to prepare for and process any experiences during the trip. If an unpleasant experience arises, the study doctor may administer a licensed medicine to help relax the participant. The nurse administering

the dose, the study therapist, and the psychiatrist are all trained in psychedelic trials. Before participating, the expectations of a psychedelic trip and how to respond (on the ward and after returning home) will be explained, and an interview with a psychiatrist will ensure suitability. Close monitoring by a nurse, therapist, psychiatrist, and/or doctor will occur during and after the dose. The study therapist will discuss the participant's experience before and after the dose. The experience with DMT might lead to a changed perspective on oneself and life; therefore, life-changing decisions are advised against for 6 weeks after the last dose. In clinical studies, physical effects such as increased blood pressure, elevated heart rate, nausea, and headaches were observed, with continuous monitoring of heart rate and blood pressure throughout the study. There is a risk of an unexpected, serious reaction to the study medicine, potentially life-threatening. Pregnant individuals or those planning to become pregnant should not participate, and immediate notification is required if pregnancy is suspected. The study medicine may affect concentration or judgment, prohibiting driving or operating machinery for 24 hours post-dose. Close monitoring of symptoms is encouraged, and any concerns or questions should be communicated to the study team. Medical benefits from the study medicine are not expected. Screening tests may provide reassurance about good health or identify treatable medical problems, but unexpected findings might lead to a referral to a GP for counseling and follow-up. Participants contribute to medical research, but continued use of the study medicine after the study is prohibited due to its classification as a Class A illegal drug. The study results will be owned by the sponsor, potentially having commercial or intellectual property value, and the participant will not receive financial benefits arising from the study.

Where is the study run from?
Hammersmith Medicines Research Limited (UK)

When is the study starting and how long is it expected to run for?
May 2022 to April 2023

Who is funding the study?
Cybin UK Ltd (formally called Small Pharma Ltd) (UK)

Who is the main contact?
Ellen James, ellen@cybin.com

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05644093

Clinical Trials Information System (CTIS)
2022-002775-10

Integrated Research Application System (IRAS)
1006227

Protocol serial number
CT026_003

Study information

Scientific 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 subjects (Part A: IM and IV doses) and subjects with little to no psychedelic experience (Part B: IM dose only)

Study objectives
SPL026 given IV or IM is safe and well tolerated in healthy participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/10/2022, Wales Research Ethics Committee 1 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0) 2920785738; wales.REC1@wales.nhs.uk), ref: 22/WA/0216

Primary study design
Interventional

Study design
Open-label study

Study type(s)
Safety

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
SPL026 (dimethyltryptamine fumarate) by intramuscular injection and intravenous infusion. Single dose or two single doses, 2-3 weeks apart.

Part A: crossover group study in psychedelic-experienced healthy participants (up to 6 participants), single IM dose of SPL026 (planned dose of 20 mg) followed by a single IV dose (27.5 mg) of SPL026 between 2-3 weeks later.

Part B: a study of healthy participants with little to no psychedelic experience (up to 24 participants) who will receive a single IM or IV dose of SPL026 (the dose and route of administration for each group will be determined based on the results from Part A and previous groups in Part B with the same route of administration).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
SPL026 (N,N-dimethyltryptamine fumarate; DMT)

Primary outcome(s)
Safety and tolerability of single doses of SPL026 DP given by intramuscular (IM) injection in healthy participants, assessed using adverse events, laboratory values, and tolerability assessments. Data collected over at least 2 weeks.

Key secondary outcome(s)
1. Safety and tolerability of single doses of SPL026 Drug Product (DP) given by intravenous (IV) infusion in healthy participants, assessed using adverse events, laboratory values, and tolerability assessments. Data collected over at least 2 weeks.
2. Pharmacokinetics of IV infusion measured using frequent blood sampling from pre-dose to 2 hours post-dose
3. Pharmacokinetics of IM infusion measured using frequent blood sampling from pre-dose to 4 hours post-dose
4. Pharmacodynamics (PD) – Wellbeing assessed using the Warwick–Edinburgh Mental Well-being Scale (WEMWBS) on day -1 and day 15 of the second dosing session
5. PD – Anxiety assessed using the State-Trait Anxiety Inventory (STAI-T) on day -1 and day 15 of the second dosing session
6. PD – Post-treatment changes assessed using Post-Treatment Changes Scale (PTCS) at 15 days of the second dosing session
7. PD – Subjective experience assessed using the Mystical Experience Questionnaire (MEQ), Ego Dissolution Inventory
(EDI), Emotional Breakthrough Inventory (EBI), Challenging Experience Questionnaire (CEQ) post-dose (before the first post-dose integration session) visual analogue scale (VAS) post-dose (after the first post-dose integration session)
8. PD – Arrhythmia measured using continuous 12-lead Holter ECG on Day -1, pre-dose, during-dosing, until at least 10 min after the 4 h (IM) and 2h (IV) post-dose PK blood sample

Completion date
05/04/2023

Eligibility

Key inclusion criteria

Part A only:
1. Healthy psychedelic-experienced female or male participants (psychedelic-experienced is defined as having at least two previous experiences, with breakthrough, of serotonergic psychedelic drugs, including but not limited to: DMT, ayahausca, LSD, LSA [morning glory seeds], DOI [2,5-Dimethoxy-4- iodoamphetamine], DOB [dimethoxybromoamphetamine], DOC [2,5-Dimethoxy-4-chloroamphetamine], 2CB [2-(4-bromo-2,5- dimethoxyphenyl)ethanamine], 2CE [1-(2,5-Dimethoxy-4-ethylphenyl)-2- aminoethane], mescaline, peyote, san pedro, ibogaine and psilocybin [including mushroom species containing psilocybin])
2. No psychedelic drug use within 6 weeks prior to dosing

Part B only:
3. Healthy female or male participants with little to no psychedelic experience (defined as having never taken serotonergic psychedelic drugs, or have only taken sub-breakthrough doses of serotonergic psychedelic drugs, in any form, <5 times, including but not limited to: DMT, ayahuasca, LSD, LSA, DOI, DOB, DOC, 2CB, 2CE, mescaline, peyote, san pedro, ibogaine and psilocybin [including mushroom species containing psilocybin])
4. No psychedelic drug use within 6 months prior to dosing

Parts A and B:
5. Aged 25-65 years
6. A body mass index (BMI; Quetelet index) in the range 18.0-33.9 kg/m2
7. Sufficient intelligence to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial
8. Willingness to give written consent to participate after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate
9. Agree to follow the contraception requirements of the trial
10. Agree not to donate blood or blood products during the study and for up to 3 months after the (last) administration of the trial medication
11. Willing to refrain from psychedelic drug use (excluding the study drug) during the trial and until the follow-up call
12. Willingness to give written consent to have data entered into the Overvolunteering Prevention System (TOPS)
13. Willing to be contacted by email and video call, and have online access
14. Has veins deemed suitable for cannulation (IV infusion and/or blood sampling)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
25 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
14

Key exclusion criteria
1. Current or previously diagnosed mental health disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria
2. First degree relative with schizophrenia spectrum or other psychotic disorders, or bipolar and related disorders.
3. Disposition judged by the investigator (or delegate) to be incompatible with the establishment of rapport with therapy team and/or safe exposure to DMT.
4. Woman who is pregnant or lactating, or pre-menopausal woman who is sexually active and not using a reliable method of contraception (see section 11).
5. Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the participant.
6. Presence of acute or chronic illness, condition or infection, or history of chronic illness or condition (including psychological and neurological [eg seizure] disorder) considered sufficient to invalidate the participant's participation in the trial or make it unnecessarily hazardous.
7. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease or any of the following cardiovascular conditions: arrhythmia, a clinically significant screening ECG abnormality or family history of long QT syndrome or sudden death, artificial heart valve, current or any history of hypertension, or any other significant current or history of cardiovascular condition, that may affect safety in the opinion of the investigator.
8. History of serious suicide attempts (ie those that require hospitalisation); as assessed by the BSS.
9. Presence or history of severe adverse reaction to any drug or a history of sensitivity to serotonergic psychedelic drugs.
10. Use of a prescription medicine (except oral contraceptives or any hormone therapy), certain herbal supplements (eg St John's Wort, to be reviewed by trial physician), or over-the-counter medicine, during the 28 days before the first dose of trial medication. Use of acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (eg ibuprofen) is permitted up to 4 h before the first dose of trial medication.
11. Receipt of an investigational product (including prescription medicines) as part of another clinical trial within the 3 months before (first) admission to this study; in the follow-up period of another clinical trial at the time of screening for this study.
12. Presence or history of drug or alcohol abuse, or intake of more than 14 units of alcohol weekly.
13. Daily cannabis use or cannabis dependence as defined by ICD10.
14. Use of cannabis in the 24 h before each study visit.
15. Evidence of drug abuse on urine testing (with the exception of cannabis).
16. Unable to be nicotine-free (refrain from smoking or nicotine-containing products) for 24 h before and until the morning after dosing.
17. Blood pressure and pulse rate in the supine and standing position at the screening examination outside the ranges: blood pressure 80-150 mm Hg systolic; 30-100 mm Hg diastolic; pulse rate 40-100 beats/min. Borderline values (i.e. values that are within 5 mm Hg of the range for blood pressure or 5 beats/min of the range for pulse rate) will be repeated. Participants can be included if the repeat value is within range or still borderline but deemed not clinically significant by the investigator.

18. QTcF value at screening greater than 450 msec (men) or 470 msec (women) on 12-lead ECG. Triplicate measurements will be made, and a mean QTcF value higher than 450 msec (men) or 470 msec (women) will lead to exclusion. A repeat (in triplicate) is allowed on one occasion for determination of eligibility.
19. Possibility that the participant will not cooperate with the requirements of the protocol.
20. Positive test for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
21. Loss of more than 400 mL blood during the 3 months before the trial, eg as a blood donor.
22. Phobia of needles or blood.
23. Objection by General Practitioner (GP) to participant entering the trial.

Date of first enrolment
03/01/2023

Date of final enrolment
22/03/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hammersmith Medicines Research Limited
Cumberland Avenue
London
United Kingdom
NW10 7EW

Sponsor information

Organisation
Cybin UK Ltd

Funder(s)

Funder type
Industry

Funder Name
Cybin UK Ltd

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to commercial sensitivity.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other unpublished results	version 1	12/01/2024	20/03/2024	No	No