A 3-part study to investigate the safety, pharmacodynamics and pharmacokinetics of increasing doses of intravenously administered N,N-dimethyltryptamine (DMT) and deuterated DMT (CYB004) in healthy smokers and non-smokers

Published: 17-01-2022
Last updated: 05-04-2024

Part A:- Evaluate the safety of increasing doses of a single dose continuous DMT infusion over 90 minutes in healthy smokers - Characterize the pharmacokinetics of a single dose DMT administered continuously over 90 minutes in healthy smokers -...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54291

Source
ToetsingOnline

Brief title
Safety, PK and PD of DMT and CYB004 in healthy smokers and non-smokers

Condition

- Other condition
- Mood disorders and disturbances NEC

Synonym

1 - A 3-part study to investigate the safety, pharmacodynamics and pharmacokinetics ... 13-05-2025

nicotine dependence, smoking

Health condition

Substance use disorders: Tobacco and Nicotine Addiction

Research involving
Human

Sponsors and support

Primary sponsor: Cybin IRL Limited
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: continuous infusion, DMT, PK-PD

Outcome measures

Primary outcome

Part A:

- Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit.

- Concomitant medication throughout the study at every study visit.

- Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)) as per assessment schedule.

- Clinical laboratory tests (Hematology, blood chemistry and urinalysis) as per assessment schedule.

- ECG parameters (Heart Rate (HR) (bpm), PR, QRS, QT, QTcB, QTcF) as per assessment schedule.

- Occurrence of psychotic symptoms as measured with the BPRS.

- Occurrence of central serotonergic toxicity as measured with the Hunter criteria.

- Occurrence of suicidal thoughts and ideations (CSSRS).

- Plasma concentrations of DMT.

- PK parameters: AUCinf, AUClast, CL, Cmax, t1/2, tmax, Vz, Vss.

- Dose-normalized PK parameters: AUCinf, AUClast, Cmax.

- Neurocart test battery

• Saccadic eye movements:

o saccadic reaction time (second),

o saccadic peak velocity (degrees/second), and

o saccadic inaccuracy (%);

• Smooth pursuit eye movements:

o percentage of time the eyes of the subjects are in smooth pursuit of the

target (%);

• Body sway:

o antero-posterior sway (mm);

• Adaptive tracking:

o average performance (%);

• Visual Analog Scales (VAS) according to Bond and Lader to assess:

o mood (mm),

o alertness (mm), and

o calmness (mm).

• VAS Bowdle to assess:

o subjective psychedelic effects (mm).

• VAS Drug Rating to assess:

o positive or negative drug effect (mm).

- Changes in subjective psychedelic. experience rating scales that include the HRS, MEQ and 5D-ASC administered retrospectively.

- Changes in intensity score (from the Real-time Intensity Scale) from baseline to the end of infusion.

- Serum ACTH, cortisol and prolactin.

- DMT plasma concentrations.

- Changes in intensity score from baseline to the end of infusion.

- Changes in subjective psychedelic experience rating scales that include the HRS, MEQ and 5D-ASC administered retrospectively.

Part B:

- Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit.

- Concomitant medication throughout the study at every study visit.

- Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)) as per assessment schedule.

- Clinical laboratory tests (Hematology, blood chemistry and urinalysis) as per assessment schedule.

- ECG parameters (Heart Rate (HR) (bpm), PR, QRS, QT, QTcB, QTcF) as per assessment schedule.

- Occurrence of psychotic symptoms as measured with the BPRS.

- Occurrence of central serotonergic toxicity as measured with the Hunter criteria.

- Occurrence of suicidal thoughts and ideations (CSSRS).

Part C:

- Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit.

- Concomitant medication throughout the study at every study visit.

- Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)) as per assessment schedule.

- Clinical laboratory tests (Hematology, blood chemistry and urinalysis) as per assessment schedule.

- ECG parameters (Heart Rate (HR) (bpm), PR, QRS, QT, QTcB, QTcF) as per assessment schedule.

- Occurrence of psychotic symptoms as measured with the BPRS.

- Occurrence of central serotonergic toxicity as measured with the Hunter criteria.

- Occurrence of suicidal thoughts and ideations (CSSRS).

- Neurocart test battery

• Saccadic eye movements:

o saccadic reaction time (second),

o saccadic peak velocity (degrees/second), and

o saccadic inaccuracy (%);

• Smooth pursuit eye movements:

o percentage of time the eyes of the subjects are in smooth pursuit of the

target (%);

• Adaptive tracking:

o average performance (%);

- Visual Analog Scales (VAS) according to Bond and Lader to assess:

• mood (mm),

• alertness (mm), and

• calmness (mm).

- VAS Bowdle to assess:

• subjective psychedelic effects (mm).

- VAS Drug Rating to assess:

• positive or negative drug effect (mm) and

• any drug effects (mm).

- Changes in subjective psychedelic. Experience rating scales that include the

HRS, MEQ and 5D-ASC administered retrospectively.

- Changes in intensity score (from the Real-time Intensity Scale) from

baseline to the end of infusion.

- Serum ACTH, cortisol and prolactin.

- PK parameters: AUCinf, AUClast, CL, Cmax, t1/2, tmax, Vz, Vss.

- Dose-normalized PK parameters: AUCinf, AUClast, Cmax.

Secondary outcome

NA only exploratory

Study description

Background summary

Over the last three decades, there has been a resurgence of interest in the potential application of central nervous system active compounds that induce psychedelic, dissociative, and entactogenic effects in various mental and addiction-related disorders. N,N-dimethyltryptamine (DMT) is a naturally occurring psychoactive compound. DMT is a potent agonist at the 5-HT2A receptor, through which (not unlike other serotonergic psychedelics), it exerts many of its subjective, visual, and potentially therapeutic effects.When administered intravenously as a bolus injection, CNS effects of DMT peak within 2-5 minutes and dissipate rapidly, with effects returning to baseline (or close to) following roughly 30 minutes post administration. However, one drawback of IV administration of DMT is its high, and up until now largely unexplained, variability in PK in humans. Several strategies are being developed to decrease this variability, one of which is deuteration of the DMT molecule, which entails the selective replacement of protium hydrogen (1H) isotope atoms with deuterium hydrogen (2H) isotope atoms. This deuteration is anticipated to improve the pharmacokinetic profile of DMT whilst maintaining pharmacodynamic effects. Therefore, Cybin IRL limited has developed CYB004, in which 10 protium hydrogen atoms are substituted with 10 deuterium atoms. Preclinical data shows that CYB004 exhibited a similar in vitro and in vivo pharmacology as DMT, but an increased exposure and delayed metabolism in dogs after intravenous (IV) administration. Consequently, CYB004 could have higher potential for clinical application when compared to DMT.
As nicotine addiction is associated with a high mortality rate and efficacious pharmacological treatment is lacking, smoking cessation following DMT and therefore potentially also CYB004 administration is a potentially promising clinical research area. Observational studies, anecdotal reports, and ceremonial use of 5-HT2A receptor agonists such psilocybin and ayahuasca were associated with reduced smoking behaviour. Since DMT and CYB004 are also 5-HT2A agonists, there is potential for clinical interest in both compounds as a novel smoking cessation therapies. In addition, both DMT and CYB004 may have clinical benefits in other psychiatric disorders including mood and anxiety disorders. However, prior to exploring the clinical efficacy of DMT and CYB004 in nicotine users or other populations, it is crucial to establish their safety profile and, pharmacokinetic-pharmacodynamic (PK-PD) relationship at increasing doses, as well as the most optimal infusion scheme to induce sustained psychedelic effects in smoking and non-smoking subjects.

Study objective

Part A:
- Evaluate the safety of increasing doses of a single dose continuous DMT

infusion over 90 minutes in healthy smokers
- Characterize the pharmacokinetics of a single dose DMT administered continuously over 90 minutes in healthy smokers
- Characterize the pharmacodynamics of a single dose DMT administered continuously over 90 minutes in healthy smokers
- Establish the minimum DMT dose required to produce moderate subjective psychedelic effect

Part B:
- Confirm the safety of increasing doses of DMT administered IV over 60 minutes (5 minute bolus followed by a 55 minute continuous infusion) in healthy non-smokers.

Part C:
• Cohort 1:
o Evaluate the safety of increasing doses of deuterated DMT (CYB004) administered IV over maximally 60 minutes (bolus of maximally 10 minutes followed by a continuous infusion of maximally 55 minutes) in healthy non-smokers.
o Characterize the pharmacokinetics (PK), pharmacodynamics (PD) and PK-PD relationship of increasing doses of CYB004 administered IV over maximally 60 minutes (bolus of maximally 10 minutes followed by a continuous infusion of maximally 55 minutes) in healthy non-smokers.
• Cohort 2 (optional):
o If needed optimize the CYB004 infusion scheme (i.e. duration of administration and/or total dose) of a relevant safe dose identified in cohort 1 in healthy non-smokers

Study design

Part A:
Adaptive ascending single-dose, double-blind, randomized, placebo-controlled design.

Part B:
Open label, fixed order, 2-way crossover rising dose design.

Part C:
Cohort 1: randomized, double-blind, 3-way crossover rising dose, interspersed placebo-controlled design
Cohort 2: optional cohort to optimize the infusion scheme. Randomized, double-blind, 3-way crossover rising dose, interspersed placebo-controlled design

Intervention

Part A
0.12 mg/kg DMT or placebo (0.9% saline)
18.2 mg DMT or placebo (0.9% saline)
36.4 mg DMT or placebo (0.9% saline)
72.8 mg DMT or placebo (0.9% saline)

Part B
Two doses of DMT

Part C
Cohort 1 and 2: Placebo or two doses of CYB004

Study burden and risks

The principal mitigations for potential risks of the study drug are:
- The selection of dose levels that were previously shown to be safe and tolerable in subjects.
- Thorough preparation of the study subjects regarding the trial and selection of subjects that have had a prior experience with hallucinogenic drugs as this is deemed to reduce the risk of negative psychological reactions.
- Selection of subjects that have no prior history of psychiatric illness or family history of psychiatric illness, as this will reduce the chances of subjects developing psychiatric complaints due to the study drug significantly.
- Prespecified safety monitoring procedures.
- The trial facility, where close monitoring can be performed and rapid institution of appropriate care can be given. Potential risks can be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical trial.

In addition to the potential risks associated with study drug administration, there is minimal risk associated with trial procedures including insertion of a canula for withdrawing blood (limited to < 500 mL) and non-invasive procedures including vital sign assessments, electrocardiograms (ECGs) and PD assessments. Overall, the benefit-risk profile is considered appropriate for this trial

Contacts

Public
Cybin IRL Limited

One spencer Dock North Wall quay .
Dublin D01X9R7
IE
Scientific

Cybin IRL Limited

One spencer Dock North Wall quay .
Dublin D01X9R7
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy male and female volunteers.
2. Aged 21 - 60 years inclusive.
3. Part A: Regular use of nicotine (5-10 cigarettes daily).
Part B and C: non-smokers, defined as individuals who have never smoked tobacco or used nicotine or tobacco containing products, or individuals with no use of nicotine or tobacco containing products in the past 2 months.
4. Self-report of at least one prior hallucinogen drug experience that included a meaningful altered state of consciousness (a state in which the subject experienced phenomena that altered his psychological functioning, such as loss of ego boundaries, impaired control of actions and cognition, disembodiment, changed meaning of percepts, visual alterations and audio-visual synesthesia) the past 5 years. Hallucinogenic substances can include psilocybin, LSD, DMT, ayahuasca, mescaline, ibogaine, 2C-drugs (such as 2CB, 2CI and 2CE) and/or ketamine.
5. Participant has a body mass index (BMI) between 18.0 and 30.0 kg/m2 inclusive (BMI=weight/height2).
6. Subject must be healthy based on physical examination, medical history, vital signs, and 12-lead ECG. Minor abnormalities in ECG, which are not considered to be of clinical significance by the investigator, are acceptable.
7. Subjects must be healthy based on clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities to be not clinically

significant. This determination must be recorded in the subject's source documents and initialed by the sub investigator.*
8. Agree to refrain from using any psychoactive drugs, including alcoholic beverages within 24 hours of each drug administration.

Exclusion criteria

1. Subject has a history of or current liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, any inflammatory illness or any other illness, which are considered to be of clinical significance by the investigator.
2. Clinically relevant abnormal history, physical finding,12-lead safety ECG12-lead safety ECG (e.g. PQ/PR interval > 210ms, presence of Left Bundle Branch Block (LBBB), AV Block (second degree or higher), or a permanent pacemaker or implantable cardioverter defibrillator [ICD]), or laboratory value at screening that could interfere with the objectives of the trial or the safety of the volunteer.
3. Subject has a history of or current hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg).
4. Presence or history of cardiovascular disease, including acute coronary syndrome or angina, ischemic disease, ventricular arrhythmias or cardiac transplantation as determined by self-report during review of medical history.
5. Subject has a history of chronic or frequent migraines.
6. Females of childbearing potential with positive urine pregnancy at screening or the day of the first treatment.
7. Subject has a history of drug or alcohol use disorder according to DSM-IV or DSM 5 within the past five years.
8. Subject has a positive test result(s) for alcohol and/or drugs of abuse (including: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, and benzodiazepines) at screening or admission to the clinical unit.*
9. Current or history of any clinically relevant psychiatric disorder as classified according to DSM-IV or DSM 5 (e.g. psychotic disorder e.g. schizophrenia/schizo-affective disorder, bipolar disorder Type I or Type II, personality disorder, major depressive disorder/persistent depressive disorder, obsessive-compulsive disorder, panic disorder, anorexia nervosa, bulimia nervosa, generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD) or autism spectrum disorder (ASD).
10. Family history of a relevant psychiatric disorder in first-degree relatives. Psychiatric history in second degree relatives will be discussed on a case to case basis.
11. Persistent psychological effects following the previous use of psilocybin, LSD, DMT, ayahuasca, mescaline, ibogaine, 2C-drugs (such as 2CB, 2CI and 2CE) and/or ketamine. Such effects might include but are not limited to anxiety,

depressed mood, paranoid ideation and/or hallucinations (including hallucinogen persisting perception disorder - HPPD) or recurrent flash-backs related to use.
12. Risk of suicide, as judged by an Investigator, based upon available source information -including the C-SSRS or family history of suicide -indicating current suicidal ideation or a history of active suicidal ideation or suicide attempts
13. Positive SARS-CoV-2 rapid antigen test analysis prior to first dosing.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-02-2022
Enrollment:	74
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[1-3]. N,N-dimethyltryptamine
Generic name:	DMT
Product type:	Medicine
Brand name:	CYB004
Generic name:	Deuterated DMT

Ethics review

Approved WMO Date:	17-01-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	31-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-005207-12-NL
CCMO	NL79463.056.22