A Two-Part, Adaptive, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose (SAD) Study to Evaluate Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Intravenous and Intramuscular GM-2505 in Healthy Volunteers

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To characterize the safety and tolerability of single intravenous (IV) doses (Part A) and intramuscular (IM) doses (Part B) of GM-2505 in healthy volunteers.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON56273

Source
ToetsingOnline

Brief title
SAD, safety, PK, PD of GM2505 in healthy volunteers

Condition

- Mood disorders and disturbances NEC

Synonym
depression, Major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Gilgamesh Pharmaceuticals
Source(s) of monetary or material Support: Gilgamesh Pharmaceuticals

Intervention

Keyword: Depression, FIH, Healthy volunteers

Outcome measures

Primary outcome

Adverse events, hematology, serum chemistry, urinalysis, vital signs, 12-lead

ECG, occurrence of psychotic symptoms (BPRS), occurrence of suicidal thoughts

and ideations (C-SSRS), occurrence of central serotonergic toxicity (Hunter*s

Serotonin Toxicity Criteria), and safety-EEG (continuous recording)

Secondary outcome

Plasma and urine PK parameters for GM-2505

Urine PK parameters

NeuroCart assessments

Clinical Rating Scales

Other PD parameters

Study description

Background summary

The pharmacological treatment of major depressive disorder (MDD) with currently available antidepressant drugs is characterized by considerable ineffectiveness. A significant proportion of patients with MDD are considered treatment resistant since they fail to recover despite (sequential) treatment

with monoamine modulating drugs, and/or various augmentation strategies with lithium and/or second-generation antipsychotic drugs. In addition, therapeutic effects with conventional antidepressants are only achieved following several weeks of treatment, and patients who do achieve adequate symptomatic relief often experience burdensome adverse effects and/or residual depressive symptoms. Taken together, the development of more effective and rapidly acting antidepressant drugs with favorable side-effect profiles is currently ongoing.

GM-2505 is a novel psychedelic drug currently under development for the treatment of major depressive disorder (MDD). Its in vitro and in vivo pharmacology have been extensively profiled, and supports its primary activity as a 5-HT2A agonist with an approximately 4-fold higher potency than DMT, and to a lesser extent, a 5-HT transporter (SERT) antagonist and low potency reversible inhibitor of monoamine oxidase A (MAO-A). GM-2505 is therefore expected to produce an extended hallucinogenic effect relative to DMT and to evoke molecular mechanisms related to the enhancement of neuroplasticity.

Study objective

To characterize the safety and tolerability of single intravenous (IV) doses (Part A) and intramuscular (IM) doses (Part B) of GM-2505 in healthy volunteers.

Study design

This is a two-part, adaptive, single-ascending dose, randomized, placebo-controlled, double-blind safety and tolerability study of single dose IV infusions (Part A) and single dose IM injections (Part B) of GM-2505, or placebo (saline) in healthy male and female volunteers.

Intervention

GM-2505 or placebo

Study burden and risks

This phase 1 trial has been designed to mitigate the known risks associated with psychedelic drugs and 5-HT agonists and/or 5-HT releasers in general, and the potential risks based on the nonclinical toxicity data GM-2505 in particular. As this trial will be conducted in healthy volunteers, there is no expected clinical benefit to trial participants. The principal mitigations for these potential risks include the maintenance of an appropriate safety margin based on nonclinical study drug exposure, appropriate selection of the trial population, prespecified safety monitoring procedures, and the selection of the trial facility, where close monitoring can be performed and rapid institution

of appropriate care can be given.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy female or male subjects, 18 to 55 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical, surgical a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis. 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.
2. Subject has a body mass index (BMI) between 18.0 and 30.0 kg/m2 inclusive (BMI=weight/height2) at screening.

3. 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 perception, visual alterations, and audio-visual synesthesia) in 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.
4. Subjects must be willing to adhere to the prohibitions and restrictions specified in the protocol, including attending all study visits, preparatory and follow-up sessions, and completing all study evaluations.
5. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose and procedures required for the study and are willing to participate in the study. Agree to refrain from using any psychoactive drugs from 30 days before first dosing and until the last follow-up visit and to refrain from using alcoholic beverages within 48 hours prior to admission of each treatment period.

Exclusion criteria

1. Clinically significant current or previous liver or renal insufficiency, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, metabolic or inflammatory illness, or any other illness that would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements according to the investigator.
3. Subject has a history of or current hypertension (resting systolic blood pressure > 130 mmHg or diastolic blood pressure >90 mmHg) at screening.
5. Resting heart rate (HR) greater than 100 or less than 45 beats per minute (bpm) at screening.
7. Clinically significant personal or familial history of epilepsy, seizures, convulsions, or other seizure disorder (excluding febrile seizures as a child), previous head trauma or other risk factor for seizure.
8. Clinically significant current or previous psychiatric disorder according to DSM 5. Specifically, current or previous psychotic disorders and bipolar disorder will be excluded.
9. Family history of a psychotic disorder (whether in the context of bipolar disorder, schizophrenia or schizoaffective disorder) in first-degree and second-degree relatives.
10. Clinically significant current or previous suicidality based on the C-SSRS and psychiatric history indicating current suicidal ideation or a history of active suicidal ideation or suicide attempts
11. Subject has a current or history of drug or alcohol use disorder according to the to DSM-IV and/or DSM 5 within the past 12 months.
12. Use of psychoactive substances (including ketamine, esketamine, MDMA,

cannabinoids, and nitrous oxide), during the 6 weeks prior to screening. Single/occasional use may be allowed at the discretion of investigator.
13. Ingestion of psychedelics (including psilocybin, DMT/ayahuasca, LSD, another serotonergic psychedelic) during 4 weeks prior to screening.
14. 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 flashbacks related to use.
15. 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.
16. Female subjects with a positive urine pregnancy test or who are lactating at screening or admission to the clinical unit, or women of childbearing potential (WOCBP) who are unwilling to use an effective form of contraception (as defined under lifestyle regulations) for the duration of the study and for 180 days after the last dose.
17. Sexually active male subjects who are unwilling to use an effective form of contraception (as defined under lifestyle regulations) for the duration of the study and for 90 days after the last dose.
18. Use of more than 5 cigarettes (or other tobacco or nicotine products with equivalent nicotine dose) daily within the previous month before the first dose administration, and/or unable or unwilling to not smoke during the in-house periods.
19. Subject has received an investigational drug or used an investigational medical device within 3 months before dosing or are currently enrolled in an investigational study.
20. Subject has known allergies, hypersensitivity, or intolerance to DMT and/or GM-2505 or its excipients (refer to IB).
21. Donation or loss of blood over 500 mL within three months prior to screening.
22. Participant has previously participated in a previous cohort or study part investigating GM-2505

Additional Exclusion Criteria (B only)
23. A Fitzpatrick skin type grade 6, which would preclude the assessment of injection site reactions.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-11-2022
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GM-2505
Generic name:	Not applicable

Ethics review

Approved WMO

Date:	12-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	01-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	08-12-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2023
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	EUCTR2022-003014-37-NL
CCMO	NL82521.056.22