A Three-Part, Adaptive, Randomized, Double blind, Placebo Controlled First in Human Study to Evaluate Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Single and Multiple Ascending Oral Doses of GM-1020 and the Effect of Food on Single Dose GM-1020 in Healthy Volunteers.

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To characterize the safety and tolerability of ascending single oral doses (part A) and ascending repeated oral doses (part B) of GM-1020 and the effect of food on single dose GM-1020 (part C) in healthy volunteers.

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

Summary

ID

NL-OMON53597

Source
ToetsingOnline

Brief title
SAD and MAD safety, PK and PD, PK and Food Effect of GM-1020

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: Pharmaceutical company;Gilgamesh Pharmaceuticals

Intervention

Keyword: Depression, FIH, Healthy volunteers, NMDAr Ant

Outcome measures

Primary outcome

Part A, Part B

Safety and tolerability endpoints:

AE*s, vital signs, 12-lead ECG, , laboratory safety tests (routine

haematology, biochemistry and urinalysis), occurrence of psychotic symptoms

(BPRS),emergence of suicidal thoughts and ideations (CSSRS) modified observer*s

assessment of alertness and sedation scale (MOAA/S), and concomitant

medications.

Part C

Plasma and urine PK endpoints GM-1020 and metabolites

Secondary outcome

Part A

Plasma and urine PK endpoints GM-1020 and metabolites.

PD endpoints: Neurophysiological/neuropsychological test battery (Neurocart);

Rating scales; and behavioral assessments

Part B

Plasma and urine PK endpoints GM-1020 and metabolites.

PD endpoints:

o Visual Analogue Scales Bond and Lader (VAS B&L)

o VAS Bowdle (VAS Bowdle) and VAS Drug rating (subjective drug effects) and

Drug Effects Questionnaire (DEQ)

o Pharmaco-EEG (pEEG)

Rating scales:

o Clinician-Administered Dissociative Symptoms Scale (CADSS)

o 5-Dimension Altered States of Consciousness Rating Scale (5D-ASC)

o Mystical Experiences Questionnaire (MEQ30)

o Real-time intensity scale

behavioral assessments

Part C

Safety and tolerability endpoints

AE*s, vital signs, 12-lead ECG, , laboratory safety tests (routine

haematology, biochemistry and urinalysis), occurrence of psychotic symptoms

(BPRS),emergence of suicidal thoughts and ideations (CSSRS) modified observer*s

assessment of alertness and sedation scale (MOAA/S), and concomitant medications

PD endpoints:

o Visual Analogue Scales Bond and Lader (VAS B&L)

o VAS Bowdle (VAS Bowdle) en Drug Effects Questionnaire (DEQ)

Rating scales:

o Clinician-Administered Dissociative Symptoms Scale (CADSS)

o 5-Dimension Altered States of Consciousness Rating Scale (5D-ASC)

Study description

Background summary

The pharmacological treatment of major depressive disorder (MDD) with currently available antidepressant drugs is characterized by considerable ineffectiveness. 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. In addition, 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. Taken together, the development of more effective and rapidly acting antidepressant drugs with favorable side-effect profiles is needed.

The non-competitive glutamate N-Methyl-D-aspartate receptor (NMDAR) antagonist ketamine exists in two enantiomers (R-) and (S-) ketamine. Racemic (R,S)-ketamine demonstrates robust and rapidly occurring antidepressant efficacy 24h after intravenous (IV) administration in MDD patients that do not respond to monoamine-based drugs. It is therefore unique in terms of mechanism-of-action and onset of antidepressant effects compared to conventional antidepressant drugs

GM-1020 is a novel synthetic arylcyclohexylamine structural analog of arketamine that has been optimized to be orally bioavailable while exhibiting a similar pharmacological profile to (R-)ketamine

Study objective

To characterize the safety and tolerability of ascending single oral doses (part A) and ascending repeated oral doses (part B) of GM-1020 and the effect of food on single dose GM-1020 (part C) in healthy volunteers.

Study design

Part A (single ascending dose (SAD)) of this study will evaluate the safety, PK and PD of ascending single oral doses of GM-1020 by applying a double-blind, randomized, placebo-controlled design in healthy male and female volunteers.

Part B (multiple ascending dose (MAD)) of this study will evaluate the safety, PK and PD of ascending repeated oral doses of GM-1020 by applying a randomized, double-blind, placebo-controlled design in healthy male and female volunteers.

Part C (single dose (SAD)) will consist of an open-label, randomized, 2-period crossover study in healthy male and female volunteers.

Intervention

Part A: single dose of GM-1020 or placebo

Part B: 4 doses of GM-1020 or placebo (every other day in a timespan of 1 week)

Part C: single dose of GM-1020, 2 times

Study burden and risks

The target disease population for future treatment with GM-1020 is MDD patients. Therefore, a study population of healthy volunteers between 18 and 55 years is deemed appropriate for this first-in-human ascending single dose and repeat dose study as these subjects are best to reflect the target population. The population is not expected to derive any benefit from participating in this study. The following effects are anticipated in healthy human subjects in the current study: changes in heart rate and/or blood pressure, shortening of PR and QT interval, changes in appetite, vomiting, tremors, ataxia and dissociative effects. This phase 1 trial has been designed to mitigate the known risks associated with NMDA-receptor antagonists as a class in general and the potential risks based on the nonclinical toxicity data GM-1020 in particular. All study drug administrations will be done in the clinic under medical supervision. The subjects receiving any study drug will remain in the clinic for at least 24 hours after each study drug administration. Thus, the subjects can be closely monitored for any adverse signs during the different treatments. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

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. Subjects must be willing to adhere to the prohibitions and restrictions specified in the protocol, including attending all study visits and completing all study evaluations.

4. 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 current or previous psychiatric disorder according to DSM 5.
8. Family history of a psychotic disorder in first-degree and second-degree relatives.
9. 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
10. Subject has a current or history of drug or alcohol use disorder according to DSM 5 within the past 12 months.
11. Structural use of psychoactive substances (including ketamine, esketamine, MDMA, cannabinoids, or psychedelics) during the 6 weeks prior to screening. Ingestion of psilocybin, DMT, LSD, MDMA, or another serotonergic psychedelic within the last 4 weeks.
12. 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.
13. Subject has a positive test result(s) for alcohol and/or drugs of abuse (including opiates, cocaine, amphetamines, methamphetamines, cannabinoids, ketamine and benzodiazepines) at screening or admission to the clinical unit.

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:	Recruitment stopped
Start date (anticipated):	15-11-2022
Enrollment:	116
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GM-1020
Generic name:	Not applicable

Ethics review

Approved WMO Date:	29-09-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2023
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2023
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	EUCTR2022-003013-11-NL
CCMO	NL82520.056.22