A randomized, double-blind, placebo-controlled, Phase 2b trial with an open-label extension to determine the safety and efficacy of GH001 in patients with treatment-resistant depression.

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To determine the efficacy of a single day individualized dosing regimen (IDR) of GH001 compared with placebo in improving depressive symptoms as assessed by MADRS in patients with treatment-resistant depression (TRD) at the end of the 7-day double-...

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

Summary

ID

NL-OMON53737

Source
ToetsingOnline

Brief title
GH001-TRD-201

Condition

- Mood disorders and disturbances NEC

Synonym
depression, treatment-resistant depression

Research involving
Human

Sponsors and support

Primary sponsor: GH Research Ireland Limited
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: 5-MeO-DMT, GH001, Major depressive disorder, Treatment resistant depression

Outcome measures

Primary outcome

• Mean change in MADRS from Baseline to Day 7.

Secondary outcome

Efficacy assessments

• Clinician-rated scales:

o Clinical Global Impression Severity (CGI-S)

o Hamilton Rating Scale for Anxiety (HAM-A)

• Patient-reported outcome:

o Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form

(Q-LES-Q-SF)

Safety assessments

• Adverse events

• Clinical safety laboratory tests

• Vital signs and weight

• Electrocardiograms (ECGs)

• Physical examinations

• Spirometry

• Columbia-Suicide Severity Rating Scale (C-SSRS)

• Modified Observer*s Assessment of Alertness and Sedation scale (MOAA/S)

• Clinician Administered Dissociative States Scale (CADSS)

• Brief Psychiatric Rating Scale positive symptoms (BPRS+)

• Clinical Assessment of Discharge Readiness (CADR)

• Urine drug and alcohol screen

Psychoactive effect assessments

• Peak Experience Scale (PES)

• 30-item Mystical Experience Questionnaire (MEQ30)

• Challenging Experience Questionnaire (CEQ)

• Psychoactive effects (PsE) duration

Study description

Background summary

Major depressive disorder (MDD) is a serious mental health condition characterized by recurring episodes where feelings of sadness, loss of interest, and other heightened negative emotions occur most of the day, nearly every day. A collaborative study funded by the United States National Institute of Mental Health demonstrated that approximately 37% of patients with MDD did not achieve a response despite 2 treatment steps, a patient population referred to by regulatory authorities as patients with treatment-resistant depression (TRD). Only 2 pharmacotherapies have been approved specifically for the treatment of TRD: esketamine (Spravato®) and a combination of olanzapine and fluoxetine (Symbyax®). The latter is not approved in EU.
mebufotenin is a psychoactive drug from the class of tryptamines with high potency, fast onset (generally within 30 seconds), and short duration

(generally 5 to 30 minutes) of psychedelic effects, with no apparent tachyphylaxis (based on assessment of psychedelic effect intensity) even after short-term re-administration. It can be found in a wide variety of trees and shrubs, as well as in the venom of Bufo alvarius toads. mebufotenin from natural or synthetic sources has a long history of naturalistic use, where its ability to induce altered states of consciousness, often described as *ego-dissolution*, has been applied in spiritual or self-exploratory contexts. Due to significant first pass metabolism via monoamine oxidase A, mebufotenin is not orally active, which is why in naturalistic use it has been most commonly consumed via inhalation after vaporization.
GH001 is an inhalation formulation of synthetic mebufotenin for use with a vaporizer device to form an aerosol for inhalation. The sponsor has completed two Phase 1 trials of GH001 in healthy volunteers (GH001-HV-101 [n = 22] and GH001-HV-103 [n = 46]) and a Phase 1/2 trial in patients with TRD (GH001-TRD-102 [n = 16]). In all trials, administration of GH001 via inhalation was observed to be well-tolerated with no severe or serious adverse events. Efficacy was assessed in GH001-TRD-102, where patients were given GH001 as a single dose (12 mg [n=4] or 18 mg [n=4]) or in an IDR of up to 3 increasing doses (6 mg, 12 mg, and 18 mg [n=8]) on a single day. Applying the IDR, 7/8 patients (87.5%) achieved remission, defined as a MADRS total score of <=10, at the primary endpoint at D7 after GH001 dosing, with a mean MADRS reduction versus baseline of -24.4 (P <0.0001), which was numerically superior to the outcome achieved with single 12 mg and 18 mg doses of GH001 in the single dose part of the GH001-TRD-102 trial, where 2/4 patients (50%) and 1/4 patients (25%) achieved a remission (MADRS <=10) at D7 after dosing, with mean MADRS reductions versus baseline of -21.0 and -12.5, respectively. These efficacy data in patients with TRD support further study of the GH001 IDR in a randomized, controlled setting with larger patient numbers.

Study objective

To determine the efficacy of a single day individualized dosing regimen (IDR) of GH001 compared with placebo in improving depressive symptoms as assessed by MADRS in patients with treatment-resistant depression (TRD) at the end of the 7-day double-blind (DB) Part 1.

Study design

This is a Phase 2b clinical trial in patients with TRD consisting of a screening period of up to 6 weeks prior to Baseline, a 7-day randomized, placebo-controlled, DB Part 1 and a 6-month, single-arm, OLE Part 2. All patients directly transition from Part 1 into Part 2 on Day (D) 7 of the DB Part 1.

Intervention

GH001 is an inhalation formulation of synthetic 5-methoxy-N,N-dimethyltryptamine (mebufotenin, 5-MeO-DMT) for use with a vaporizer device (the Volcano Medic 2 Vaporization System) to form an aerosol for inhalation.
GH001 will be supplied as individually packaged mebufotenin powder in vials and individually packaged absolute (>=99.5% [volume]) alcohol solvent for reconstitution at the clinical site. It is administered as an Individualized dosing regime consisting of up to 3 increasing doses of GH001 (6 mg, 12 mg, and 18 mg) on a single day, where the second and third doses are only administered if the patient did not achieve intense PsE. After reconstitution, the drug product solution is transferred using a pipette to a stainless-steel filling pad within an aluminium dosing capsule. The dosing capsule is then loaded into the filling chamber of a first Volcano Medic 2 vaporizer to evaporate the alcohol at a low temperature and is then transferred to a second Volcano Medic 2 vaporizer to vaporize the mebufotenin at a high temperature. The vaporized mebufotenin is collected in a balloon that is subsequently detached from the vaporizer. After a mouthpiece is attached to the balloon, the mebufotenin aerosol is inhaled by the patient.
Placebo will be prepared using the same preparation process using only alcohol solvent, leading to an empty dosing capsule after alcohol evaporation in the first vaporizer, so that after transfer into the second vaporizer, placebo will consist of air only in the balloon for administration.
During the DB Part 1, a blinding bag is placed over the balloon to conceal the contents of the balloon.

Study burden and risks

Section 4.4 of the protocol :

The specific properties of mebufotenin (fast onset and short duration of PsE, high propensity to induce a PE, and no tolerance development even after short-term re-administration) may be therapeutically beneficial in TRD.
Based on findings from the previous Phase 1/2 clinical trial in TRD, GH001 IDR dosing may induce rapid remission in patients with TRD; this will be assessed as the primary endpoint in the present trial.
Based on the results from previous GH001 clinical trials in healthy volunteers (GH001-HV-101 and GH001-HV-103) and patients with TRD (GH001-TRD-102), the administration of mebufotenin appears to have a low risk of adverse reactions across the tested doses (refer to the current GH001 Investigator*s Brochure). This is supported by reports from naturalistic use of mebufotenin, despite large variability in dosing and wide inter-patient variability in the occurrence of psychedelic experiences. Possible acute effects of treatment during the psychoactive phase may include enhancement of tactile awareness, distortions of the perception of time and space, intense emotions such as fear or euphoria, visual and auditory hallucinations, loss of physical control and coordination, confusion or dissociation, and short-term unresponsiveness. Signs such as closing or blinking eyes, crying, laughing, movement (including

thrashing and rolling around), heavy breathing, nausea, vocalization (including grunting, mumbling, talking, or shouting), and delusional interactions with the environment may be observed. Complete or partial amnesia for the experience is possible after higher doses. To mitigate the risk of accidental injury, including possible vomiting and subsequent aspiration, administration of GH001 will only be performed in the clinic under the supervision of 2 study personnel in a clinical setting equipped for emergency care.
With the exception of temporary, non-clinically relevant increases in heart rate and blood pressure shortly after administration of GH001, no noteworthy changes in vital signs were reported in the completed clinical trials with GH001. In particular, no respiratory symptoms of clinical significance have been reported in the clinical trials, and no signs of bronchoconstriction were seen from the peak expiratory flow rate assessments systematically performed in GH001-HV-103. To address potential risks, patients with clinically significant heart and/or lung disease, and hypertension are excluded from this trial and vital signs will be measured before and after dosing and as required to monitor for potential hypertension, tachycardia, and impaired respiration. To avoid interference with the psychoactive experience, intense stimuli such as blood pressure measurements with an upper arm cuff should be avoided during the acute psychoactive phase and, in this phase, only heart and oxygen saturation should be monitored with a simple finger cuff method.
A potential risk associated with administration of psychedelics is the occurrence of acute challenging experiences, which can be characterized by anxiety, panic, or paranoia. The risk of such experiences will be mitigated by patient selection and preparation, and the availability of support during and after the experience. In the GH001 program, only 4 instances of mild anxiety were reported to date.
A further risk described with administration of psychedelics is a phenomenon of reoccurring, mild, self-limiting drug-like experiences after the acute substance effects have worn off. With GH001, re-experiencing of parts of the acute psychoactive experience (as defined by Medical Dictionary for Regulatory Activities [MedDRA] preferred terms flashback, hallucination, and sensory disturbance) was seen infrequently in the GH001-HV-101 and GH001-TRD-102 studies, primarily in periods of rest; all cases were mild in intensity and resolved spontaneously during the 7-day study period. No such cases were seen in the GH001-HV-103 study during the 30-day study period. From the literature, some users of this class of drugs have also reported that psychological difficulties, including resurfacing of acute effects, can last for prolonged periods after the experience, referred to as hallucinogen persistent perception disorder. No such lasting psychological difficulties have been described in the GH001 program or in other modern clinical studies with psychedelic agents. In the present trial, telephone support (TPnD1) and follow-up visits (TPnD7) are provided to identify issues early, and to provide support and therapy as required.
No cases of frequent use of mebufotenin with development of tolerance and/or withdrawal symptoms have been reported and the class of psychedelics in general is considered to have very low dependence potential.

The reproductive toxicity of GH001 has not yet been investigated. Reproductive and embryofetal developmental risks from IDR dosing in this trial will be mitigated through use of effective means of birth control in male patients who are not surgically sterilized and female patients of childbearing potential, exclusion of pregnant women, pregnancy testing, and restriction of sperm donation in male patients.
The withdrawal of antidepressant medication in patients with severe or treatment-resistant mood disorders can be conducted safely and ethically. In the present trial, withdrawal of such medication will only take place in a patient that has been evaluated objectively as having very limited response or no response to said therapy, and only after diligent clinical evaluation, for which the patient*s general practitioner and/or psychiatrist will be involved as needed. Antidepressant medication will not be discontinued for the sole purpose of allowing patients to participate in the trial. Any patient who has their antidepressant or other therapy withdrawn will be instructed to contact the clinical site on the emergence of deterioration or negative consequences of such withdrawal, and appropriate measures will be taken to ensure adequate care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients are eligible for the trial if all the following criteria are met, unless they fulfil >=1 of the exclusion criteria:
1. Is informed about the trial, has given informed consent in writing, and is willing and able to comply with all requirements and rules of the trial.
2. Is in the age range between 18 and 64 years (inclusive) at the time of informed consent.
3. Meets the trial criteria for TRD as assessed by a study psychiatrist:
a. Meets the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria for single-episode MDD or recurrent MDD, without psychotic features confirmed by the Mini-International Neuropsychiatric Interview (MINI) 7.0.2 with current episode duration of <=2 years.
b. The current MDE must be deemed *valid* based upon the Massachusetts General Hospital State versus trait Assessability Face and Ecological validity Rule of 3Ps (MGH-SAFER) criteria interview.

For full details please refer to the Protocol.

Exclusion criteria

Patients who meet any of the following criteria prior to the first dose of study drug are not eligible for randomization:
1. Has, based on history, psychiatric assessment, and evaluation of the MINI version 7.0.2 during the screening period, a first MDD episode after age 60, a current or prior diagnosis of a psychotic disorder, MDD, or other mood disorder with psychotic features, bipolar disorder, obsessive compulsive disorder, posttraumatic stress disorder, autism spectrum disorder, borderline personality disorder, schizophrenia, delusional disorder, paranoid personality disorder, schizoaffective disorder, clinically significant intellectual disability, antisocial personality disorder, schizotypal personality disorder, or any other psychiatric comorbidity that renders the patient unsuitable for the trial according to a study psychiatrist.
2. Has significant suicide risk as defined by (a) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, during the screening period, or at Baseline; or (b) suicidal behaviors within the past year; or (c) clinical assessment of significant suicidal risk during clinical interview; or (d) non-suicidal self-injury within the past year.
3. Has 1 or more first degree relatives with a current or prior diagnosis of

bipolar disorder, psychotic disorder, or other mood disorder (including MDD) with psychotic features.
4. Undergoing systematic psychotherapy (including cognitive behavioral therapy [CBT]) that is planned to be modified or planning to initiate psychotherapy during the trial. CBT must have been ongoing for the last 3 months prior to Baseline.
5. Has any current or past clinically significant condition (e.g., severe infection, severe pulmonary disease, uncontrolled hypertension, uncontrolled diabetes, severe cardiovascular disease, valvulopathy, pulmonary hypertension, myocardial infarction, angina, or clinically significant arrythmia within the past year, severe hepatic or severe renal failure, brain disorder including seizure, stroke, dementia, aneurysm, history of intracerebral hemorrhage, degenerative neurologic diseases, meningitis, encephalitis, and head injury with loss of consciousness) that may interfere with the interpretation of the trial results, constitute a health risk for the patient, or that otherwise renders the patient unsuitable for the trial according to the investigator*s judgement.

For full details please refer to the Protocol.

Study design

Design

Study phase:	2
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):	05-08-2024
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	Volcano Medic 2 Vaporization System
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	mebufotenin
Generic name:	5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT)

Ethics review

Approved WMO Date:	07-12-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2024

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2022-000574-26-NL
CCMO	NL82721.018.23