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A dose-finding and proof-of-concept study of the efficacy and safety of MSP-1014.OX in patients with major depressive disorder

Submission date
06/01/2023

Recruitment status
No longer recruiting

Registration date
28/06/2023

Overall study status
Completed

Last Edited
20/09/2023

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
This is an adaptive trial that will be conducted in two parts. The main aim is to assess the safety, cardiovascular (heart) effects, pharmacokinetics (what the body does to a drug), and pharmacodynamic (what a drug does to the body) profile of MSP-1014.OX in patients with major depressive disorder (MDD) who are still experiencing some symptoms despite taking an antidepressant.

Who can participate?
Patients aged 18 years and over with MDD who are still experiencing some symptoms despite taking an antidepressant for at least 8 weeks

What does the study involve?
In Part 1, participants will receive three single doses of MSP-1014.OX (30 mg, 50 mg, 70 mg) each 4 weeks apart. Part 2 compares the effectiveness and safety of the maximum tolerated dose of MSP-1014 identified in Part 1 to placebo (dummy drug). In this part of the trial, participants will receive a course of psychotherapy accompanied by either MSP-1014.OX or placebo and will be followed up for 8 weeks to assess whether MSP-1014.OX is effective in reducing symptoms of depression.

What are the possible benefits and risks of participating?
MSP-1014.OX is a prodrug of psilocin, the active metabolite of psilocybin. Recent clinical trials have demonstrated that psilocybin has a profile of safety for participants with a range of mental health conditions. It is well-tolerated and induces no serious, nor any unexpected adverse events. Nevertheless, we acknowledge the risks associated with the intervention. It is likely that as part of the psychotherapy, participants may choose to talk about challenging topics, which could potentially cause transient anxiety and distress. It is possible that memories associated with trauma, grief, or intense emotional disturbance will be re-experienced.
There is a risk of the participants becoming harmed, traumatised or re-traumatised when overwhelming emotions and memories are revisited if the participant is not sufficiently prepared or supported. The ‘set and setting’ is a term used to explain the parameters of a

person's mindset (set) and the environment (setting) of the therapeutic psychedelic experience. This risk of harm is minimised by providing high quality training to the research team, and assuring the 'set' and 'setting' is optimal throughout, by taking a participant-centred approach. The preparation sessions and pre-intervention measures are designed to assist the participants to prepare, ensure their suitability/capacity, and facilitate coping and processing skills. The environment of the dosing session is designed to promote meaningful and safe experiences; and specially trained therapists will be present throughout the dosing session. The dosing room will be decorated with appropriate lighting and aesthetics, and music and eyeshades will be available to encourage introspection.
The effects of psychedelic-assisted psychotherapy can create an environment in which the participants are able to address and embrace deeply rooted challenges. Such issues can provoke negative psychological experiences (commonly referred to as 'bad trips') in participants, but previous studies have indicated that these are reliably temporary, leaving no persisting negative affect. Although such experiences can bring discomfort and distress to the participants, within these states there is an opportunity for growth and sustainable recovery. The therapists are specially trained to intervene effectively, so that the participant is able to endure and process therapeutic experiences that may also be uncomfortable or distressing, whilst safeguarding the process from becoming overwhelming or traumatic. In the unlikely event that the negative effects become too overwhelming or traumatic for the participant, benzodiazepines can be prescribed and used to maintain psychological safety by helping the participant de-escalate the adverse effects. Lorazepam will be administered to the participant and titrated to effect. If lorazepam is not sufficient, olanzapine will be administered. The participant will be directly monitored and required to remain at the test site until assessed and discharged by a psychiatrist. Where deemed necessary, emergency arrangements will be made to allow participants to remain at the dosing site for overnight monitoring.
It is anticipated that some participants might have other vulnerabilities in addition to their symptoms related to their diagnosis of major depressive disorder, including risk factors of suicidality. The risk of suicidality could increase during the process of completing questionnaires, discussing sensitive issues, and potentially addressing traumatic memories. The risk of suicide will be minimised by exercising clinical judgement to exclude participants who are considered to be of significant suicidal risk. Also, regular monitoring for changes in participants' suicidal ideation will be assessed using the Sheehan Suicide Tracking Scale (S-STS). The therapists are trained in safeguarding and responding to suicidality risk, and therefore will provide a high level of care to ensure the safety of participants, and be attentive to identifying changes in participant suicidality risk. Participants will also be provided with a contact card with the relevant research team contacts, and availability hours, and contacts to signpost the participant to relevant services in case of an emergency. Not only do findings portray psilocybin-assisted therapy to be of low risk in regard to suicidality, amongst healthy populations it is indicated that psilocybin-assisted therapy could play a key role in reducing suicidality.

Where is the study run from?
Clerkenwell Health (UK)

When is the study starting and how long is it expected to run for?
January 2023 to October 2024

Who is funding the study?
Mindset Pharma (Canada)

Who is the main contact?
Clare Knight, clare@clerkenwellhealth.com
Dr Emilio Arbe, emilio@clerkenwellhealth.com

Contact information

Type(s)
Public

Contact name
Ms Clare Knight

Contact details
120 Aldersgate St
London
United Kingdom
EC1A 4JQ
+44 (0)7825 664 326
clare@clerkenwellhealth.com

Type(s)
Principal investigator

Contact name
Dr Emilio Arbe

Contact details
39 Welbeck Street
London
United Kingdom
W1G 8DR
+44 (0)7889 371 047
emilio@clerkenwellhealth.com

Additional identifiers

Integrated Research Application System (IRAS)
1006861

Protocol serial number
MSP_CH_01

Study information

Scientific Title
An adaptive-design, phase IIa/IIb, open-label, multiple-ascending-dose, dose-finding study to assess the safety, cardiovascular effects, pharmacokinetics and pharmacodynamic profile of 30 mg, 50 mg, and 70 mg of MSP-1014.OX in major depressive disorder (MDD) patients with partial or no response to SSRIs followed by a double-blind, randomised, placebo-controlled, proof-of-concept, efficacy and safety study of the selected dose of MSP-1014.OX in MDD patients with partial or no response to SSRIs

Study objectives

Primary objectives:
Part 1: dose finding to assess the safety and tolerability of MSP-1014.OX at three doses: 30 mg, 50 mg, and 70 mg.
Part 2: proof-of-concept to assess the efficacy of the selected dose of MSP-1014.OX versus placebo in the reduction of symptoms of depression.

Secondary objectives:
Part 1
1. PK profile of psilocin from MSP-1014.OX 30 mg, 50 mg, and 70 mg
2. To assess the acute, cognitive subacute effects and biomarkers of MSP-1014.OX
3. To assess the effect of MSP-1014.OX on MDD symptoms at the three dose levels
4. To assess the effect of MSP-1014 on patient's belief about the efficacy of treatment
5. To assess the effect of MSP-1014 on emotional breakthrough during the psychedelic experience
6. To assess the dose-response relationship and correlations between secondary endpoints.

Part 2:
1. To compare the rates of response following treatment with MSP-1014.OX
2. To compare biomarkers between MSP1014.OX and placebo
3. To compare the safety of MSP-1014.OX
4. To assess the subacute cognitive effects of MSP-1014.OX
5. To compare the effect of MSP-1014.OX on patient's belief about the efficacy of treatment
6. To assess the effect of MSP-1014 on emotional breakthrough during the psychedelic experience
7. To assess the effect of MSP-1014 on patient-reported, health-related quality of life

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, ref: 23/EE/0032

Primary study design
Interventional

Study design
Part 1: open-label dose-finding; Part 2: double-blind randomized placebo-controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Major depressive disorder

Interventions
This adaptive design clinical trial is to be conducted in two parts:
Part 1 is a phase IIa, open-label, multiple-ascending dose, dose-finding study to assess the safety, cardiovascular effects, pharmacokinetics, and pharmacodynamic profile of three oral ascending doses of MSP-1014.OX, namely 30 mg, 50 mg, and 70 mg taken orally, four weeks apart, by MDD patients with partial or no response to SSRIs. Part 1 of the study aims to include 10 evaluable patients with the dose selected for part 2 based on the maximum tolerated dose. Participants

will receive 3 sessions of preparatory psychotherapy in the two weeks prior to the first dose of MSP-1014.OX and two sessions of integration therapy following each dose. Participants will be followed up for one week after the final dose.

Part 2 of the clinical trial is a phase IIb, double-blind, 1:1 randomised, placebo-controlled, proof-of-concept, efficacy and safety study of the selected dose of MSP-1014.OX in MDD patients with partial or no response to SSRIs. Randomisation services will be provided by Sealed Envelope. Part 2 of the study will include approximately 60 patients, although this could increase to a maximum of 82 after interim analysis of the first 40 participants. Half of participants will be allocated to MSP-1014.OX and the other half will be allocated to placebo. All participants will receive 3 sessions of preparatory psychotherapy in the two weeks prior to the dosing session (MSP-1014.OX or placebo) and three sessions of integration therapy in the two weeks following the dosing session. All participants will complete 4-week and 8-week post-baseline follow-up visits.
The selected patient population for both parts of the study are patients with a DSM-5 defined MDD diagnosis with moderate to severe symptoms of depression, as defined by a HAM-D score > 17, despite treatment with an adequate dose SSRI for at least 8 weeks.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
MSP-1014.OX

Primary outcome(s)
Part 1: adverse events and changes in cardiovascular parameters (HR, BP, and QTc) that raise a safety concern such as a hypertensive crisis (systolic BP >160 mmHg or diastolic BP >110 mmHg), a QTc prolongation >20 msec, any signs or symptoms or serotonin syndrome, or any other adverse event that in the opinion of the investigator should preclude that patient from further dosing. Adverse events and changes in cardiovascular parameters will be collected from informed consent until the completion of the final follow-up visit.

Part 2: Changes in depression symptoms as measured by scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) at 4-weeks post baseline.

Key secondary outcome(s)
Part 1:
1. Psilocin plasma concentrations at 20, 40, 60, 80, 120, 3 4, 6, 8, 24 h after dose
2. Subjective psychedelic intensity as measured on a 1-10 scale at 20, 40, 60, 80, 120 min, 3, 4, 6, 8 h after dose
3. Sub-acute cognitive effects as measured by the Brief experiential avoidance questionnaire (BEAQ) at baseline, 7 days, and 6 weeks post the last dose
4. Sub-acute cognitive effects as measured by the Psychological flexibility (Psy-flex) at baseline, 7 days, and 6 weeks post the last dose
5. Sub-acute cognitive effects as measured by the Mindful attention awareness scale (MAAS) at baseline, 7 days, and 6 weeks post the last dose
6. Sub-acute cognitive effects as measured by the BDNF at baseline, 0, 40, 60, 80, 120 min, 3, 4, 6, 8, 24 h after dose

7. Changes in depression symptoms measured by Beck’s Depression Inventory (BDI) at baseline, 7 days, and 6 weeks post the last dose
8. Patient impression of improvement as measured by the Patient’s Global Impression of Change (PGIC) at 7 days and 6 weeks post the last dose
9. The effect of on emotional breakthrough as measured by the Emotional Breakthrough Inventory (EBI) during each dosing session
10. The dose response relationship and correlations between the secondary endpoints

Part 2:
1. Changes in depression symptoms as measured by scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, week 4 & week 8 2. Changes in biomarkers as measured by BDNF at baseline, 0 min, 60 min, 3 h, and 6 h after drug administration
3. Adverse events from informed consent to completion of final follow-up
4. Sub-acute cognitive changes as measured by the Brief experiential avoidance questionnaire (BEAQ) at baseline, week 4 & week 8
5. Sub-acute cognitive changes as measured by the Psychological flexibility (Psy-Flex) at baseline, week 4 & week 8
6. Sub-acute cognitive changes as measured by the Mindful attention awareness scale (MAAS) at baseline, week 4 & week 8
7. Patient impression of improvement as measured by the Patient’s Global Impression of Change (PGIC) at baseline, week 4 & week 8
8. The effect of on emotional breakthrough as measured by the Emotional Breakthrough Inventory (EBI) during each dosing session
9. Changes in health-related quality of life as measured by the EQ-5D-5L at baseline & week 8

Completion date
30/10/2024

Eligibility

Key inclusion criteria
1. Aged 18 years and above
2. Male or female
3. DSM-5 defined MDD with partial response SSRI monotherapy (HAM-D score >17) or no response
4. Able to communicate well in English and follow study procedures
5. Any history of suicide attempts/suicidal ideation; the subject scores 'yes' on item 4 or 5 of the Suicidal Ideation section of the Columbia Suicidality Scale Scoring if this ideation occurred in the past 12 months, or 'yes' on any item of the Suicidal Behaviour Section, and the opinion of the investigator
6. Medically suitable as determined by screening including a personal interview, a medical questionnaire, a physical examination, an electrocardiogram (ECG), and blood tests
7. Currently taking a first course of SSRI antidepressant treatment for at least 8 weeks

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Treatment with any other antidepressant medication other than the currently prescribed SSRI antidepressant
2. Current or past diagnosis of schizophrenia, psychotic disorder, bipolar disorder I and II, delusional disorder, paranoid personality disorder, schizoaffective disorder, borderline personality disorder, or judged to be incompatible with establishment of rapport or safe exposure to psilocybin, as assessed through medical history and the Mini International Neuropsychiatric Inventory (MINI)
3. Family history of schizophrenia, schizoaffective disorder, or bipolar affective disorder
4. Anyone on a research study of an investigational drug or who has been on a clinical trial within 1 month of enrollment
5. Scores from the screener and baseline Columbia Suicide Severity Rating Scale (C-SSRS) that indicate that the participant is of clinically significant risk of suicide. A decision will be formed based on C-SSRS scores and used in combination with other clinically significant data at screening and baseline.
Judged to be of high suicide or self-harm risk following psychological assessment at screening or baseline.
6. Currently receiving psychotherapy other than that which forms far this study
7. Current (<1 year) alcohol or drug abuse identified as moderate or severe during screening in accordance with ICD-11 criteria, through the MINI 7.0.2
8. Any other reason that might compromise safe exposure to psilocin and the development of a therapeutic relationship necessary for psychological support
9. Previous use of psychedelics in lifetime

Medical Exclusion Criteria:
1. Females who are pregnant, breastfeeding or of childbearing potential who are unwilling or unable to use an effective form of contraception (or abstinence) for the duration of the study. Women will be required to conduct a serum pregnancy test at the in-person screening visit and a urine test prior to dosing at the drug-assisted therapy session. Male participants who do not agree to use contraception for 2 weeks following each dosing session to mitigate the risk of pregnancy will also be excluded.
2. A diagnosis of epilepsy or at significant risk of seizures based on medical history
3. Cardiovascular conditions including stroke (less than 1 year before providing informed consent [IC]), myocardial infarction (<1 year from IC), uncontrolled hypertension (blood pressure >140/90 mmHg) or clinically significant arrhythmia within 1 year of IC
4. Anyone who, at screening, has clinically significant findings on physical examination, including vital signs (HR below 60 or above 100 bpm, blood pressure below 90/60 or above 140/90), ECG (ST greater than 450 msec), and positive alcohol breath test
5. An estimated glomerular filtration rate (eGFR) of <45 ml/min/1.73 m^2
6. Results falling above 2.5 times the upper reference level on alanine aminotransferase 0-45 IU /L, aspartate aminotransferase 0-50 IU/L, gamma-glutamyl transferase 0-70 IU/L (male), 0-40 IU /L (female)
7. Results falling above 1.5 times the upper reference level on bilirubin 3-20 µmol/L

8. Results falling above 1.0 times the upper reference level on conjugated bilirubin 0-14 µmol/L
9. Results falling above 1.0 times the upper reference level on alkaline phosphatase 90-300 IU/L
10. Any clinically significant renal, pulmonary, gastrointestinal, hepatic, or other illness that could affect the interpretation of results or be a potential health risk for the person if they were to be included in the study
11. Below 16 or above 35 kg/m² Body Mass Index (BMI) score
12. Those whose urine drug test is positive for psychoactive substances at in-person screening, or dosing visit
13. Anyone with organic brain injury or diagnosed with any cognitive impairment

Date of first enrolment
01/03/2023

Date of final enrolment
31/07/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Clerkenwell Health trial unit
39 Welbeck Street
London
United Kingdom
WG1 8DH

Sponsor information

Organisation
Clerkenwell Health

Funder(s)

Funder type
Industry

Funder Name
Mindset Pharma

Results and Publications

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No