Safety and efficacy of repeated low dose D-lysergic acid diethylamide (LSD) D-tartrate (MM-120) as treatment for ADHD in adults: a multi-center, randomized, double- blind, placebo-controlled Phase 2a Proof of Concept Trial

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Primary ObjectiveTo assess the treatment efficacy vs placebo of repeated low doses (20 µg) of LSD for six weeks in adult patients with ADHD measured by Adult Attention Deficit Investigator Symptom Rating Scale (AISRS).Secondary Objectives1. To...

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

Summary

ID

NL-OMON52408

Source
ToetsingOnline

Brief title
Safety and efficacy of low dose MM120 in ADHD

Condition

- Other condition

Synonym
ADHD

Health condition

Attention Deficit Hyperactivity Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Mind Medicine, Inc.
Source(s) of monetary or material Support: Mind Medicine;Inc.

Intervention

Keyword: Attention Deficit Hyperactivity Disorder (ADHD), Efficacy, Lysergic acid diethylamide (LSD), Safety

Outcome measures

Primary outcome

Primary endpoint:

Mean change from baseline in ADHD symptoms, as assessed by the AISRS after 6 weeks of treatment. The AISRS total score consists of 18 items from the original Attention- Deficit/Hyperactivity Disorder - Rating Scale (ADHD-RS), which were derived based on DSM-5 criteria for ADHD. The ADHD-RS includes 9 items that address symptoms of inattention, and 9 items that address symptoms of impulsivity and hyperactivity. Each item is rated from 0 to 3. The AISRS total score can range from 0 to 54. A higher score corresponds to a worse severity of ADHD.

Secondary outcome

Secondary endpoints:

ADHD-related endpoints:

* key secondary endpoint: change from baseline in AISRS after 1 week (2 doses) of treatment.

* occurrence of patients who experience at least a 1-point decrease in the CGI-S

* change from baseline in CGI-S after 1 week (2 doses) of treatment and after 6 weeks of treatment

* change from baseline in patient self-assessment by the Adult ADHD Self-Report Scale (ASRS) and Connors* Adult ADHD Rating Scale (CAARS).

Safety Endpoints

* vital signs (supine blood pressure, heart rate)

* 12-lead safety ECG

* psychological and/or physiological adverse events

* Safety laboratory evaluation and Urine pregnancy testing

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

Study description

Background summary

There is a growing interest in the use of psychedelic substances for health-related purposes, including symptom relief for disorders like anxiety, depression, and pain (Nichols et al., 2017). Although the focus of recent clinical trials have used high doses of these substances, anecdotal evidence supports the potential therapeutic utility of lower doses of psychedelic substances in reducing symptomatology of a range of mental and physiological disorders (Anderson et al., 2019a; Anderson et al., 2019b; Fadiman et al., 2019; Hutten et al., 2019a; Hutten et al., 2019b; Lea et al., 2020; Passie, 2019; Polito et al., 2019; Prochazkova et al., 2018). The internet has a number of surveys, chat rooms and coaches touting the benefits of psychedelics, particularly LSD at sub-perceptual doses to treat ADHD, anxiety, and depression. It has yet to be shown whether a psychedelic experience as induced by a *full* regular dose is necessary to produce symptom relief, or whether (repeated) sub-perceptual doses have therapeutic potential as well. Recently microdosing, the practice of repeatedly using low doses of psychedelics like lysergic acid diethylamide (LSD) and psilocybin (Kuypers et

al., 2019; Passie, 2019), has gained considerable media attention, where it is portrayed as a performance enhancing activity (Hutten et al., 2019b), and as a treatment for certain diseases like depression, anxiety and ADHD. In contrast to a regular dose (approximately 100 mcg) that is characterized by perceptual changes, a microdose (approximately 10 to 20 mcg) does not induce relevant perceptual alternations (Bershad et al., 2019; Family et al., 2020; Kuypers et al., 2019; Passie, 2019). The most widely suggested practice is taking one-tenth of a regular, recreational dose of a psychedelic once every three days (Fadiman et al., 2019; Kuypers et al., 2019; Passie, 2019).
Clinical study evidence regarding the efficacy of microdosing with psychedelics for symptomatic relief is lacking. However, recent surveys have provided data on potential benefits of microdosing LSD. Specifically, microdosing psychedelics was rated more effective than conventional therapies for the treatment of ADHD by persons using psychedelics (Hutten et al., 2019b). Users mostly report microdosing psychedelics for performance enhancement (Hutten et al., 2019a; Lea et al., 2019; Lea et al., 2020) and to improve mental health (Lea et al., 2019; Lea et al., 2020). Other reasons are mood enhancement and symptom relief, curiosity, and enhancing empathy (Hutten et al., 2019a). Taken together, that survey data indicate that people microdose as self-medication therapy for mental health as alternative or adjunct to conventional therapy (Lea et al., 2020). Adverse effects of microdosing include stronger-than-expected psychedelic effects, anxiety, and physical adverse effects (Lea et al., 2020). Other perceived limitations include issues related to dosing, taking illegal substances, limited or no mental health or cognitive improvement, unpleasant *off* days, only short-term benefits, and concerns about dependence and drug-related risks (Lea et al., 2019). Large other non-published survey data also indicates that people microdose to enhance mood, creativity, focus, and sociability. Concerns about adverse health effects are rather small. However, there is no controlled data on either the efficacy or adverse effects of microdosing psychedelics, including LSD. Therefore, the present study aims to investigate the effectiveness of microdosing with LSD for treatment of ADHD in line with a common but not-controlled practice. The present study will include an assessment of the pharmacokinetics and acute effects of 20 mcg of LSD over 6 hours during first dosing at the hospital. The same dose will then be administered twice weekly and effects compared with placebo in a double-blind manner over 6 weeks regarding benefits in adult patients with ADHD.

Study objective

Primary Objective
To assess the treatment efficacy vs placebo of repeated low doses (20 µg) of LSD for six weeks in adult patients with ADHD measured by Adult Attention Deficit Investigator Symptom Rating Scale (AISRS).
Secondary Objectives
1. To assess treatment efficacy vs placebo measured by change from baseline in AISRS after 1 week of treatment.

2. To assess treatment efficacy vs placebo based on the proportion of patients who experience at least a 1-point decrease in the Clinical Global Impression - Severity of Illness Scale (CGI-S).
3. To assess treatment efficacy vs placebo measured by change from baseline in CGI-S.
4. To assess the safety and tolerability by Adverse Event (AE) and Serious Adverse Event (SAE) assessment.

Study design

This study is a multi-center, randomized, double-blind, placebo-controlled Phase 2a study of low dose MM-120 (20 µg) compared with a placebo administered for 6 weeks (twice a week on a 3/4-day schedule [± 1 day]).

Intervention

There will be 2 arms:
* Arm 1-Placebo: a total of 26 patients will receive a placebo identical in appearance to the investigational medicinal product (IMP) administered orally twice weekly (e.g., Tuesday/Friday) for 6 weeks.
* Arm 2-MM-120: a total of 26 patients will receive 20 µg of M-120 administered orally twice weekly for 6 weeks.

Study burden and risks

The total time investment for the participant is estimated at approximately 26 hours.
This is divided over a maximum of 15 visits over a period of 14 weeks.
This includes the time a participant spends keeping a daily diary.
During participation in the study, a blood sample is taken 13 times (7 times 7,5 ml via an inserted intravenous catheter and 6 times 10 ml via venipuncture).
At each visit the participant is asked to fill in a number of questionnaires.
Prior to participation a screening visit takes place to see if the participant is physically and mentally eligible to participate.
During this visit it is also checked whether the criterion of having sufficient ADHD complaints is met.
If a participant qualifies for participation and uses ADHD medication, he or she will be asked to discontinue this from the medical screening until the end of participation in the study.
For all visits, on which the participant is given a dose of LSD, they are asked to come to the clinic with a caregiver, or be prepared to take a taxi home and not drive a car or use heavy equipment or other dangerous activities if they are under the influence for the rest of the evening, until the next morning.
The use of LSD can have side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Ability and willingness to provide written, informed consent prior to initiation of any
study-related procedures and to adhere to all study requirements.
NOTE: The subject (i.e., not a legally authorized representative) must be cognitively
able to understand the requirements of the study and provide the informed consent.
2. Age >= 18 and <= 65 years at screening.
3. Subjects with the diagnosis of Diagnostic and Statistical Manual of Mental Disorders-
5 (DSM-5) ADHD, as determined by clinical evaluation and confirmed by structured interview (MINI).
4. AISRS total score of >=26 at screening.

5. CGI-S score of >=4 at screening.
6. Must be willing to receive IMP dose twice weekly. On Day 1, the subject will come to
the clinic and must be willing to take a taxi or public transportation home or be
accompanied by a caregiver and not drive a car, use heavy equipment, or participate in
any other dangerous activity for the remainder of the day after receiving IMP (NOTE:
at any protocol visit after Day 1 dosing, dosing visits may occur at the subject*s home
at the discretion of the PI, conducted by one of the study investigators or delegate and
administered under supervision followed by the performance of the same procedures
done at the clinic including safety monitoring. If early withdrawal is considered due to
any safety issue identified, the Sponsor*s medical monitor should be notified. If a
remote visit is conducted due to any reason related to the COVID-19 pandemic,
notification must be sent to the Medical Monitor*s dedicated email address and Urgent
Safety Measures as outlined in this protocol must be followed.)
7. Must be willing to refrain from more than 6 standard alcoholic drinks per week
(1 standard drink corresponds to 0.1 L wine, 0.3 L beer, or 4 cL liquor), more than 10
cigarettes a day, and more than 2 cups of coffee a day throughout the study treatment
period (6 weeks) and until the last study visit is complete (EoS or ET).

Exclusion criteria

1. Past or present diagnosis of a primary psychotic disorder or first-degree relative with a
psychotic disorder.
2. Past or present bipolar disorder (DSM-5).
3. Other current psychiatric disorders that, in the opinion of the Investigator or medical
supervisor, may confound the results of the study (e.g., obsessive-compulsive disorder,
dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa or bulimia
nervosa).
4. Subjects with past (> 1 month prior to the screening visit) or present

substance use
disorder (except nicotine, provided subject does not smoke more than 10 cigarettes a
day).
5. Somatic disorders including Central Nervous System (CNS) involvement of cancer,
severe cardiovascular disease, untreated hypertension, severe liver disease (liver
enzyme increase by more than 3x the upper limit of normal except unconjugated hyperbilirubinemia due to Gilbert*s Disease, per Investigator), severely impaired renal
function (estimated creatinine clearance < 50 mL/min by CKD-EPI formula), or anything else that, in the judgment of the Investigator or medical supervisor, poses too
great a potential for side effects.
6. Any lifetime history of suicide attempt; or recent (within 6 months prior to the screening
visit) active suicidal thoughts or ideation (defined as a suicidal ideation score of 2 or
greater in the Columbia-Suicide Severity Rating Scale [C-SSRS]); or endorsement of
any suicidal behavior on the C-SSRS within the past 6 months prior to the screening
visit.
7. Likely to require psychiatric hospitalization during the course of the study.
8. Once consent is signed, subject not willing or able to stop any prescription or nonprescription
ADHD medications during screening and prior to the baseline visit through final study visit (EoS or ET). A list of prohibited medications is provided in Appendix 1.
9. Plan to start, stop, or alter the use of any medications, supplements, or other therapeutics
from Baseline until EoS or ET (see Appendix 1 for list of prohibited medications).
10. Plan to start, stop or alter the use of psychotherapy, massage, meditation, acupuncture,
hypnosis, yoga, or other similar therapy/activity from the time of providing informed
consent until EoS or ET.
11. Use of potent CYP2D6 inhibitors; moderate CYP2D6 inhibitors by Investigator discretion (see Section 5.5.1.1 and Appendix 3).
12. Likely to need use of any psychiatric medications with the potential to confound
interpretation of study results or impact safety, at the discretion of the Investigator, in
the 10 weeks following Baseline up to EoS or ET (see Appendix 1 for list of prohibited

medications).
13. Use of investigational medication/treatment in the past 30 days prior to the screening
visit.
14. Subjects with a positive urine drug screen (with the exception of THC or metabolites)
at Screening OR Baseline.
15. Clinically significant abnormal baseline laboratory values, VSs, and ECG that include
the following:
a. Have evidence of clinically significant hepatic disorder (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3X ULN (except for Gilbert*s disease), and
b. Any clinically significant abnormal metabolic or hematologic screen, per Investigator or medical supervisor decision
c. Exclusionary blood pressure: >140 mm Hg (systolic) or >90 mm Hg (diastolic); heart rate <45 beats/minute or >90 beats/minute after an approximately 5-minute supine or semi-supine rest
NOTE: If the first measurement of a subject*s heart rate is > 90 beats/minute, a second recording is allowed after an additional approximately 5-minute supine rest
d. Exclusionary ECG parameters: QTcF > 450 msec (men), QTcF >470 msec (women)
e. Any clinically significant abnormal electrocardiogram (ECG) finding (e.g., uncontrolled atrial fibrillation, ischemia) at Screening (Visit 1) or Baseline (Visit 2), as determined by the Investigator or medical supervisor (in consultation with a cardiologist, if needed.
16. Any other condition, therapy, laboratory abnormality, or other circumstance that, in the
opinion of the Investigator or medical supervisor, may pose additional risk to the subject
from participation in the study, may interfere with the subject*s ability to comply with
study procedures, may make participation in the study not in the subject*s best interest
or may confound the results of the study.
17. Prior history or ongoing neuropsychiatric signs or symptoms associated with COVID-
19 such as development of, or current disorder, during or after a COVID-19 infection
including anxiety, memory loss, confusion, depression, delirium, agitation, or psychosis.
18. Women of childbearing potential (WOCBP) (i.e., physiologically capable of becoming
pregnant) who are unwilling or unable to use a highly effective method of contraception, as defined in Appendix 2, for the duration of the study, OR Men physiologically capable of fathering a child who are sexually active with WOCBP

but
are unwilling or unable to use barrier contraception (e.g., condom with or without
spermicidal cream or jelly) for the duration of the study.
NOTE: See Appendix 2 for definitions of WOCBP and highly effective methods of contraception and for information about unacceptable methods of contraception.
19. Women who are currently pregnant or breastfeeding or plan to become pregnant or
breastfeed during the study.
20. Men who plan to donate sperm during the study.
21. Use of weight loss drugs within 21 days of screening until the end of study.
22. Subjects who are either unable or unwilling to consume alcohol in any amount (including due to religious or personal reasons).
23. Subjects who have a change in AISRS score of >=13-points between screening and
baseline visits.

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:	Recruitment stopped
Start date (anticipated):	12-01-2022
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO Date:	18-05-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-11-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2020-001098-55-NL
ClinicalTrials.gov	NCT05200936
CCMO	NL73910.068.20