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A clinical trial of 5 mg psilocybin plus psychological support vs 25 mg psilocybin plus psychological support in adults with generalised anxiety disorder

Submission date
17/07/2024

Recruitment status
Stopped

Registration date
25/09/2024

Overall study status
Stopped

Last Edited
15/10/2026

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
The aim of this study is to compare the effectiveness and safety of 5 mg psilocybin plus psychological support with 25 mg psilocybin with psychological support in adults with a diagnosis of generalised anxiety disorder (GAD) who may or may not be taking selective serotonin reuptake inhibitors (SSRIs).

Who can participate?
Patients aged 18 - 70 years with GAD who are still experiencing moderate to severe symptoms

What does the study involve?
Participants will receive two separate doses of either 5 mg of psilocybin or 25 mg of psilocybin, 1 month apart in combination with psychological support. GAD symptoms are measured at week 8. Participants will take part in a screening period of up to 4 weeks, a treatment period of 7 weeks and a follow-up period of 22 weeks. In total, participants will take part for up to 33 weeks.

What are the possible benefits and risks of participating?
Consciousness-expanding effects that may occur directly after administration: psilocybin may influence the patient's feelings (euphoria, joy, but also fear and panic), it may induce altered perception through the senses, a distortion of time and space and it may alter how the patient's body feels. In some cases, this can be experienced as emotionally challenging and cause short periods of paranoia. Physically, this can manifest as a rapid heart rate, raised blood pressure, or a feeling of tightness, nausea, headache, agitation, dizziness, rapid eye movements and dilated pupils.
Other side effects may occur after administration: It may induce a mild headache. In rare cases, some people report an ongoing disturbance in their vision and unpleasant sensations, emotions or charged memories long after the drug has left the body.
The present trial has implemented various precautions to minimize this risk. This includes dosing based on a dose range that has been shown to be safe in healthy volunteers and patients with

common mental disorders. Furthermore, the use of other drugs or medications with known cross-reactions is not permitted.
The trial drug will only be administered in a supervised setting with the presence of a medical doctor and only after extensive medical and psychiatric suitability testing. No fatalities have been observed in other modern clinical studies with consciousness-expanding substances that have implemented similar precautions.
Participants will be provided with a 24-hour contact phone number where they can reach the clinical team in case of questions, psychological difficulties, or medical problems during the course of the trial.
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. This risk of harm is minimised by ensuring that therapists are appropriately qualified and experienced and by providing high-quality training trial-specific training to therapists and the research team. 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.
It is anticipated that some participants might have other vulnerabilities in addition to their symptoms related to their diagnosis of GAD, 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 Columbia Suicide Severity Rating Scale at every study visit. Trial 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, availability hours, and contacts to signpost the participant to relevant services in case of an emergency
Some of the clinical trial assessments may cause discomfort. A blood draw may be painful and the patient may get a bruise or tenderness where the needle goes into the skin. Having blood taken may also cause the patient to feel nauseated and/or lightheaded. When performing the ECG the patients may have mild irritation, slight redness, or itching of the skin where the stickers (electrodes) are placed. It may be necessary to shave the area on their chest for the placement of stickers directly on the skin. This risk of harm is minimised by providing high-quality training to the research team.

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

When is the study starting and how long is it expected to run for?
January 2026 to April 2027

Who is funding the study?
Psychennex Pty Ltd (UK)

Who is the main contact?
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Integrated Research Application System (IRAS)
1009576

Central Portfolio Management System (CPMS)
60699

Protocol serial number
PSY_CH_001

Study information

Scientific Title
A Phase IIb multicentre, randomised, double-blind, two-arm trial comparing the efficacy and safety of 25 mg psilocybin plus psychological support versus 5 mg psilocybin plus psychological support in adults with severe generalized anxiety disorder (GAD) (PSiGAD2)

Acronym
PSiGAD2

Study objectives
Primary objectives:
To assess the efficacy of two doses of 25 mg psilocybin with psychological support versus two doses of 5 mg psilocybin with psychological support in the reduction of GAD symptoms in participants with severe GAD (who may or may not be taking concurrent selection serotonin reuptake inhibitor [SSRI] antidepressants).

Secondary objectives:
To assess the effects of 25 mg psilocybin plus psychological support versus 5 mg psilocybin plus psychological support on the following:
1. Change in GAD-7-measured GAD symptoms
2. Change in HAM-A-measured GAD symptoms
3. Rates of GAD clinical response (>50% reduction in baseline HAM-A) and remission (>7 on HAM-A)
4. Change in impairment of functioning
5. Change in satisfaction with quality of life
6. Change in loss of workplace productivity
7. Change in utilisation of healthcare services
8. Change in depression symptoms
9. Emotional breakthrough during the psychedelic experience
10. Safety and tolerability
11. Proportion of participants who complete both dosing sessions
12. Efficacy of masking

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 24/09/2024, East of Scotland Research Ethics Service (EoSRES) (Tayside Medical Science Centre, George Pirie Way, Ninewells Hospital, Dundee, DD1 9SY, United Kingdom; +44 1224 558458; tay.eosres@nhs.scot), ref: 24/ES/0060

Primary study design
Interventional

Study design
Parallel-group double-blind randomized controlled trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Generalised anxiety disorder

Interventions
This is a randomised, double-blind trial with two treatment arms, comparing the efficacy and safety of 5 mg psilocybin plus psychological support with 25 mg psilocybin with psychological support in adults with a diagnosis of generalised anxiety disorder (GAD) who may or may not be taking selective serotonin reuptake inhibitors (SSRIs). There will be two separate doses (1 month apart) containing either 5 mg or 25 mg doses of psilocybin given via oral administration with a glass of water. Capsules of psilocybin 25 mg and 5 mg psilocybin are matched for weight, colour, taste, and smell. Participants will be randomly allocated at a ratio of 1:1 to arm 1 or arm 2, using a web-based system (Sealed Envelope) and will be stratified according to SSRI treatment status. Participants will take part in a screening period of up to 4 weeks, a treatment period of 7 weeks and a follow-up period of 22 weeks. In total, participants will take part for up to 33 weeks.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
PSX-001 (psilocybin trihydrate)

Primary outcome(s)
The efficacy of two doses of 25 mg psilocybin with psychological support versus two doses of 5 mg psilocybin with psychological support in the reduction of GAD symptoms in participants with severe GAD (who may or may not be taking concurrent selective serotonin reuptake inhibitor (SSRI) antidepressant). This will be calculated by assessing the change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at week 8, irrespective of treatment discontinuation.

Key secondary outcome(s)
1. Change in GAD symptoms measured using Generalised Anxiety Disorder 7-item Scale (GAD-7) from baseline to weeks 4, 8, 11, 20 and 29. The GAD-7 score is calculated by assigning scores of

0, 1, 2, and 3, to the response categories of “not at all,” “several days,” “more than half the days,” and “nearly every day,” respectively, and then adding together the scores for the seven questions. GAD-7 total score for the seven items ranges from 0 to 21, with scores of 5, 10, and 15 representing cut-points for mild, moderate, and severe anxiety, respectively.
2. Change in GAD symptoms measured using HAM-A from baseline to weeks 3, 4, 7, 11, 20 and 29. Each item is scored on a basic numeric scoring of 0 (not present) to 4 (severe): >17/56 is taken to indicate mild anxiety; 25–30/56 is considered moderate–severe.
3. Rates of GAD clinical response (>50% reduction in baseline HAM-A) and remission (>7 on HAM-A) at weeks 3, 4, 8, 11, 20 and 29.
4. Change in impairment of functioning via the change in Sheehan Disability Scale (SDS) from baseline to weeks 4, 8, 11, 20 and 29. Respondents are asked to indicate how much their symptoms have disrupted their regular activities over the past week, and each subscale can be scored independently or combined into a single total score representing a global impairment rating, ranging from 0 to 30, with higher scores indicative of significant functional impairment. Subscale scores greater than 5 suggest impairment in that subscale area.
5. Change in satisfaction with quality of life via change in Warwick–Edinburgh Mental Well-being Scale (WEMWBS) from baseline to weeks 4, 8, 11, 20 and 29. The scale is scored by summing responses to each item answered on a 1 to 5 Likert scale. The minimum scale score is 14 and the maximum is 70.
6. Change in loss of workplace productivity via the change in Lost Workplace Productivity (LWP) measure from baseline to weeks 4, 8, 11, 20 and 29. Lost productivity is calculated as follows: LWP = A + [B *(1-C)]. Where A = Hours Missed from paid job(s) because of symptoms, B = Hours working at paid job(s) despite interference of symptoms, C = Percent effectiveness while working at paid job(s). Variables A and B are collected via the SDS. Variable C is collected through an additional question asking participants to estimate “On days that you went to school or work in the last week despite feeling impaired by your symptoms, how effective do you feel that you were?” This is scored as a percentage where 0% = completely impaired; no work was achieved and 100% = completely unimpaired; achieved the same amount of work as without symptoms.
7. Change in utilisation of healthcare services via the change in Healthcare Utilisation (HU) measure from baseline to weeks 4, 8, 11, 20 and 29. Frequency data will be collected on previous 3-month utilisation of various healthcare services including primary care (visits to GPs, health clinics, psychologists, psychiatrists, dentists, physiotherapists, counsellors, mental health clinic or other primary care providers), hospitalisations, and emergency department (ED) visits.
8. Change in depression symptoms via the change in Patient Health Questionnaire - depression module (PHQ-9), measured from baseline to weeks 4, 8, 11, 20 and 29Participants rate how often they have been bothered by a given symptom over the past two weeks, with response options 0 (not at all), 1(several days), 2 (more than half the days) 3 (nearly every day). Total scores range from 0 to 27 with scores of ≥5, ≥10, ≥20 representing mild, moderate and severe levels of depression, respectively, and a total score above 10 suggestive of meeting diagnostic criteria for MDD.
9. Emotional breakthrough during the psychedelic experience measured using the Emotional Breakthrough Inventory (EBI) at each dosing session. The EBI consists of six statements such as “I felt able to explore challenging emotions and memories” and asks about “emotional release”, “closure”, “emotional breakthrough” and “resolution of conflict”. Participants rate the extent to which they agree with each statement on a 0–100 scale (with 0 being “No, not more than usually” and 100 being “Yes, entirely or completely”).
10. Safety and tolerability via adverse events (AE) associated with participation in the trial including vitals (blood pressure, heart rate, respiratory rate, temperature), Electrocardiogram (ECG) and Colombia Suicide Severity Rating Scale (C-SSRS) from baseline through to week 29.
11. Proportion of the total number of participants who complete both dosing sessions.
12. Efficacy of masking via the efficacy of masking questionnaire at each dosing session (Visit 6

and Visit 10). The response will be captured using a 5-point Likert-type scale with anchors: I am positive I received the high dose drug, I think I received the high dose drug, I cannot tell whether I received the high dose drug or the low dose drug, I think I received the low dose drug, I am positive I received the low dose drug.

Exploratory outcome measures:
13. The correlation between participants' expectancy of improvement, GAD symptoms and patient impressions of change in each arm via the Credibility-Expectancy Questionnaire (CEQ) at each dosing visit and HAM-A and Patient Global Impression of Change (PGIC) at weeks 4, 8, 11, 20 and 29.
14. The correlation between therapeutic alliance and rapport, the quality of the psychedelic experience and GAD symptoms in each arm via the Sesson Rating Scale (SRS) at each psychological support session, EBI at each dosing session and HAM-A at weeks 4, 8, 11, 20 and 29.

EEG/ECG outcome measures:
1. Change in resting-state connectivity and complexity and heart rate variability via 10 min resting-state EEG and ECG at baseline and weeks 4, 8, and 29. These are collected during two resting state conditions: eyes open (EO) for a 5-minute duration and eyes closed (EC) for another 5 minutes. During the eyes-open condition, participants are directed to concentrate on a cross displayed on the screen, and for the eyes-closed condition, participants are instructed to remain relaxed while ensuring they do not fall asleep.
2. Change in neural responses to emotional faces via the Emotional faces task (EEG, performance and ECG) at baseline and weeks 4, 8, and 29. During the training session of the task, 36 face images with either a happy, sad or neutral expression are sequentially presented to the participant and subsequently repeated for a total of two views and the participant is instructed to memorize the images. Following the training session, the same target images are interspersed in 36 additional nontarget emotional face images. The participant indicates whether the images are target or nontarget with a keystroke. For each acquisition, three repetitions of the task are administered sequentially for a total of 108 Target and 108 nontarget stimuli for analysis and a total duration of 24 minutes.
3. Change in auditory habituation via the Auditory Oddball task (EEG, performance and ECG) at weeks 4, 8 and 29. The AO task plays a standard tone with a frequency of 1000 Hz (non-target) and a duration of 150 ms, and a deviant tone with a frequency of 500 Hz (target) with a duration of 150 ms. Participants are instructed to press the space bar as quickly as possible in response to the deviant (target) tone and ignore the standard (non-target) tone. A total of 500 stimuli (80 percent standard and 20 percent deviant) will be played with an inter-stimulus interval of 1 second. The total task duration is 8 minutes.
4. Correlation between change in resting-state EEG connectivity with change in clinical measures via the resting-state EEG/ECG correlates of HAM-A, GAD-7, SDS, WEMWBS, LWP, HU and PHQ-9 at baseline, week 4, 8 and 29. Correlation between change in neural responses to emotional faces and change in clinical measures via the Emotional faces tasks and auditory oddball EEG correlates of HAM-A, GAD-7, SDS, WEMWBS, LWP, HU & PHQ-9 at baseline and week 4, 8 and 29.

Completion date
30/04/2027

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
1. Aged 18 - 70 years
2. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)/International Classification of Diseases 11th Revision (ICD-11) defined GAD as the primary diagnosis, with severity indicated by a HAM-A score >25
3. Any sex or gender
4. Body Mass Index 18 - 35 kg/m²
5. Medically suitable as determined by screening including a past medical history, family history, drug history, social history, physical examination and investigations, including an electrocardiogram (EEG) and blood tests.
6. Refrain from taking contraindicated or excluded medications, including herbal, complementary or over-the-counter medications, or have safely tapered and washed out from excluded medications in accordance with the washout period specified in the protocol.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
70 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Any clinically significant, untreated or unstable illness (e.g., hepatic, renal or cardiovascular functions)
2. Type 1 diabetes or insulin dependent type 2 diabetes
3. A diagnosis of epilepsy or at significant risk of seizures based on medical history
4. Positive urine drug test for psychoactive substances at in-clinic screening visit or dosing visits
5. Positive alcohol breathalyser test at the in-clinic screening visit or dosing visits
6. Female participants who are pregnant, breastfeeding or of childbearing potential who are unwilling or unable to use a highly effective method of contraception
7. Participation in another clinical trial of an investigational drug within 30 days or 5 half-lives of the drug (whichever is longest) prior to screening
8. Allergy, hypersensitivity or other Adverse Reaction (AR) to previous use of psilocybin, other hallucinogens, rescue medication and their excipients microcrystalline cellulose
9. Anyone with organic brain injury
10. Treatment with any other antidepressant medication other than a currently prescribed permitted SSRI which must be a stable dose (constant for at least 6 months with no plan to

increase)
11. Diagnosed with or having a first degree-relative family history of any of the following psychiatric disorders: schizophrenia or prodromal symptoms, any bipolar disorder, or other psychotic disorder as assessed during screening
12. Any history of suicide attempts or behaviours as indicated by reporting "yes" on any item of the Suicide Behaviour Section of the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 5 years
13. History of suicidal ideation with some intent to act within the last 12 months prior to screening; the participant scores "yes" on item four or item five of the Suicidal Ideation section of the C-SSRS
14. Judged to be of high suicide or self-harm risk following psychological assessment at screening or baseline
15. Judged to be unfit for psilocybin-assisted therapy based on assessments made during psychological support sessions prior to first dosing session
16. Current or recent treatment with prohibited medications
17. History of hallucinogen use disorder, or any use in the past 1 year, or >25 lifetime uses
18. History of electroconvulsive treatment (ECT) or transcranial magnetic stimulation treatment, ketamine, or vagal nerve stimulation
19. Current (within 12 months) alcohol or drug abuse identified as moderate or severe during screening through medical history and the Mini International Neuropsychiatric Interview (MINI) 7.0.2

Date of first enrolment
01/04/2026

Date of final enrolment
01/01/2027

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
Incannex Healthcare Limited

Funder(s)

Funder type
Industry

Funder Name
Psychennex Pty Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available