

CLINICAL STUDY REPORT

Psilocybin in Depression Resistant to Standard Treatments (PsiDeR) Trial

A randomised, placebo-controlled trial of psilocybin in treatment resistant depression: a feasibility study

Sponsor Protocol Code:	PsiDeR
EudraCT Number:	2018-003573-97
ClinicalTrials.gov Identifier:	NCT04959253
ISRCTN number:	Not applicable (trial registered on ClinicalTrials.gov and EudraCT)
REC Number:	20-LO/0206
IRAS Project ID:	252750
Investigational Medicinal Product (IMP):	Psilocybin (3-[2-(Dimethylamino)ethyl]-1H-indol-4-yl dihydrogen phosphate), 25mg per os
Indication:	Treatment Resistant Major Depressive Disorder (TRD/MDD)
Development Phase:	Phase 2
Study Begin (FPFV):	21 June 2021
Study End (LPLV):	18 December 2024
Report Version & Issue Date:	Version 1.0
Co-Sponsor Name and Address:	King's College London South London and Maudsley NHS Foundation Trust
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Chief Investigator:	Professor Allan Young

SIGNATURE PAGE

By signing below, I approve the contents of this Clinical Study Report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

This was a non-commercial academic trial; the results of this study are not intended to be used in a licensing application.

Chief Investigator:	Printed name	Signature
Professor Allan Young	Professor Allan Young Sep 6, 2026 16:21 BST	DocuSigned by: Professor Allan Young 9932E5AB0ECF4A9...

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1. Ethics

Independent Ethics Committee or Institutional Review Board

The study protocol and all substantial amendments were reviewed and approved by the Health Research Authority and National Research Ethics Service Committee London – London Brent (REC reference: 20-LO/0206). The trial was registered with the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) under EudraCT number 2018-003573-97.

Ethical conduct of the study

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki the principles of Good Clinical Practice (GCP) and in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, the Research Governance Framework for Health and Social Care, the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. The trial protocol and substantial amendments were reviewed by internal R&D, REC, HRA and MHRA.

Subject information and consent

Potential trial participants were initially screened by telephone or online survey by a member of the study team. Those who were deemed potentially eligible were invited to a face-to-face screening assessment. Final study inclusion and written informed consent was obtained by a study psychiatrist. Participants were provided with a Participant Information Sheet and given sufficient time to consider their participation. All participants gave written informed consent prior to any study-specific procedures being undertaken. Separate consent forms were available for the optional open-label extension and neuroimaging add-on studies.

2. Data Monitoring

An independent Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) provided oversight of the trial. The TSC included independent clinical experts and patient/public representatives. The DMEC included independent statistical and clinical experts who reviewed unblinded safety data at pre-specified intervals. Both committees reported to the sponsor. Meeting dates, membership, and terms of reference for both committees are held by the Trial Management Group.

TSC/DMEC Members: Celia Morgan, Winston Banya, Michael Bourne, Ian Roullier, Sarah Markham, Chao Huang, James Rucker, Tim Mantingh, Ben Carter, Petrina Chu, Catherine Bird. Specific meeting dates and recommendations are held by the Trial Management Group.

3. Sponsors, Investigators and Trial Sites

Co-Sponsors	King's College London Contact: Ann Marie Murtagh King's Health Partners Clinical Trials Office F16 Guy's Tower, Guy's Hospital, Great Maze Pond, London, SE1 9RT
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	Tel: +44 020 71885732 Email: QM.KHPCTO@kcl.ac.uk South London and Maudsley NHS Foundation Trust Maudsley Hospital, Denmark Hill, London, SE5 8AZ
Chief Investigator	Professor Allan Young PO72, The Centre for Affective Disorders Institute of Psychiatry, Psychology & Neuroscience King's College London 16 De Crespigny Park, London, SE5 8AF Tel: 02078480088 Fax: 02078480298 Email: allan.young@kcl.ac.uk
Principal Investigator	Dr James Rucker PO72, The Centre for Affective Disorders Institute of Psychiatry, Psychology & Neuroscience King's College London 16 De Crespigny Park, London, SE5 8AF Tel: 02078480088 Fax: 02078480298 Email: james.rucker@kcl.ac.uk
Trial Site(s)	NIHR/Wellcome Trust Clinical Research Facility King's College Hospital, Denmark Hill, London, UK Centre for Mental Health Research and Innovation (CMHRI) 5 Windsor Walk, Camberwell, London, UK
Funding	National Institute for Health Research (NIHR) Grant reference: CS-2017-17-007

4. Co-Investigators, Statistician, Laboratories, Database Management

Statistician	Dr Ben Carter Department of Biostatistics & Health Informatics Institute of Psychiatry, Psychology & Neuroscience King's College London, 16 De Crespigny Park, London, SE5 8AF Tel: 02078480305 Fax: 02078480298 Email: ben.carter@kcl.ac.uk
Statistical Analysis	King's Clinical Trials Unit (KCTU) Institute of Psychiatry, Psychology & Neuroscience King's College London
Randomisation Service	King's Clinical Trials Unit (KCTU) web-based randomisation service
IMP Manufacturer / Supplier	Drug substance: Onyx Scientific Ltd for Compass Pathways Ltd Formulation: Juniper Pharma Services Ltd Packaging / Distribution: Fisher Clinical Services UK Ltd (Langhurstwood Road, Horsham, West Sussex, RH12 4QD, UK)
IMP Dispensing Pharmacy	Maudsley Hospital Pharmacy, King's College Hospital NHS Foundation Trust
Database Management	Trial data recorded on a secure, password-protected database managed by the Principal Investigator (Dr James Rucker). Data analysis conducted using Stata version 18.0 and R version 4.1.1 (or later).
Co-Investigators & Study Team	Tim Mantingh, Jess Kerr-Gaffney, Catherine Bird, Nadav Liam Modlin, Kete Campbell-Coker, Sadie Hambleton, Paige Seath, Rebecca Hignett, Diede Fennema, Elliot Hampsey, Dimosthenis Tsapekos, Rebecca J.

	Thomas, Joseph Cattell, Hassan Jafari, Petrina Chu, Camilla Day, Anya Borissova, Miranda Lloyd, Theo Boardman-Pretty, Mathieu Seynaeve, Famia Askari, Michael Creed, Luke Baxter, Raphael Rifkin-Zybutz, Matt Butler, Luke A. Jelen (All: King's College London and/or South London and Maudsley NHS Foundation Trust)
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5. Study Synopsis

Title of clinical trial	A randomised, placebo-controlled trial of psilocybin in treatment resistant depression: a feasibility study
Protocol Short Title/Acronym	(Psi)locybin in (De)pression (R)esistant to standard treatments (PsiDeR) trial
Study Phase	Phase 2
Sponsor name	King's College London / South London and Maudsley NHS Foundation Trust
Chief Investigator	Professor Allan Young
EudraCT number	2018-003573-97
REC number	20-LO/0206
IRAS Project ID	252750
Medical condition or disease under investigation	Major Depressive Disorder (MDD) – Treatment Resistant (TRD)
Investigational Medicinal Product (IMP)	Psilocybin 25mg per os (5 × 5mg HPMC capsules)
Purpose of clinical trial	To evaluate the feasibility, safety and preliminary efficacy of psilocybin, given under psychologically supportive conditions, in a randomised, blinded trial design in adult participants with treatment resistant major depressive disorder.
Primary objective	To evaluate the feasibility of a randomised, controlled trial design in which a single dose of psilocybin 25mg PO vs placebo is given to adult participants with treatment resistant major depressive disorder (TRD), under psychologically supportive conditions, with 6 weeks of follow up, by measuring recruitment rates, dropout rates and by estimating the variance of the primary outcome measure (MADRS) to inform the design of a phase 3 trial.
Secondary objectives	1. To assess the clinician-rated efficacy of psilocybin 25mg vs placebo via: (a) change in MADRS total score from Baseline to Week 3; (b) proportion demonstrating MADRS response ($\geq 50\%$ decrease) at Weeks 1, 3 and 6; (c) proportion in MADRS remission (total score ≤ 10) at Weeks 1, 3 and 6. 2. To assess participant-rated efficacy via: (a) QIDS-SR-16 response ($\geq 50\%$ decrease, Baseline to Week 3); (b) QIDS-SR-16 remission (total score ≤ 5) at Weeks 1, 3 and 6. 3. To assess participant-rated efficacy via MVAS total score and individual items from Baseline to Days 1, 7, 21 and 42 after treatment. 4. To evaluate safety and tolerability based on adverse events, changes in vital signs and suicidal ideation/behaviour (Columbia Suicide Severity Rating Scale, CSSRS).
Exploratory objectives	1. To explore the acceptability, tolerability and safety of delivering >1 dose of psilocybin via an optional 12-week open-

	label extension. 2. Exploratory analyses of predictors and mediators of treatment response.
Trial Design	Two-arm, double-blind, randomised, placebo-controlled, between-subjects design
Primary endpoints	Recruitment rates, dropout rates and estimation of the variance of the primary outcome measure (MADRS)
Planned number of subjects	60 (30 per arm)
Actual number randomised	60 (30 psilocybin, 30 placebo)
Summary of eligibility criteria	1) Age 25 - 80 years 2) Fluent in the English language 3) Fulfil Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-5) criteria for current single or recurrent episodes of MDD of at least moderate severity but without psychotic features, as defined on the MINI 7.0. 4) 17-item HAM-D score ≥ 14 . 5) Have failed to respond to 2 or more antidepressants prescribed at the minimum effective dose for at least 6 weeks OR at least 1 antidepressant prescribed at the minimum effective dose for at least 6 weeks AND a course of evidence-based psychotherapy given for at least 6 sessions. 6) For those aged ≥ 60 years, the first episode of depression must have started prior to their 60th birthday.
IMP, dosage and route of administration	Psilocybin 25mg, single oral dose (5 $\times$ 5mg HPMC capsules)
Comparator product(s)	Matching placebo (5 $\times$ 5mg HPMC capsules, Starch 1500 only)
Maximum duration of treatment per subject	1 day (single dose administration)
Follow-up duration	6 weeks (core RCT); up to 12 additional weeks for those consenting to open-label extension (OLE). Total maximum involvement: up to 26 weeks.
Planned trial period	September 2020 – February 2025
Actual recruitment period	21 June 2021 – 03 July 2024
Version and date of final protocol	v1.21, 15 August 2024

6. Glossary of Terms

Abbreviation	Definition
5D-ASC	5-Dimension Altered State of Consciousness Scale
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
ASRM	Altman Self-Rating Mania Scale
CI	Chief Investigator
CMHRI	Centre for Mental Health Research and Innovation
CRF	Clinical Research Facility
CSSRS	Columbia Suicide Severity Rating Scale
DePAS	Delayed Psychedelic After Effects Scale
DMEC	Data Monitoring and Ethics Committee

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EQ-5D-5L	EuroQoL 5-Dimension 5-Level Scale
PPFV	First Patient First Visit
GAD-7	Generalised Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Rating Scale
HPMC	Hydroxypropylmethylcellulose
HPPD	Hallucinogen Persisting Perception Disorder
IME	Important Medical Event
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ITT	Intention to Treat
KCTU	King's Clinical Trials Unit
KCL	King's College London
KHP	King's Health Partners
LPLV	Last Patient Last Visit
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini Neuropsychiatric Inventory
MSM	Maudsley Staging Method
MTI	Maudsley Treatment Inventory
MVAS	Maudsley Visual Analogue Scales (3-item)
NHS	National Health Service
NIHR	National Institute for Health Research
OLE	Open-Label Extension
PANAS	Positive and Negative Affect Scale
PI	Principal Investigator
PsiDeR	Psilocybin in Depression Resistant to treatment
QIDS-SR-16	Quick Inventory of Depressive Symptoms – Self Report (16-item)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SLaM	South London and Maudsley NHS Foundation Trust
SOC	System Organ Class
SP	Screening and Preparation Phase
STAI	State-Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRD	Treatment Resistant Depression
TSC	Trial Steering Committee
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

7. Publication (reference)

Rucker, J. J., Mantingh, T., Kerr-Gaffney, J., Bird, C., Chu, P., Modlin, N. L., Campbell-Coker, K., Hambleton, S., Seath, P., Hignett, R., Fennema, D., Hampsey, E., Tsapekos, D., Thomas, R. J., Cattell, J., Jafari, H., Day, C., Borissova, A., Lloyd, M., ... Young, A. H. (2026). Psilocybin-assisted therapy for treatment-resistant major depressive disorder in a public healthcare setting: a randomized controlled trial. *Nature Medicine*. <https://doi.org/10.1038/s41591-026-04541-0>

Rucker J, Young AH, *et al*. Psilocybin-assisted therapy for the treatment of resistant major depressive disorder (PsiDeR): protocol for a randomised, placebo-controlled feasibility trial. *BMJ Open* 2021;**11**:e056091. doi: 10.1136/bmjopen-2021-056091

8. Study Period (years)

The planned trial period was September 2020 to February 2025. The trial opened to recruitment on 21 June 2021 (date of first participant consent and screening; First Patient First Visit, FPFV). Recruitment was completed on 03 July 2024, when the 60th participant was randomised.

Last Patient Last Visit (LPLV): 18 December 2024

All 60 randomised participants attended the dosing visit (V3). Recruitment was not interrupted and the trial was not terminated prematurely. End of trial was defined as date of database lock, which happened on 28 August 2025.

9. Phase of Development

This was a Phase 2, randomised, double-blind, placebo-controlled feasibility trial. The primary purpose was to establish the feasibility parameters necessary to design a future Phase 3 confirmatory trial of psilocybin-assisted therapy in treatment resistant major depressive disorder.

10. Objectives

Primary Objective

To evaluate the feasibility of a randomised, controlled trial design in which a single dose of psilocybin 25mg per os vs placebo is given to adult participants with treatment resistant major depressive disorder (TRD), under psychologically supportive conditions, with 6 weeks of follow up, by measuring recruitment rates, dropout rates and by estimating the variance of the primary outcome measure (MADRS) to inform the design of a Phase 3 trial.

Secondary Objectives

1. To assess the clinician-rated efficacy of psilocybin 25mg compared to placebo via: (a) the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from Baseline to 3 weeks after treatment; (b) the proportion of participants demonstrating a response to treatment, defined as a $\geq 50\%$ decrease in MADRS total score from Baseline to Week 3 (also

assessed at Weeks 1 and 6); (c) the proportion of participants in remission, defined as a MADRS total score ≤ 10 at Week 3 (also assessed at Weeks 1 and 6).

2. To assess the participant-rated efficacy of psilocybin 25mg compared to placebo via: (a) the proportion of participants demonstrating a response, defined as a $\geq 50\%$ decrease in QIDS-SR-16 total score from Baseline to Week 3 (also assessed at Weeks 1 and 6); (b) the proportion of participants in remission, defined as a QIDS-SR-16 total score ≤ 5 at Week 3 (also assessed at Weeks 1 and 6).

3. To assess participant-rated efficacy via the Maudsley Visual Analogue Scale (MVAS) total score and individual items from Baseline to Day 1, Week 1, Week 3 and Week 6 after treatment.

4. To evaluate the safety and tolerability of psilocybin in participants with TRD based on adverse events (AEs), changes in vital signs and suicidal ideation/behavior measured using the Columbia Suicide Severity Rating Scale (CSSRS).

Exploratory Objectives

1. To explore the acceptability, tolerability and safety of delivering more than one dose of psilocybin by collecting safety data and participant narrative data from an optional 12-week open-label extension to the trial.

2. Exploratory analyses of predictors and mediators of response to treatment.

11. Background and Context

Major depressive disorder (MDD) is a disabling and economically costly mental health problem, affecting approximately 300 million people worldwide. Its prevalence in England is estimated at 29–42 per thousand people. Treatment resistant depression (TRD), defined as failure to respond to at least two antidepressants at therapeutic dose for at least 6 weeks, affects one third of those who suffer from clinical depression, and is associated with a poorer prognosis, higher economic burden and increased risk of suicide attempt and completion. Treatment options with best evidence for efficacy in TRD include ketamine, esketamine, adjunctive psychotherapy, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS); however, access to these specialised treatments is limited.

There have been few breakthrough pharmaceutical treatments for MDD since the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the late 1980s. In response, clinicians and researchers have revisited earlier psychiatric treatments, including the classical psychedelic drugs, which were investigated as potential treatments before prohibition in 1970. The active metabolite of psilocybin, psilocin, is a partial agonist of the 5-HT_{2A} receptor and is thought to account for many of the characteristic subjective effects, including heightened emotions, mystical experiences, altered perceptions and ego dissolution. These subjective effects may facilitate psilocybin's putative therapeutic effects.

Modern clinical research into psilocybin began again in the 2000s. Our group previously conducted a phase 1 randomised, placebo-controlled safety study in 89 healthy volunteers (1:1:1 allocation to placebo, 10mg or 25mg psilocybin), with no SAEs or AEs leading to withdrawal reported, and no negative cognitive effects compared to placebo. Prior to this trial, an open label pilot study in 20 patients with TRD in England reported substantial and durable reductions in depression severity with no serious adverse events. The current trial was the first to specifically assess the feasibility of an RCT design within an NHS setting in England using a true placebo control.

12. Methodology

Conceptual Framework

This was a two-arm, double-blind, randomised, placebo-controlled, between-subjects feasibility trial with a central 'core' RCT element and three optional 'orbiting' elements: (1) collection of additional biological samples (blood), (2) neuroimaging (fMRI), and (3) an open-label extension (OLE). The optional elements required separate informed consent and participants could withdraw from them at any time without affecting their participation in the core trial.

Trial Sites

All study visits took place at the NIHR/Wellcome Trust Clinical Research Facility (CRF) at King's College Hospital, Denmark Hill, London, UK, or at the Centre for Mental Health Research and Innovation (CMHRI), 5 Windsor Walk, Camberwell, London, UK.

Recruitment

Trial participants were recruited from secondary care referrals, primary care referrals, IAPT (Improving Access to Psychological Therapies) service referrals, established clinical trial registries, and directly via word of mouth and advertising in the community and on social media.

Trial Duration

Each participant's total involvement in the core trial was between 7 and 14 weeks, comprising a Screening and Preparation (SP) phase of 1–8 weeks, a single Dosing Visit (Day 0), and a 6-week Follow-Up Phase. Participants who consented to the OLE could be involved for up to 26 weeks in total.

Visit Schedule

The visit schedule comprised: V1 Screening (Days -56 to -7); V2 Baseline (Day -1); V3 Dosing/Treatment (Day 0); V4 Follow-Up 1 (Day 1, +1 day window); V5 Follow-Up 2 (Week 1, ± 1 day); V6 Follow-Up 3 (Week 3, ± 2 days); V7 Follow-Up 4 / Study End (Week 6, +7/-3 days). The Dosing Visit took place 1–3 days after the Baseline Visit.

During the Screening and Preparation Phase, participants underwent medical and psychiatric screening, supervised withdrawal from antidepressant medications (washout of 1–8 weeks, depending on the medication), and received at least 3 hours of psychological preparation over at

least 2 separate sessions with a dedicated therapist. Clinical risk was monitored weekly during this phase.

Randomisation

Randomisation was performed by the King's Clinical Trials Unit (KCTU) using a web-based randomisation service with minimisation, balanced by sex (male/female), age group (25–59 vs ≥60 years) and prior psilocybin use (yes/no). The allocation sequence was concealed from all researchers and the trial statistician.

Blinding

Both treatments were delivered in 5 identical opaque HPMC capsules. All participants and members of the study team present during the Dosing Visit were blinded to treatment allocation. Allocation concealment was maintained by the Maudsley Hospital Pharmacy. Emergency unblinding was available 24 hours per day via the on-call pharmacist. MADRS assessments were done by blinded raters who were external and independent to the study team.

Dosing Visit

Both treatment arms were delivered in identical settings at the NIHR CRF or CMHRI. The treatment environment was a quiet, neutrally furnished room with adjustable lighting, a reclining seat or bed, and two chairs for the therapist and chaperone. Participants were given an eye mask and earphones through which they listened to a curated playlist of relaxing music. A therapist and chaperone were present at all times. Participants were required to remain at the CRF until clinically determined safe to leave (minimum 4–6 hours after ingestion). A rescue medication protocol using oromucosal midazolam 2.5–5mg was available for extreme distress unresponsive to non-pharmacological intervention.

Follow-Up Phase

The 6-week follow-up phase comprised four visits: Day 1 (V4), Week 1 (V5), Week 3 (V6) and Week 6 (V7). At each visit, participants met with their therapist for up to 90 minutes for psychological integration support. Clinical outcome, safety and mechanism measures were administered at each visit as per the schedule of assessments.

Open-Label Extension (OLE)

Participants who completed the 6-week follow-up and met eligibility criteria were offered a 12-week open-label extension. Those consenting received a single open-label dose of psilocybin 25mg under identical conditions to the core trial dosing visit (OLE2), with follow-up visits at 1 day, 1 week, 3 weeks, 6 weeks and 12 weeks after the OLE dose.

Psychological Support Model

All participants received psychological preparation before the Dosing Visit, support during the Dosing Visit (therapist and chaperone present throughout), and integration therapy after the Dosing Visit. Therapists and chaperones were volunteers with appropriate professional credentials and honorary contracts with the sponsoring NHS Trust. The number of hours of psychological support for each participant was recorded as an independent variable.

Schedule of Events

Table 1. Schedule of events

Study Team Administered Measures and Procedures													
Visit	V1	V2	V3	V4	V5	V6	V7/ OLE1	OLE2	OLE3	OLE4	OLE5	OLE6	OLE 7
Day	-56 -7	-1	0	1	7	21	41	42#	43	49	63	84	126
Week	-8 - -1	0	0	0	1	3	6	6#	6	7	9	12	18
Location	KCH Clinical Research Facility/CMHRI												
Window	N/A	-3	N/A	+1	+/- 1	+/- 2	+7/- 3	NA#	+/- 1 **	+/- 1 **	+/- 2 **	+/- 3 **	+/- 7 **
Length of Visit (hrs)*	4	6	8	4	6	4	4	8	4	2	4	2	2 r
Informed Consent	15						(15)						
Medical History	15	10	10										
Inc/Exc criteria	15	10					(15)						
Prior/concom. meds	15	10	5	5	5	5	5	5	5	5	5	5	5
Physical examination	10	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***	10 ***
Collateral	30	30					30						
AE/SAE	15	15	15	15	15	15	15	15	15	15	15	15	15
Clinical lab. blood tests	15	15		15					15				
ECG	15			15					15				
Vitals	5	5	5	5			(5)	5	5				
Weight	5	5					5					5	
Urinalysis	5												
Urine drug screen	5						(5)						
Urine/serum pregnancy test	5	5					(5)						
Bloods (additional)		15		15	15	15	15						
Neuroimaging		90			90								
Mobile phone/fitness watch							15					15	
Psych. support & SI (flexible schedule +/- remote)		60	360	60	60	60	60	360	60	60	60	60	60
IMP			15					15					
MINI	60												
HAM-D-17	10	10											
MSM	5												
MADRS		10			10	10	10			10	10	10	10
CSSRS	5	5		5	5	5	5		5	5	5	5	5
YMRS		5		5	5	5	5		5	5	5	5	
MTI*	10												
STAR-C		5			5	5	5			5	5	5	
Participant Administered Measures and Procedures													
QIDS-SR-16	5	5			5	5	5			5	5	5	5
GAD-7		5			5	5	5			5	5	5	5
CTS		5											
STAI		5			5	5	5			5	5	5	
STAR-P		5			5	5	5			5	5	5	
DESS		10											
5D-ASC				15					15				

ASRM		5			5	5	5			5	5	5	5
SCL-90		10			10								
DePAS					5	5	5			5	5	5	
EQ-5D-5L		5				5	5				5	5	5
WSAS	5	5				5	5				5	5	5
TAS		5					5					5	
PANAS		5		5	5	5	5		5	5	5	5	5
SCSS		5		5			5		5				
SCST		5				5	5				5	5	
CES				5					5				
TSDI		5					5						
WEMWBS		5				5	5				5	5	
CNS		5				5	5				5	5	
SAPAS	5	5					5					5	
THINC-it	20	20			20		20			20		20	
ETB		20			20		20			20		20	
MVAS	5	5		5	5	5	5		5	5	5	5	
(X) = If consent to OLE given	r = remote visit available				SI = Structured Interview				*joint completion with clinician				
	#up to 5 weeks after V7, if logistically necessary				***if clinically indicated				**relative to date of OLE2				
Medic Task	Nurse/RA Task				Therapist Task				Participant Task				

13. Number of Patients (planned and analysed)

Planned

The planned sample size was 60 participants (30 per arm). This sample size was chosen to satisfy the primary feasibility objectives (estimation of recruitment rates, dropout rates and variance of the MADRS) to power a future Phase 3 trial. No formal hypothesis testing power calculation was performed, as this was a feasibility trial.

Analysed

Between 21 June 2021 and 03 July 2024, 75 participants consented and were screened for eligibility. Sixty participants (80% of those screened) were randomised. Fifteen participants were ineligible following full screening. All 60 randomised participants attended the Dosing Visit (V3). One participant in the placebo arm withdrew prior to providing follow-up MADRS data (personal reasons) and was excluded from the mixed models analysis; all 60 were included in the primary feasibility analyses.

Table 2. Missingness primary outcome

	Psilocybin arm	Placebo arm
Participants screened/consented	75 (overall)	
Eligible at screening	62 (overall; 83%, 95% CI: 72–90%)	
Randomised	30	30
Attended dosing visit (V3)	30	30

Completed Week 1 follow-up (V5) MADRS	30	29
Completed Week 3 follow-up (V6) MADRS	30	29
Completed Week 6 follow-up (V7) MADRS	30	29
Withdrew during study	0	1 (personal reasons, prior to Week 1)

Table 3. Participant retention & withdrawal

Patient	Comments
1 (Placebo arm)	Withdrew prior to providing follow-up MADRS data for personal reasons unrelated to the study. Included in the primary feasibility ITT analysis; excluded from mixed models for clinical outcomes. No safety concerns.

No participants were withdrawn for safety reasons. No rescue medication was administered during any Dosing Visit.

14. Diagnosis and Main Criteria for Inclusion

Medical diagnosis

Major Depressive Disorder (MDD), Treatment Resistant (TRD). Diagnosis confirmed by the Mini Neuropsychiatric Inventory (MINI) version 7.0 and clinical interview by a study psychiatrist, using DSM-5 criteria.

Inclusion criteria

- Age 25 - 80 years
- Fluent in the English language
- Fulfil Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-5) criteria for a 294 primary diagnosis of current single or recurrent episodes of MDD of at least moderate severity but without psychotic features as defined on the MINI 7.0. Positive and primary diagnoses on the MINI 7.0 will be subject to confirmation at clinical interview by a psychiatrist.
- 17-item HAM-D score ≥ 14 .
- Have failed to respond to 2 or more antidepressants prescribed at the minimum effective dose for at least 6 weeks OR at least 1 antidepressant prescribed at the minimum effective dose for at least 6 weeks AND a course of evidence-based psychotherapy given for at least 6 sessions.
- For those aged ≥ 60 years, the first episode of depression must have started prior to their 60th birthday.

Key exclusion criteria

- Diagnosis of bipolar disorder, psychotic disorder (non-substance-induced), drug or alcohol dependence syndrome, personality disorder, or dementia (all DSM-5, confirmed at clinical interview).
- Personal history of ≥ 1 suicide attempt in the past year requiring hospitalisation.
- Diagnosis of uncontrolled diabetes, hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg on three separate readings), cardiac failure (NYHA Class IV), renal failure (GFR ≤ 29 mL/min), liver failure, cardiac arrhythmia (except AF), epilepsy, cerebrovascular accident/intracerebral trauma, myocardial infarction within 1 year.
- Biochemical or ECG abnormalities determined as clinically significant.
- Women of childbearing potential not using adequate contraception; pregnant or breastfeeding women.
- Enrolled in another drug trial.
- Hypersensitivity to psilocybin or any excipient.
- Unable to provide informed consent.
- Other personal circumstances or behaviour judged incompatible with safe psilocybin exposure.

15. Test Product, Dose and Mode of Administration

Baseline therapy

Prior to the Dosing Visit, participants were required to withdraw from all antidepressant and antidepressant augmentation medications under the supervision of a study psychiatrist. Washout duration was a minimum of 1 week and a maximum of 8 weeks, depending on the medication. Hypnotic medications (zopiclone, zolpidem or zaleplon within BNF dosage) for insomnia, or a benzodiazepine (lorazepam or diazepam) or promethazine for anxiety/withdrawal phenomena, were permitted during the SP phase. All other medications for non-psychiatric medical conditions were permitted, provided they did not interact unfavorably with the IMP.

Table 4. Investigational Medicinal Product (IMP)

IMP Name	Psilocybin
IUPAC Name	3-[2-(Dimethylamino)ethyl]-1H-indol-4-yl dihydrogen phosphate
Other Common Name	4-Phosphoryloxy-N,N-dimethyltryptamine
Chemical Formula	C ₁₂ H ₁₇ N ₂ O ₄ P
Molar mass	204.27 g/mol
Physical Form	Solid (white crystalline powder); soluble in water/saline
Dosage form	Immediate-release solid dosage form in HPMC capsules (No. 4, white)
Dose	25mg (5 × 5mg HPMC capsules), single oral dose
Manufacturer of drug substance	Onyx Scientific Ltd for Compass Pathways Ltd
Manufacturer of formulated IMP	Juniper Pharma Services Ltd

IMP packaging / distribution	Fisher Clinical Services UK Ltd, Langhurstwood Road, Horsham, West Sussex, RH12 4QD, UK
IMP dispensing / storage	Maudsley Hospital Pharmacy (Schedule 1 possession and dispensing licence held). Stored in accordance with Schedule 1 requirements. IMP transported to the CRF in a locked box on the day of administration.
Prescribers	Dr James Rucker and Professor Allan Young (both hold Schedule 1 prescribing licences issued by the UK Home Office).
CESP number	986583 (IMP Dossier held by MHRA)

Table 5. Dose of IMP administered

Study Arm	n	Dose administered
Psilocybin	30	Psilocybin 25mg (5 × 5mg HPMC capsules), single oral dose
Placebo	30	Placebo (5 × 5mg HPMC capsules, Starch 1500 only), single oral dose

All 60 randomised participants attended the Dosing Visit and received their full dose (all 5 capsules). Compliance was 100%. The duration of action of psilocybin 25mg was approximately 4–6 hours; all participants were observed at the CRF or CMHRI for this period.

16. Duration of Treatment

The maximum duration of treatment for a participant in the RCT phase was one day (single oral dose at V3). Including the open-label extension, participants who received a second dose of psilocybin (OLE2) had a maximum total treatment duration of two single-dose days over the course of the study. No participant received more than two doses of psilocybin in total (one in the core RCT and one in the OLE).

17. Reference Therapy, Dose and Mode of Administration

The comparator was an identical-appearing placebo consisting of 5 × 5mg HPMC capsules containing Starch 1500 only. All placebo capsules were manufactured by Juniper Pharma Services Ltd and packaged by Fisher Clinical Services UK Ltd under identical conditions to the active IMP. The placebo was administered in the same setting and manner as the active IMP.

18. Criteria for Evaluation: Endpoints

Primary Endpoint (Feasibility)

- Recruitment rate: proportion of participants found eligible at screening and subsequently randomised (with 95% confidence intervals).
- Retention rate: proportion of randomised participants completing each follow-up visit with at least the MADRS completed.

- Estimation of the variance of the primary outcome measure (MADRS total score) to inform the sample size calculation for a future Phase 3 trial.

Secondary Endpoints (Efficacy)

1. The change in MADRS total score from Baseline (V2) to Week 3 (V6) after treatment.
2. Proportion of participants demonstrating a MADRS treatment response ($\geq 50\%$ decrease in total score from Baseline) at Week 3; also assessed at Weeks 1 and 6.
3. Proportion of participants in MADRS remission (total score ≤ 10) at Week 3; also assessed at Weeks 1 and 6.
4. Proportion of participants sustaining MADRS response at Week 6 (defined as $\geq 50\%$ decrease at or before Week 3, maintained at Week 6).
5. Change in MVAS total score and individual items from Baseline to Day 1, Week 1, Week 3 and Week 6.
6. QIDS-SR-16 response ($\geq 50\%$ decrease from Baseline) at Week 3; also at Weeks 1 and 6.
7. QIDS-SR-16 remission (total score ≤ 5) at Week 3; also at Weeks 1 and 6.
8. Time to restarting antidepressant medication.

Safety Parameters

- Adverse events (AEs) and serious adverse events (SAEs): number, type, severity (using CTCAE grading where applicable), and relatedness to study medication, coded using MedDRA.
- Suicidal ideation and behaviour: Columbia Suicide Severity Rating Scale (CSSRS), administered at all follow-up visits.
- Manic symptoms: Young Mania Rating Scale (YMRS) and Altman Self-Rating Mania Scale (ASRM), at all follow-up visits.
- Vital signs (blood pressure, heart rate, temperature) at V2, V3 and V4.
- Clinical laboratory investigations (full blood count, biochemistry, thyroid function) at screening, V2 and V4.
- ECG at screening and V4.
- Hallucinogen Persisting Perception Disorder: assessed using the HPPDS at follow-up.
- Delayed Psychedelic After Effects Scale (DePAS) at Weeks 1, 3 and 6.

19. Statistical Methods

Statistical analyses were pre-specified in a Statistical Analysis Plan (SAP) developed by the King's Clinical Trials Unit (KCTU) and approved prior to database lock. All analyses were conducted in Stata version 18.0; R version 4.1.1 (or later) was used for data visualisation. No significance testing or p-values were pre-specified as primary inferential tools; the purpose of the analysis was to estimate feasibility parameters and effect sizes for planning a future trial.

Analysis of Feasibility Variables

Feasibility parameters (recruitment rate, eligibility rate, randomisation rate, follow-up rate, measure completion rates) were reported as proportions with corresponding 95% confidence intervals (Clopper-Pearson method).

Analysis of Efficacy Variables

Adjusted mean differences (aMD) between arms on continuous clinical outcomes (MADRS, QIDS-SR-16, GAD-7, EQ-5D-5L VAS, WSAS, MVAS, WEMWBS) were estimated using mixed linear regression models with an intention-to-treat (ITT) population. Models included post-treatment measures as dependent variables with a random intercept at participant level. Fixed effects were fitted for: baseline measure of outcome; trial arm; design factors (sex, age group, prior psilocybin use); time; and an arm*time interaction term. Standardised effect sizes (Cohen's d) were derived by dividing aMDs by the pooled baseline SD of the outcome. Missing follow-up data were handled using maximum likelihood estimation under the missing at random (MAR) assumption. Missing baseline covariates were mean-imputed.

Secondary binary outcomes (MADRS response, MADRS remission, QIDS-SR-16 response, QIDS-SR-16 remission, GAD-7 moderate anxiety) were analysed using mixed logistic regression with random intercepts at participant level, adjusting for baseline, trial arm, minimisation factors, time and an arm*time interaction. Marginal odds ratios (ORs) and 95% CIs were reported.

Any restarting of antidepressants by participants was recorded at each follow-up visit..

Analysis of Safety Variables

Adverse events were summarised descriptively by trial arm as counts of events and counts of unique participants experiencing events. Severity, relatedness and action taken were summarised by arm. SAEs were listed individually with MedDRA coding. Safety scale data (CSSRS, YMRS, ASRM, PANAS, DePAS) were summarised descriptively at each timepoint by arm and overall, using median (IQR) for continuous measures.

20. Changes in the Trial Plan

The trial protocol was amended on multiple occasions throughout the course of the trial. The final protocol version was v1.21 (15 August 2024). Key changes from the original protocol across successive versions included updates to: blinding procedures, the code-break procedure, the compassion experience scale, sample collection procedures, the open-label extension window, blood collection procedures, secondary outcomes, blinding and expectancy questions, study end date, safety data reporting details, and sponsor contact details. All substantial amendments were reviewed and approved by the REC/HRA, MHRA and local R&D prior to implementation.

Table 6. Protocol version history

Version	Date	Summary of Changes
v1.00	02-Jan-2020	IRAS Submission
v1.10	11-Mar-2020	Updated in line with REC feedback

v1.13	09-Aug-2020	Updated in line with MHRA feedback
v1.14	06-Jan-2021	Changes to blinding procedure, code break procedure, compassion experience scale
v1.15	19-Jan-2021	Removal of BioResource. Updates to sample collection procedures
v1.16	28-Sep-2021	Updates to open label extension window
v1.17	05-May-2022	Updates to blood collection procedures
v1.18	24-Nov-2022	Updates to secondary outcomes, blinding and expectancy questions, study end date
v1.19	15-Sep-2023	Updates location of visits
v1.20	08-Feb-2024	Updates to study end date and safety data reporting details
v1.21	15-Aug-2024	Sponsor contact details updated

Protocol Deviations

No serious breaches or major protocol deviations occurred during the conduct of this trial.

21. Summary – Conclusions

Demographic data

The following table summarises the demographic and baseline characteristics of the study population. Data are from the intention-to-treat (ITT) population (N = 60). Demographics were balanced between arms. Median age at randomisation was 40.8 years (IQR: 35.2–52.3), and 30/60 (50%) were female. Median Maudsley Staging Method (MSM) score at screening indicated most participants had moderate treatment resistance, with a chronic course of illness.

Table 7. Baseline characteristics trial population

Characteristic	Psilocybin (n=30)	Placebo (n=30)
Age, years: median (IQR)	41.7 (38.6–57.0)	40.2 (33.7–52.0)
Age 25–59 years, n (%)	27 (90%)	27 (90%)
Age ≥60 years, n (%)	3 (10%)	3 (10%)
Female sex, n (%)	15 (50%)	15 (50%)
Prior psilocybin use, n (%)	4 (13%)	5 (17%)
MADRS total, mean (SD)	29.7 (4.8)	29.5 (7.3)
QIDS-SR-16 total, mean (SD)	16.1 (3.9)	15.6 (5.3)
GAD-7 total, mean (SD)	11.5 (4.6)	12.1 (5.2)
HAM-D-17 at screening, median (IQR)	18.5 (16.0–21.0)	17.0 (15.0–21.0)
Maudsley Staging Method score, median (IQR)	8.0 (7.0–10.0)	8.0 (7.0–9.0)
Years with significant depression, mean (SD)	20.9 (10.2)	19.2 (10.3)
Ethnicity, n (%)		
Ethnicity – n (%) White	24 (80%)	21 (70%)
Mixed or multiple ethnic groups	2 (7%)	4 (13%)
Asian or Asian British	3 (10%)	4 (13%)
Black, African, Caribbean, or Black British	1 (3%)	0 (0%)
Other ethnic group	0 (0%)	1 (3%)
Highest level of completed education - n (%)		

Postgraduate degree	14 (47%)	11 (37%)
Undergraduate degree	10 (33%)	15 (50%)
Other	6 (20%)	3 (10%)
Missing	0 (0%)	1 (3%)
Monthly take-home household income - n (%)		
0 - £1999	8 (27%)	6 (20%)
£2000 - £3999	7 (23%)	10 (33%)
£4000 - £6000	6 (20%)	8 (27%)
>£6000	6 (20%)	4 (13%)
Declined to disclose	3 (10%)	2 (7%)
Employment category - n (%)		
Craft and related trades workers	4 (13%)	3 (10%)
Elementary occupation	1 (3%)	2 (7%)
Managers	2 (7%)	0 (0%)
Professional	17 (57%)	21 (70%)
Service and sales workers	3 (10%)	2 (7%)
Skilled agricultural forestry & fishery worker	1 (3%)	0 (0%)
Technicians and associate professionals	2 (7%)	2 (7%)
Sexual orientation		
Heterosexual	25 (83%)	26 (87%)
Gay or lesbian	5 (17%)	4 (13%)
Bisexual	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
1st degree family history of depression - n (%)		
No	15 (50%)	12 (40%)
Yes	15 (50%)	18 (60%)

Primary outcome

Primary feasibility parameters are summarised in the table below. No success metrics were pre-specified. Eligibility and randomisation rates were high, and the retention rate was excellent (59/60 completing MADRS at all follow-up visits). The between-group difference in MADRS at Week 3 was -10.41 (95% CI: -14.86 to -5.95; Cohen's d = -1.70), indicating a clinically significant improvement in the psilocybin arm compared to placebo, which was sustained at Week 6.

Table 8. Primary feasibility parameters

Feasibility parameter	Result (95% CI)
Participants consented and screened	75
Eligibility rate (eligible/screened)	83% (62/75; 95% CI: 72–90%)
Randomisation rate (randomised/consented)	80% (60/75; 95% CI: 69–88%)
Attendance at dosing visit (V3)	100% (60/60)
Retention (MADRS completion at Week 1)	98% (59/60, 95% CI: 91–100%); 1 placebo arm withdrawal
Retention (MADRS completion at Week 3)	98% (59/60)
Retention (MADRS completion at Week 6)	98% (59/60)
MADRS variance (SD at baseline, overall)	6.1 (SD)
Between-group MADRS difference at Week 3 (aMD, 95% CI; Cohen's d)	-10.41 (-14.86 to -5.95); d = -1.70

Between-group MADRS difference at Week 6 (aMD, 95% CI)	-12.92 (-17.37 to -8.47)
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Table 9. Secondary clinical outcomes at baseline and follow-up

Outcome	Baseline PBO / PSI	Week 1 PBO / PSI	Week 3 PBO / PSI	Week 6 PBO / PSI
MADRS total, mean (SD)	29.5 (7.3) / 29.7 (4.8)	26.7 (8.3) / 15.2 (9.0)	28.8 (7.5) / 18.3 (12.3)	29.3 (7.9) / 16.3 (11.1)
MADRS response, n (%)	—	1 (3%) / 16 (53%)	1 (3%) / 13 (43%)	1 (3%) / 15 (50%)
MADRS remission (score ≤10), n (%)	—	2 (7%) / 10 (33%)	1 (3%) / 12 (40%)	1 (3%) / 12 (40%)
QIDS-SR-16 total, mean (SD)	15.6 (5.3) / 16.1 (3.9)	13.7 (5.4) / 8.1 (4.7)	14.2 (4.6) / 9.0 (5.9)	14.6 (5.0) / 9.2 (5.6)
QIDS-SR-16 response, n (%)	—	3 (10%) / 15 (50%)	0 (0%) / 15 (50%)	1 (4%) / 13 (43%)
QIDS-SR-16 remission (score ≤5), n (%)	—	3 (10%) / 10 (33%)	1 (4%) / 12 (40%)	2 (7%) / 10 (33%)
GAD-7 total, mean (SD)	12.1 (5.2) / 11.5 (4.6)	11.3 (5.3) / 5.8 (4.2)	12.5 (4.7) / 7.2 (5.6)	11.7 (5.6) / 6.6 (4.9)
GAD-7 moderate anxiety (score ≥10), n (%)	—	17 (59%) / 6 (20%)	21 (75%) / 10 (33%)	18 (62%) / 5 (17%)
MADRS adjusted mean diff. (95% CI)	—	-11.44 [- 15.89, - 6.98]	-10.41 (-14.86, -5.95)	-12.92 (-17.37, -8.47)
Cohen's d (MADRS)	—	—	-1.70	—

PBO = Placebo arm; PSI = Psilocybin arm. All Ns for psilocybin = 30; placebo N = 29 at follow-up (1 withdrawal). Response = ≥50% decrease from baseline. All data from ITT analysis.

Safety results

A total of 287 non-serious adverse events (AEs) were recorded during the RCT phase: 123 in the placebo arm and 164 in the psilocybin arm. Of these, 184/287 (64%) were assessed as not related to study medication. Summary data are presented in the table below; MedDRA-coded listings by System Organ Class are provided in the appendices.

Two serious adverse events (SAEs) and two IMEs were recorded across the trial (including the open-label phase): one in the placebo arm and three in the psilocybin arm (see SAE listing below). All SAEs and IMEs in participants who received psilocybin (in either the RCT or OLE phase) were deemed not related to study medication. The one IME in the placebo arm (depressed mood, life-threatening severity, occurring in the OLE phase) was deemed possibly related to study medication. No SAEs occurred during the core RCT phase in participants who received psilocybin; the single IME during the OLE phase was a breast mass in the psilocybin arm (moderate severity, not related, no specific action required).

Clinical safety scales (CSSRS suicidal ideation, YMRS) did not show clinically meaningful changes from baseline in either arm across the follow-up period. No rescue medication was required during any Dosing Visit.

Table 10. Serious Adverse Events (RCT+OLE)

MedDRA code	Medical description	Severity	Relatedness	Phase	Arm
10006187	Breast cancer	Moderate	Not related	RCT	Psilocybin
10083753	Localised infection	Severe	Not related	Open-label extension	Psilocybin (OLE)
10042458	Suicidal ideation	Life-threatening	Possibly related	Open-label extension	Placebo→OLE
10037234	Psychosis	Severe	Not related	Open-label extension	Psilocybin (OLE)

Notes: (1) The breast mass SAE (MedDRA 10006264) was the only IME occurring during the core RCT phase; this was in a participant who received psilocybin. Outcome: not resolved at trial end. (2) All OLE-phase SAEs were reported during the open-label extension. The localised infection SAE (hospitalisation, start 03Sep2022, resolved 07Sep2022) was not related to study medication. (3) The depressed mood SAE (life-threatening, start 07Nov2023, outcome resolving) occurred in a participant originally allocated to the placebo arm who subsequently received open-label psilocybin; deemed possibly related. (4) The drug-induced psychosis SAE (start 04Nov2024, outcome unknown) developed in a participant treated with high doses of corticosteroids for an unrelated physical health problem; psychosis resolved once steroids were withdrawn; deemed not related to study medication. (5) There were no deaths.

There were no Suspected Unexpected Serious Adverse Reactions (SUSARs) reported during the trial.

22. Conclusion

This randomised, double-blind, placebo-controlled feasibility trial of psilocybin-assisted therapy for treatment resistant major depressive disorder, the first RCT in this population to assess feasibility within an NHS setting in England, met its primary feasibility objectives. Eligibility and randomisation rates were high (83% eligible, 80% randomised), retention was excellent (98% MADRS completion at all follow-up visits), and the variance of the primary outcome measure (MADRS) was estimated to support the design of a future Phase 3 trial.

Significantly greater improvements in depressive symptoms were observed in the psilocybin arm compared with placebo, with a very large effect size at Week 3 (aMD = -10.41, 95% CI: -14.86 to -5.95; Cohen's d = -1.70) that was sustained at Week 6 (aMD = -12.92, 95% CI: -17.37 to -8.47). Response and remission rates were substantially higher in the psilocybin arm at all follow-up timepoints. However, blinding was not maintained (100% of psilocybin participants and 70% of

placebo participants correctly guessed their allocation); expectancy effects in both groups likely account for some of the between-group difference observed.

Psilocybin administration was well tolerated. Adverse events were predominantly non-serious, mild in severity, and the majority were assessed as not related to study medication. Clinical safety scales measuring suicidality and mania did not show clinically meaningful changes across time. No rescue medication was required during any dosing session, and no SUSARs were reported. These findings support the conduct of a future confirmatory Phase 3 trial.

23. Date of Report

24 August 2026. Report version: 1.0

APPENDICES

i) Summary of treatment-emergent AEs and ARs in the per protocol population

The table below lists all treatment-emergent non-serious adverse events per body system category. AEs are listed for both the RCT phase and the open-label extension phase: 251 AEs in the psilocybin arm and 241 AEs in the placebo arm.

Table 11. Non-serious adverse events (RCT+OLE)

	Placebo N events = 241	Psilocybin N events = 251	Overall N events = 492
	(reporters = 29)	(reporters = 30)	(reporters = 59)
Body system category			
Neurological	69 (26)	75 (29)	144 (55)
Mood/Psychological	26 (18)	51 (19)	77 (37)
Respiratory infection	41 (19)	24 (13)	65 (32)
Gastrointestinal	25 (16)	24 (15)	49 (31)
Musculoskeletal/pain	19 (14)	22 (15)	41 (29)
Reproductive	6 (5)	6 (4)	12 (9)
Skin/ocular	5 (5)	3 (2)	8 (7)
Medication or substance related	5 (5)	13 (10)	18 (15)
General fatigue/tiredness	10 (7)	13 (11)	23 (18)
Other	35 (17)	20 (14)	55 (31)
Other event details			
Relatedness - n (%)			
Not related	151 (63%)	111 (44%)	262 (53%)
Possibly related	50 (21%)	96 (38%)	146 (30%)
Related	40 (17%)	44 (18%)	84 (17%)
Intensity - n (%)			
Mild	158 (66%)	173 (69%)	331 (67%)
Moderate	78 (32%)	71 (28%)	149 (30%)
Severe	5 (2%)	7 (3%)	12 (2%)
Outcome - n (%)			
Resolved	216 (90%)	217 (86%)	433 (88%)
Resolving	13 (5%)	25 (10%)	38 (8%)
Not resolved	10 (4%)	9 (4%)	19 (4%)
Resolved with sequelae	1 (0%)	0 (0%)	1 (0%)
Unknown	1 (0%)	0 (0%)	1 (0%)
Action taken - n (%)			
None	138 (57%)	172 (69%)	310 (63%)
Medication required	95 (39%)	76 (30%)	171 (35%)
Other	8 (3%)	3 (1%)	11 (2%)
Adverse event of special interest (AESI) - n (%)			
Not AESI	239 (99%)	249 (99%)	488 (99%)
AESI	2 (1%)	2 (1%)	4 (1%)

ii) Summary of treatment-emergent SAEs in the study population

Table: Listing of Serious Adverse Events for all participants

MedDRA Code	Medical Description	Intensity	Outcome	Relatedness	Action	Start Date	End Date	Arm
10006187	Breast cancer	Moderate	Not resolved	Not related	None	31 Aug 2024	Ongoing	Psilocybin (RCT)
10083753	Localised infection	Severe	Resolved	Not related	Hospitalisation	06Sep2022	07Sep2022	Psilocybin (OLE)
10042458	Suicidal ideation	Life-threatening	Resolving	Possibly related	Other	07Nov2023	Ongoing	Placebo→OLE
10037234	Psychosis	Severe	Resolved (on steroid withdrawal)	Not related	Hospitalisation	04Nov2024	Resolved	Psilocybin (OLE)

iii) Summary of treatment-emergent SARs in the study population

No treatment-emergent SARs were identified in this study

iv) Protocol Deviations

Table 12. Protocol deviations tracker

Protocol Deviation Tracker			
Study Title / R&D Number:	PsiDeR / IRAS 252750		
Investigator:	James Rucker		
Site Name / Number:	N/A - single site		
Pt#	Visit	Deviation	Comment
P052, P053, P054	N/A	Participants initially consented to superseded OLE ICF v1.11 in error	
P054, P057, P062, P063, P065, P067, P068	N/A	Participants re-consented to OLE PIS/ICF v1.13 before C&C approval	
P067	N/A	re-consent to OLE PIS/ICF v1.13 was not obtained in error	
P068	N/A	Participant was initially consented to Main PIS v1.26 before C&C approval	
P061	OLE2	respiratory rate prior to dosing not obtained in error	
P065	V5	ETB not completed due to time constraints	
P028	V2	PANAS, SCSS, SCST, WEMWBS, CNS, SAPAS missed by participant and not completed	
P028	V6	STAR-C not completed in error	
P054	V2	CNS, SCSS, SCST, WEMWBS and SAPAS not completed by participant in error	
P054	OLE4	QIDS-SR-16, GAD-7, STAI, ASRM, PANAS were completed but have data has gone missing/corrupted	
P075	OLE6	study team forgot to record weight	

P032	OLE6	study team forgot to record weight	
P036	V7/OLE1	study team forgot to record weight	
P036	OLE6	study team forgot to record weight	
P041	OLE4	STAR-C not completed in error	
P044	V2	STAR-C not completed in error	
P044	OLE4	STAR-C not completed in error	
P044	OLE6	study team forgot to record weight	
P047	OLE6	study team forgot to record weight	
P049	V6	STAR-C not completed in error	
P049	OLE6	study team forgot to record weight	
P051	V5	STAR-C not completed in error	
P051	OLE6	study team forgot to record weight	
P053	OLE6	study team forgot to record weight	
P067	V4	visit had to be done remotely due to participant having no transport - not completed: ECG, CES, 5D-ASC, PANAS, SCSS, routine bloods, vital signs	
P067	V6	visit was completed remotely and therefore the following not completed: nursing tasks, QIDS-SR-16, GAD-7, STAI, STAR_P, ASRM, DePAS, EQ-5D-5L, WSAS, PANAS, SCST, WEMWBS, CNS	
P068	V3	study nurse forgot to record resp rate	
P072	V7/OLE1	SCST not completed - missed by participant and study team	
P039	OLE6	study team forgot to record weight	
P074	OLE3	Study medic forgot to complete GCI in eCRF	File note 20
P072	OLE3	5D-ASC not completed by participant	

Certificate Of Completion

Envelope Id: F124517D-DA19-877E-8140-D253681549F1

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Subject: Complete with Docusign: PsiDeR_Clinical_Study_Report_v1.0_final.pdf

Source Envelope:

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Initials: 0

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04-Sep-26 | 14:10

kathryn.1.lobb@kcl.ac.uk

Signer Events

Professor Allan Young

allan.young@kcl.ac.uk

Professor

King's College London

Security Level: Email, Account Authentication
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Signature

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Jeanette Hansen

jeanette.hansen@kcl.ac.uk

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Witness Events

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Notary Events

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