Cover Page

BPL-003-203 Clinical Study Protocol

Clinical Trial Protocol Title: An Open-Label, Phase 2a Single Dose Study in Patients With Alcohol Use Disorder

NCT Number: NCT05674929

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CLINICAL STUDY PROTOCOL

An Open-Label, Phase 2a Single Dose Study in Patients with Alcohol Use Disorder

Protocol Number:	BPL-003-203
EudraCT Number:	2022-000810-33
Compound:	BPL-003
Phase:	Phase 2a
Indication:	Alcohol Use Disorder
Version and Date of Protocol:	Version 7.0 dated 29 Aug 2024 Version 6.0, dated 3May24
Previous Version(s):	Version 5.0, dated 6 Sep 23 Version 4.0, dated 13 Mar 2023 Version 3.0 dated 3 Oct 2022 Version 2.0 dated 1 Jun 2022
Sponsor:	Beckley Psytech Ltd. Beckley Park, Oxford, OX3 9SY, UK

INVESTIGATOR'S AGREEMENT

Study Title: An Open-Label, Phase 2a Single Dose Study in Patients with Alcohol Use Disorder

I have received and read the Investigator's Brochure for BPL-003. I have read the BPL-003-203 protocol (version as stated in footer of page) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Principal Investigator

_____

Signature of Investigator

_____

Date

SPONSOR PROTOCOL APPROVAL

Study Title: An Open-Label, Phase 2a Single Dose Study in Patients with Alcohol Use Disorder

I have read this protocol and approve the design of this study:

Dr Matheiu Seynaeve
Senior Medical Director and Head of Psychotherapy, Beckley Psytech Ltd

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Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol. Abbreviations used only once or twice (and defined in text) or only used in tables and defined in footnotes are not included below.

Abbreviation or Specialist Term	Explanation
5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}	serotonin (5-hydroxytryptamine [5-HT]) receptors
5-HTP	5-hydroxytryptophan
5-HT	5-hydroxytryptamine (serotonin)
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
ACQ	Alcohol Craving Questionnaire
AE	adverse event
AESI	Adverse Event of Special Interest
AESS	Adverse Event of Special Situation
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{INF_obs}	area under the plasma drug concentration-time curve from the time of dosing extrapolated to infinity
AUD	alcohol use disorder
BPL	Beckley Psytech Ltd.
BPL-002	5-MeO-DMT liquid formulation of the HCl salt
BPL-003	5-MeO-DMT dry powder formulation of the benzoate salt
CDT	carbohydrate deficient transferrin
CHO	Chinese hamster ovary
CIWA-Ar	Clinical Institute Withdrawal Assessment
C_{max}	maximum (peak) plasma concentration
CGIS	Clinical Global Impression of Severity
CNS	central nervous system
COVID-19	coronavirus SARS-CoV-2
CRF	case report form

Abbreviation or Specialist Term	Explanation
C-SSRS	Columbia-Suicide Severity Rating Scale
DMT	N,N-dimethyltryptamine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDI	Ego Dissolution Inventory
ePRO	Electronic Patient Reported Outcome system
EQ-5D-5L	5-level EuroQol-5 Dimension
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCl	hydrochloride
HDD	heavy drinking days
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IP	intraperitoneal
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
K_i	inhibition constant
LSD	lysergic acid diethylamide
MADRS	Montgomery–Asberg Depression Rating Scale
MAO-A	monoamine oxidase A
MAOI	monoamine oxidase inhibitor
MDMA	3,4-methylenedioxy-methamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MEQ30	Mystical Experience Questionnaire
MHRA	Medicines and Healthcare products Regulatory Agency

Abbreviation or Specialist Term	Explanation
MINI	Mini-International Neuropsychiatric Interview
NOAEL	no-observed-adverse-effect level
PCI	potential clinical importance
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PI	Principal Investigator The Investigator who leads the study conduct at an individual study center. Every study center has a Principal Investigator.
PK	pharmacokinetic(s)
PO	by mouth
QTcF	QT interval with Fridericia's correction method
ReAQ	Reactivation Questionnaire
REC	Research Ethics Committee
RES	Research Ethics Service
RPI	relapse prevention intervention
SAE	serious adverse event
SAP	statistical analysis plan
SETS	Stanford Expectation of Treatment Scale
SIP	Short Inventory of Problems
SOP	standard operating procedures
SUD	substance use disorder
SIGMA	Structured Interview Guide for the MADRS
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse drug reaction
$t_{½}$	terminal elimination half life
TEAE	treatment-emergent adverse event
TLFB	Timeline Follow-Back
t_{max}	time to reach peak plasma concentration (C_{max})
TRD	treatment-resistant depression
UDS	Aptar Unidose
UK	United Kingdom
UN	United Nations
US	United States (of America)

Abbreviation or Specialist Term	Explanation
VAS	visual analogue scale
WHO	World Health Organization
WOCBP	woman of childbearing potential

SUMMARY OF PROTOCOL CHANGES

The main updates from Protocol version 6.0 (dated 03May2024) to Protocol version 7.0 (dated 29Aug24) are administrative changes to clarify study objectives and endpoints as detailed below.

Location	Change	Rationale
Synopsis, 3 Endpoints	Move Readiness for Discharge Questionnaire (RDQ) from secondary endpoints to primary endpoints Move Reactivation Questionnaire (ReAQ) from exploratory endpoints to primary endpoints	Correction – these are safety endpoint
Synopsis, 3 Endpoints	Remove Ego Dissolution Inventory (EDI) from secondary endpoints relating to percentage of patients experiencing a complete mystical experience	Correction - Mystical experience is assessed using the Mystical Experience Questionnaire (MEQ-30)
Synopsis, 3 Endpoints	Update secondary endpoint to include psychological change as measured with a questionnaire and semi-structured interview to correlate with methods section	Clarification – to align with methods section. Previously missed as an endpoint in error.
Synopsis, 3 Endpoints	Update exploratory endpoints to include Cravings Visual Analogue Scale (VAS) to correlate with methods section	Clarification – to align with methods section. Previously missed as an endpoint in error.
Synopsis, 3 Endpoints	Update exploratory endpoints to include Clinical Institute Withdrawal Assessment (CIWA-Ar) to correlate with methods section	Clarification – to align with methods section. Previously missed as an endpoint in error.
Synopsis, 3 Endpoints	Update exploratory endpoints to include Short Inventory of Problems (SIP) to correlate with section 9.0, Pharmacodynamic Assessments	Clarification – to align with Pharmacodynamic Assessments section 9.0. Previously missed as an endpoint in error.
Synopsis, 3 Endpoints	Update exploratory endpoints to include heading “Biomarkers”	Previously missed in error.
Synopsis, 3 Endpoints	Update exploratory endpoints to include assessment of expectations as measured by Stanford Expectation of Treatment Scale (SETS)	Clarification – to align with Pharmacodynamic Assessments section 9.0. Previously missed as an endpoint in error.
10.2.8 AEs of Special Interest (AESI)	Update to remove the 24-hour reporting timeline.	Clarification – AESIs do not need to be reported within 24 hours unless deemed serious.
10.2.8 AEs of Special Interest (AESI)	Update to remove wording on AEs observed on dosing day and add wording to clarify AEs monitored	Clarification – AEs indicative of abuse potential will be monitored unless observed before dosing
Synopsis	Add wording to heading to read Drinking Craving and Withdrawal	Previously missed and withdrawal in error

Synopsis	Remove duplicated sentence under exploratory endpoints regarding TLFB	Duplication
Synopsis	Update alcohol use parameters to include longest duration (days) of continuous abstinence, maximum number of standard units of alcohol consumed on any one day and number of heavy drinking days	Previously missed in error
Synopsis	Update to remove longest duration (days) of continuous abstinence and maximum number of standard units of alcohol consumed on any one day from alcohol use parameters	Previously added in error
Synopsis,2 Objectives, 3 Endpoints	Move The correlation of the occurrence of a "complete mystical experience" and "ego dissolution", measured by the MEQ-30 and EDI, with improvement in alcohol use and craving (measured by AQC, TLFB, EtG, CDT) from secondary endpoint to exploratory endpoint	Correction
2 Objectives, 3.3 Exploratory Endpoints	Update to include the correlation of PD effects with alcohol use related symptoms	Previously missed in error
3.3 Exploratory Endpoints	Update HDD definition to include ">="	Previously missed in error

The main updates from Protocol version 5.0 (dated 6Sep2023) to Protocol version 6.0 (dated 29Apr24) are to clarify inclusion criteria 5, update the analysis parameters of alcohol use, and include a reactivation questionnaire. Other minor and editorial updates were also made, as detailed below.

Location	**Change**	**Rationale**
Synopsis	Update date of last patient visit from July to Sep 2024	Due to delays in recruitment
Synopsis, 4.1 Study design, 4.5.1	Update from single to dual centre study	Due to inclusion of 2nd study site Clerkenwell Health
Synopsis,	Clarify that Inclusion point 1 14 days since last HDD should be calculated from point of screening	To provide clarity
Synopsis, 3.3 Exploratory endpoints	Update to parameters of alcohol use that will be assessed	To bring exploratory efficacy endpoints in line with efficacy endpoints for AUD from literature and regulatory guidance.
Synopsis, 3.3 Exploratory endpoints, SoE, 10.1.9,	Inclusion of the Reactivation Questionnaire (ReAQ) to capture information on reactivation experiences	Formal process to ensure complete information collected for this safety event.

SoE footnotes, 10.1.2 Vital Signs	Clarification of the requirements for Vital Signs measurements	To provide clarity
6.4 Patient Numbers	Update to clarify that screen failure patients may be rescreened	To provide clarity
10.1.5 ECG	Update to clarify the requirements for ECG	To provide clarity
10.1.6 Cardiac Telemetry	Update to clarify requirement to retain recordings of telemetry readings.	To ensure that all source data are retained for review if required
10.1.10.4 Drug Screen	Clarification that urine alcohol test is not required	Removal of urine alcohol test as alternative more accurate measures are in place.
10.2.8 AE of Special Interest	Update to definition of AESI	To clarify that only Suicide Ideation that is significant will be considered an AESI
Bibliography	Added reference to Ortiz Bernal 2022	To support reference in protocol
Appendix 5	Reactivation Questionnaire (ReAQ) added	

The main updates from Protocol version 4.0 (dated 13Mar2023) to Protocol version 5.0 (dated 6Sep23) are to remove the SADQ assessments at screening, reduce the heavy drinking days requirement at screening, modify the requirement for abstinence in the 72 hours prior to dosing and inclusion of a possible second cohort with a 12 mg dose . Other minor and editorial updates were also made, as detailed below.

Location	**Change**	**Rationale**
Study personnel and site contact details & Synopsis	Removal of sub-investigator and co-investigator details from protocol. Change of CRO project manager details.	Simplification and alignment with ethics requirements. Personnel change.
Synopsis & Section 4	Addition of an optional second cohort of patients with the potential for dosing at 12 mg including details of the Safety Review Committee	As the first study conducted with BPL-003 in this population it is unknown how effects of 10 mg may compare to those seen in healthy volunteers.
Synopsis & Section 4	Description of “psychotherapy” preparation sessions to “psychological support”.	Alignment of common terminology
Synopsis & Section 5 (inclusion criteria)	Inclusion criteria 4. Reduction of minimum number of HDD required at screening from 10 to 4	Alignment with other AUD study protocols
Synopsis, Section 5 (inclusion criteria) & Figure 1	Modification of abstinence requirement in 72 hours prior to dosing. Change from complete abstinence to no HDD in 72 hours before dosing day and no alcohol in 24 hours before dosing. Removal of inclusion criteria for complete abstinence requirement	Simplification of criteria and alignment with ability to assess drinking behaviour

Synopsis, Schedule of Events, Section 5	Change in time allowed for preparation sessions from 1 week to 2 weeks throughout	Allowing a longer period to safely prepare patients in alignment with other protocols.
Synopsis and Section 4.3 (Dose Selection)	Inclusion of optional 12 mg dose and updated rationale for dose selection	Data updated to support inclusion of optional 2nd cohort
Synopsis and Section 5	Change from patients "cannot" complete psychological preparation sessions if intoxicated to "should not".	Aligns with inclusion/exclusion criteria requirements of drinking behaviour and increased flexibility for clinical judgement of study team
General Medical Exclusion Criteria 1	Additional clarification of "uncontrolled cardiovascular disorders"	Providing additional details for safety
Psychiatric Exclusion 5	Additional clarification of "suicidal behaviours"	Providing additional details for safety
Exploratory Endpoints, Section 3.3	Added additional endpoints assess alcohol use through EtG and CDT measures	
Schedule of Events and Allowed Time Deviations	Increased flexibility of time window for psychological support preparation sessions and follow up visits	Practicality and logistical ease for study team and participants
Inclusion criteria, Schedule of Events, Section 9.4	Removal of SADQ assessment as inclusion requirement	Simplification for study teams
Section 1.4	Editorial update to non-clinical and clinical data presentation	Editorial – for ease of reading
Synopsis, Section 4.2	Clarification of patient numbers throughout – Up to 12.	Clarification
Schedule of Events, Section 9.9	Added details of Day the ACQ should be performed to match Schedule of Events	To clarify for ease of reading
Schedule of Events, Section 9.16	Updated timeline in which Treatment Model feedback can occur	Practicality and logistical ease for study team and participants
Schedule of Events, Section 10.1	Updated vital signs assessments to include triplicate baseline measurement and repeated measurements for BP >160mmHg	To improve accuracy of measurements and readings
7.2 7.2. Study Drug Packaging and Labeling	Changed RenaClinical to Eramol	To reflect the name change, the vendor remains the same only the name has changed.
11.7.1.5 Concentration Data	PK concentration details added	For clarity

The main updates from Protocol version 3.0 (dated 3Oct2022) to Protocol version 4.0 (dated 13 Mar 2023) are to change the Pharmacovigilance vendor, add safety details of other trials, remove the SADQ assessments and update the ECG & PK analysis to triplicate. Other minor updates were also made, as detailed below.

Location	Change	Rationale
Study personnel and site contact details, Section 10.3, 10,4 and Section 10.5	PV vendor changed to World Wide Clinical Trials	From 17 April 2023, Worldwide Clinical Trials (WWCT) is the sponsor's pharmacovigilance delegate. Device events will be expedited reporting via the SAE process
Exploratory Endpoints, Section 3.3,	SADQ assessment removed from Day 28, 49, 84. Retained only at screening. Removed as an Exploratory Endpoint	SADQ is designed as a screening scale and is not well suited to revisit as it asks the patient to recall drinking in the previous 6 month, so no value in revisiting over course of 12week study
Section 1.4.2 Previous Experience in Humans Section 4.3 Dose Selection	Safety, PK and PD results of Study BPL-003-103 Part A included.	Final data available.
Schedule of Events. Section 10.1	ECG updated to triplicate at Screening visit	To increase safety
Schedule of Events, Section 8	PK analysis updated to triplicate samples, and changed wording from measuring the plasma concentration of BPL-003 to 5MeO-DMT and its metabolites	To align with PK data from other studies and to allow assessment of 5MeO-DMT metabolites
Schedule of Events	Updated to state that CDT to be assessed in blood and not urine samples	Clarification
	Added definition of AESS & AESI	Clarification
Schedule of Events	SoE updated to separate Day 7 and Day 14, and footnotes updated accordingly	Clarification
Section 9.1	Updated typographical error that SETS would be administered on day -7 not -12	Correction
Section 6.6	Table added to define time windows for protocol events	Clarification

The following changes were made from Protocol version 2.0 (dated 1 June 2022) to Protocol version 3.0 (dated 3 Oct 2022) are to specify the dose with rationale, include video and audio recording of the dosing and therapy sessions respectively and to include some additional scales. Other minor updates were also made, as detailed below.

Location	Change	Rationale
3.4 Dose selection & other	Updated to state dose selection	Specific dose required

4.5 Risk Mitigation; 6.6 Dose	Added details of Video and audio recording of dosing and therapy respectively	For safeguarding For patient safeguarding and quality assurance and training (optionally
	Added details of assessing readiness for discharge	For patient safety
9.1 Stanford Expectation of treatment scale	Added Stanford Expectation of Treatment Scale at Day -7	To provide insight into patients' expectations of treatment
9.11 Craving VAS & Methods	Alcohol craving by VAS added at Day 0	To provide Investigator a quick insight into patients craving levels after dosing before discharge
10.2.8 Reporting Adverse Events	Updated contact details	To provide correct details
Study Personnel	Updated Sponsor contact and Pharmacovigilance provider	Updates to team and vendors
Synopsis	Study Period (years) removed	Clarification
Study Design	Dose selection	Updated based on results of Phase 1 study.
	Psychological change measures and semi structured interviews	Details added for clarification
	Psychedelic experience endpoints based on questionnaires added	To correlate to the endpoints with the study objectives
Schedule of Events	Vital signs timing updated	To reduce burden on patients during psychedelic event
Schedule of Events	Removed requirement to fast before blood tests except screening	For patient comfort as deemed unnecessary
Schedule of Events	Added clarification in footnotes on expected order of events	For clarity
1.4.2.1 Clinical Studies	Included details of additional supporting studies	For background
3.2 Secondary endpoints	Updated pharmacodynamic endpoints	To correlate to the endpoints with the study objectives
	Amended "minimum of 3 preparatory psychotherapy sessions over approximately 2 weeks" to change 2 weeks to 1 week through out	To bring in line with Schedule of events.
6.7 Patient lifestyle restrictions	Added detail of fasting blood tests and breakfast requirements and postdose requirements	For accuracy
9.9 MADRS	Clarified Sigma version	Clarified that the Structured Interview Guide for MADRS (SIGMA) is to be followed.
9.13 Patient Global Impression of Change	Clarified patient reported not investigator	Clarification
9.16 Treatment model assessments	Added Treatment model feedback and Readiness to discharge questionnaire	

10.1.2 Vital signs	Vital signs timing updated	To reduce burden on patients during psychedelic event
10.1.6 Cardiac Telemetry	Defined rules for Cardiac Telemetry	Clarification
10.2.1.1 Adverse Event	Defined rules for AE reporting	To clarify how to report AE associated with altered states of consciousness
10.3 Device Events	Added requirement to report device issues	For patient safety
11.7.2 Analysis of Safety	removed	
13 List of references	References added	
Appendix	Removed SIP & ACQ scales	Published documents, version-controlled stand-alone copies available
Appendix	Added Readiness for Discharge questionnaire	For reference, non-published document novel for this study

STUDY PERSONNEL AND SITE CONTACT DETAILS

Role in study	Name	Address and Telephone Number
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Clinical Research Facility	Catherine Bird	NIHR Wellcome Clinical Research Facility 1st Floor Cheyne Wing King's College Hospital London SE5 9RS

Role in study	Name	Address and Telephone Number
Pharmacovigilance (SAE reporting)	World Wide Clinical Trials (Jovana Vulin, Senior Associate, Pharmacovigilance)	Worldwide Clinical Trials 600 Park Offices Drive Suite 200 Research Triangle Park, NC 27709, USA **SAE reporting (primary):** drugsafety@worldwide.com (cc: safety@beckleypsytech.com) **SAE reporting (back-up):** **Fax:** +44 208 043 4813
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SYNOPSIS

Name of Sponsor/Company:
Beckley Psytech Ltd. (BPL)

Name of Investigational Product:
BPL-003 dry powder nasal spray

Name of Active Ingredient:
5-MeO-DMT (5-Methoxy-N,N-dimethyltryptamine) benzoate

Title of Study:
An Open-Label, Phase 2a Single Dose Study in Patients with Alcohol Use Disorder

Study centre(s): Centres in the United Kingdom [UK]

Chief Investigator: Dr Michael Kelleher

Studied period (years):
Estimated date first patient enrolled: March 2023
Estimated date last patient completed: Sept 2024
Phase of development: 2a

Primary Objectives:

- To assess the safety and tolerability of a single intranasal dose of BPL-003 in patients with Alcohol Use Disorder (AUD)

Secondary Objectives:

- To assess the pharmacodynamics (PD; including psychological effects) of a single intranasal dose of BPL-003 in patients with AUD
- To assess the feasibility of the treatment model for BPL-003 combined with relapse prevention psychotherapy in patients with AUD

Exploratory Objectives:

- To explore the effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy in patients with AUD on alcohol use and related symptoms
- To explore the effects of BPL-003 combined with relapse prevention psychotherapy on health-related quality of life (QOL) in patients with AUD
- To explore exposure levels after a single intranasal dose of BPL-003 in patients with AUD
- To assess the correlation of PD effects with alcohol use and related symptoms
- To determine participant expectations of treatment outcome

Study Design:
An open-label, dual-centre, Phase 2a study to evaluate the safety, tolerability, and PD effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy to assess the treatment model and explore the potential effects on alcohol use and related symptoms. This study

will assess a dry powder nasal spray formulation of 5-MeO-DMT benzoate (BPL-003). Enrolment of up to 12 patients with AUD is planned in up to 2 cohorts (Cohorts 1 and 2).

Patients will receive a single dose of 10 mg (Cohort 1) or 12 mg (Cohort 2) BPL-003. The doses selected for this study are based on a review of safety, tolerability, pharmacokinetic (PK), and PD data from the dose levels tested to date in study BPL-003-103 (a single ascending-dose study in healthy volunteers).

After completing the screening period, those patients who are confirmed as eligible will participate in a minimum of 3 preparatory psychological support sessions over approximately 2 weeks before the BPL-003 treatment session. These sessions will be conducted by a therapist with psychedelic knowledge and an AUD therapist. The last of the 3 sessions will be conducted at the clinic where the dosing will occur so that patients can become familiar with the dosing room, clinic staff and a practice run with the nasal delivery system can be completed. Baseline assessments will be completed on the BPL-003 treatment day, before BPL-003 administration. BPL-003 will be administered on the treatment day in accordance with established safety practices for psychedelic research. A minimum of 3 integration sessions will occur over approximately 2 weeks after the treatment session, together with AUD relapse prevention psychotherapy that will guide the patient through the 12-week postdose follow-up period.

If triggered by the sponsor, a Safety Review Committee (SRC) will decide upon continuation of the study at the 10 mg dose or escalation to 12 mg. The SRC will comprise of, as a minimum, one Investigator (or delegate), the Sponsor's medical monitor, and the Chief Medical Officer (or delegate). The SRC will review, as a minimum, safety, tolerability, PK and PD data up to Day 1 from at least 3 patients dosed with 10 mg BPL-003 in Cohort 1. The dose may be escalated to 12 mg only if the safety, tolerability, PK and PD at 10 mg are deemed acceptable by the SRC. Dose decisions will be documented before further dosing. Additional SRC meetings may be scheduled as required.

The study visits and procedures are outlined below:

- **Screening:** Patients will be screened up to 14 days before their psychedelic preparation session to confirm their eligibility for the study.
- **Abstinence:** Patients will be expected to have no HDD in the 72 hours prior to dosing, and no alcohol in the last 24 hours. If breath alcohol is not zero on dosing day, patients may reschedule once if they are deemed not to have completely relapsed; however, if they fail the second time, they will be excluded from the study.
- **Psychedelic preparation visits:** Following the initial Screening Visit, all patients will participate in 3 preparatory sessions over approximately 2 weeks before being dosed (patients should not undertake preparation sessions if intoxicated (clinical judgement to be applied whether the patient is able to absorb the information and build a therapeutic alliance). The aim will be to establish a therapeutic alliance with the therapists during the preparatory sessions so that patients will be well prepared for the BPL-003 treatment session and receive ongoing AUD relapse prevention psychotherapy.
- **Psychological change measures and semi-structured interviews (optional):** if patients consent to these optional assessments they will be required to complete psychological change questionnaires at 5 visits during the study on Days –3, 1, 7, 28 and 84, and 3 semi-structured interviews with a therapist on Days 1, 28 and 84 (as detailed in the Psychological Change Study Manual).
- **Dosing visit:** After completion of the 3 preparatory sessions, patients will attend the clinic for their dosing visit. Patients will be resident at the clinic from the morning of Day 0 (dosing day) until at least 4 hours postdose. BPL-003 will be administered to patients in the designated setting, and the therapist will remain with patients while patients are in an altered state of consciousness.

- **Qualitative interview (optional):** After return to a usual state of consciousness after dosing, and provided they consent, patients will be asked to have a one-to-one guided qualitative interview with independent researchers trained in microphenomenology methods to discuss their psychedelic experience (as detailed in the Qualitative Interview Study Manual). This will be done either face to face at the clinic or via video call. Psychometric scales will then be administered to provide quantitative measures of the patient's psychedelic experience.

  All patients will have their readiness for discharge assessed every 30 minutes starting 90 minutes after dosing before discharge on the dosing day. The earliest a patient can be discharged will be 4 h after receiving the dose.

- **Follow-up (for 12 weeks postdose):**

  - **Psychedelic integration sessions:** Patients will have at least 3 integration sessions, lasting approximately 60-90 min, over the 2 weeks following their dose to discuss their experience with the therapists.

  - **Relapse prevention psychotherapy:** Patients will have weekly sessions following the dose of BPL-003 as defined in the AUD Therapy Manual (can be either face to face or remote) with an AUD therapist.

Number of patients (planned):

Enrolment of patients with AUD is planned until up to 12 evaluable patients in up to 2 Cohorts have been dosed and completed Day 0 of the study. Although this study is exploratory and there is no formal sample size calculation, the sample size is estimated to be able to detect common drug-induced safety events in this patient population.

Diagnosis and main criteria for inclusion:

To be eligible to participate in this study, patients must meet the following criteria:

Inclusion Criteria:

1. Willing and able to give informed consent
2. Age 18 to 64 years at Screening
3. Diagnosed with moderate to severe AUD (based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5])
4. Minimum of 4 heavy drinking days (HDD) in the 28 days before Screening
5. No more than 14 days have elapsed since the last HDD or completion of detoxification (at point of screening), with no HDD in the 72 hours prior to dosing, and no alcohol at all in the 24 hours prior to dosing
6. Willing to abstain from using recreational drugs from Screening until end of the study
7. Willing to abstain from smoking during their time in the clinic on the day of drug administration as instructed by clinical staff
8. Willing to refrain from psychedelic drug use (excluding the study drug) from Screening until the end of the study
9. Able (in the Investigator's opinion) and willing to undertake and comply with all study requirements, with the ability to complete all protocol-required assessment tools and to comply with all study visits

10. Willing to allow their own general practitioner, and consultant if appropriate, to be informed of study participation
11. Living in stable/secure accommodation in the community
12. In possession of a personal mobile phone and able to nominate at least one locator individual (e.g., a family member, friend, or recovery mentor), with a verifiable address and a telephone number to assist with the arrangement of follow-up appointments

Exclusion Criteria:

General Medical Exclusion Criteria:

1. History of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure (BP) and heart rate (HR). This includes, but is not limited to, severe coronary artery disease, history of myocardial infarction, unstable angina, cerebrovascular accident, aneurysm or revascularization procedure within 12 months before Screening, significant valvular heart disease, heart failure of any etiology, history of a stroke or transient ischemic attack.
2. History of uncontrolled hypertension despite adequate therapy or any history of a hypertensive crisis or ongoing evidence of uncontrolled hypertension (defined as repeated supine systolic BP 140 mmHg, or diastolic BP 90 mmHg). Patients with well-controlled hypertension that has been successfully treated with anti-hypertensive medicines may be enrolled if they pass additional screening to rule out underlying cardiovascular disease.
3. Uncontrolled or insulin-dependent diabetes
4. History of seizures (including febrile and withdrawal seizures)
5. Any other clinically significant neurological, cardiovascular, pulmonary, gastrointestinal, hepatic, renal, or any other major concurrent illness that, in the opinion of the Investigator, may interfere with the interpretation of the study results or constitute a health risk for a patient if they take part in the study
6. Abnormal and, in the opinion of the Investigator, clinically significant results on the physical examination, vital signs, electrocardiogram (ECG), or laboratory tests at Screening (Visit 1)
7. Patients who are exhibiting any signs of alcohol withdrawal at Day 0 as assessed by Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)
8. Positive for alcohol at Day 0
9. Positive urine drug screen for illicit drugs or drugs of abuse
10. Currently receiving monoamime oxidase inhibitors (MAO-I), tramadol, opioids, antiviral medication, cytochrome P4502D6 inhibitors, antidepressant medication, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, lithium, antipsychotic medications, triptans, tramadol, 5-hydroxytryptophan (5-HTP), herbal preparations containing 5-HTP, St John's Wort, or any other medications or supplements that may affect serotonergic function or may interfere with the study drug (see Section 6.2.1 of the study protocol for a detailed list).
11. History of intolerance to 5-MeO-DMT, dimethyltryptamine (DMT), or related compounds
12. Any nasal obstruction, blockage, or symptoms of congestion
13. Any personal or family history of malignant hyperthermia

14. Disposition judged by the Investigator (or delegate) to be incompatible with establishment of rapport with study team and/or safe exposure to BPL-003
15. Presence of acute or chronic illness or infection or history of chronic illness or infection sufficient to invalidate the patient's participation in the study or make it unnecessarily hazardous
16. Presence or history of severe adverse reaction to any drug or drug excipient
17. Female patients who are pregnant or lactating or are of childbearing potential and not willing to use adequate forms of contraception during the study and for 1 month after completion of the study as described in the protocol
18. Male patients who are sexually active and not willing to use adequate forms of contraception during the study or for 1 month after completion of the study as described in the protocol
19. Patients who have taken part in a clinical research study in the last 4 weeks, whether or not they received an investigational medicinal product as part of that research study
20. Current criminal justice involvement with legal proceedings, which in the opinion of the Investigator means the participant may fail to complete the study protocol due to inability to complete study visits with the study site team
21. Unable to communicate in English to a level required to accept standard care and psychological intervention
22. Patients who, in the opinion of the Investigator, are not suitable to participate in the study for any other reason not mentioned in the entry criteria

Psychiatric Exclusion Criteria:

23. Personal or first-degree family history of schizophrenia, bipolar disorder, psychotic disorder (unless substance induced or due to a medical condition), delusional disorder, paranoid disorder or schizoaffective disorder, as defined by DSM-5. Personal history determined by medical records and positive diagnoses on the Mini-International Neuropsychiatric Interview (MINI) to be confirmed by the Investigator
24. Any major psychiatric disorders, with the exception of mild or moderate anxiety and/or depression, as determined by a MINI and confirmed by the Investigator
25. A clinical diagnosis of post-traumatic stress disorder (as determined by MINI)
26. Psychological therapies other than those planned per the protocol that are initiated or terminated within 21 days of baseline and for the duration of the study
27. Has suicidal ideation with some intent to act within the 12 months before Screening, per the Investigator's clinical judgment or based on the Columbia-Suicide Rating Scale (C-SSRS), corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behaviour within the 12 months before Screening. Suicidal ideation with intent to act or suicidal behaviour as assessed on Day –3 should also be excluded.
28. Suicide attempts and/or self-injurious behavior within 12 months before Screening.
29. Regular use of or dependence on other drugs other than caffeine or nicotine. Presence or history of substance use disorder (not including AUD) as defined by the DSM-5. The

Investigator will evaluate the patient's ability to abstain from using this substance during the study. The patient must have a negative recreational drug test on Day 0, before dosing

30. Any self-reported use of psychedelic compounds (phenethylamines, tryptamines, or dissociatives) in the past 6 months

Investigational product, dosage and mode of administration:

BPL-003 (5-MeO-DMT benzoate dry powder) is a psychedelic tryptamine being developed as a therapy for treatment-resistant depression (TRD) and AUD.

BPL-003 will be administered intranasally by a trained member of the study team using an Aptar Unidose (UDS) dry powder delivery system. Each dose is preloaded into the delivery device.

The doses selected for this study are 10 mg or 12mg. The doses are based on a review of the safety, tolerability, PK, and PD data from the dose levels tested to date in study BPL-003-103. The doses administered do not exceed the highest dose that was found to be safe and tolerated.

Duration of treatment:

Patients will participate in the study for approximately 16 weeks, including screening and psychedelic preparation (up to 4 weeks), and ongoing AUD relapse prevention psychotherapy over 12 weeks.

Reference therapy, dosage, and mode of administration:

All patients will receive active therapy with BPL-003.

Criteria for Evaluation:

Primary Endpoints

Safety Endpoints

- Percentage of patients with treatment-emergent adverse events (TEAEs)
- Percentage of patients with clinically significant postdose abnormal laboratory tests
- Percentage of patients with clinically significant abnormal postdose vital sign measurements (heart rate, blood pressure, and body temperature)
- Percentage of patients with postdose suicidal ideation as determined by the C-SSRS
- Change in C-SSRS score compared to Baseline at Days 7 and 84
- Readiness for discharge questionnaire
- Measure the frequency, emotional valence and functional impact of any re-activation events in the study through the Reactivation Questionnaire (ReAQ)

Secondary Endpoints

Pharmacodynamic Endpoints:

- The effects of BPL-003 as determined by the MEQ-30 and EDI
- Percentage (%) of patients experiencing a complete mystical experience, as assessed by the MEQ30 on Day 0
- Description of the BPL-003 subjective experience data (from the qualitative interview)
- Psychological change as measured with a questionnaire and semi-structured interview

Treatment Model:

- Treatment model feedback from therapists on

- Frequency and duration of psychotherapy sessions
- Implementation of therapy manuals

- Overall therapy model

Exploratory Endpoints

Pharmacokinetic:

- Blood samples to determine 5-MeO-DMT and its metabolites (including bufotenine) plasma concentrations will be taken after dosing on Day 0.

Drinking Craving and Withdrawal:

- Change in alcohol craving as measured by Alcohol Craving Questionnaire (ACQ) at Days 1, 7, 28, 56, and 84 compared to Baseline (pre-dose Day 0)
- Alcohol cravings as measured by Craving Visual Analogue Scale (VAS)
- Alcohol withdrawal symptoms as measured by Clinical Institute Withdrawal Assessment (CIWA-Ar)

Alcohol Use:

- Using the Timeline Follow-Back (TLFB) interview, the following parameters of alcohol use in the 90 days before dosing and at designated timepoints will be recorded:
  - Longest duration (days) of continuous abstinence
  - Maximum number of standard units of alcohol consumed on any one day
  - Number of Heavy Drinking Days (HDD)
  - Percentage of Heavy Drinking Days (PHDD) in 85d prior D-3 (or start of detox) vs PHDD post-dosing measured on d14, d28, d56, d84.
  - Percentage of drinking days (PDD) in 85d prior D-3 (or start of detox) vs PDD post-dosing measured on d14, d28, d56, d84.
  - Mean Units per day (UPD): In 85d prior D-3 (or start of detox) vs UPD post-dosing measured on d14, d28, d56, d84.
  - Abstinence: Percentage of Abstinent days (PAD) in 85d prior D-3 (or start of detox) vs PAD on d14, d28, d56, d84 (with biomarker verification).
  - Number of days after BPL-003 dosing to first drink
  - Number of days after BPL-003 dosing to first HDD (defined by UK government as >=7 units a day for a woman and >=9 units per day for a man)
  - Average number of standard units of alcohol consumed per week in 85d prior D-3 (or start of detox) vs post-dosing measured on d14, d28, d56, d84 (and reported referencing UK risk levels)
- Consequences of alcohol use as measured by Short Inventory of Problems (SIP)
- Biomarkers
  - Alcohol use as measured by EtG in urine at Days 1, 28, 56, 84 compared to Screening
  - Alcohol use as measured by CDT in blood at Days 28 & 84 compared to Screening

Pharmacodynamic

- The correlation of the occurrence of a "complete mystical experience" and "ego dissolution", measured by the MEQ-30 and EDI, with improvement in alcohol use and craving (measured by AQC, TLFB, EtG, CDT)

Wellbeing

- Change in Montgomery–Asberg Depression Rating Scale (MADRS) at Days 28, 56, and 84 compared to Baseline
- Change in Clinical Global Impression Severity (CGIS) at Days 1, 28, 56, and 84 compared to Baseline
- Patient Global Impression of Change (PGIC) at Days 1, 28, 56, and 84
- Change in 5-level EuroQol-5 Dimension (EQ-5D-5L) at Days 28 and 84 compared to Baseline

Expectation

- Assess positive and negative expectations as measured by Stanford Expectations of Treatment Scale (SETS)

Methods:

The following assessments will be made.

Safety and tolerability:

Patient safety will be assessed by laboratory assessments (routine haematology, clinical biochemistry, and coagulation), physical examinations, 12-lead ECGs, vital signs (blood pressure, heart rate, and temperature), and the C-SSRS. Adverse events (AEs) and concomitant medication will be recorded from Screening until the patient's last visit. Nasal site reaction will be assessed after dosing.

Pharmacodynamic:

Mood, depression, and CGIS will be assessed at Screening, Days 0, 1, 28, 56, and 84.

BPL-003 subjective experiences will be assessed using the MEQ30 and the EDI.

Changes in drinking behaviour including alcohol intake and cravings will be assessed weekly until Day 84 using the Alcohol TLFB and ACQ. Alcohol craving will also be assessed using a Craving VAS before and after dosing on Day 0.

Markers of alcohol use will be assessed at multiple timepoints, e.g., breath (Day 0 only), blood (Screening, Day – 3, 28 and 84) and urine (Screening and Days 1, 28, 56, and 84).

Alcohol withdrawal symptoms using CIWA-Ar will be assessed at Day 0.

Quality of life will be assessed by EQ-5D-5L at Screening and Days 28 and 84.

Patients will be invited to complete an optional semi-structured interview on Days 1 and 84 and to complete optional online psychological change questionnaire on Days -3, 1, 28, and 84.

Details of the methodology, interview structure and psychological changes measures can be found in the Psychological Change Study Manual.

Statistical methods:

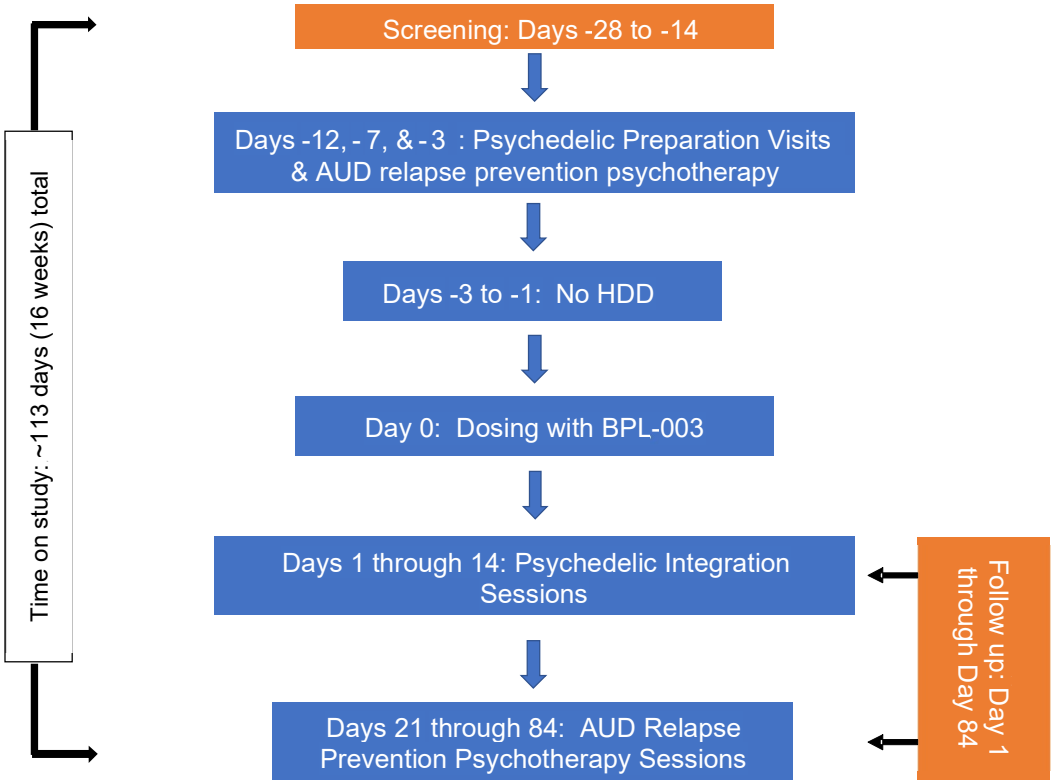
This is an exploratory study and there are no null hypotheses to be tested.

Summary statistics will be presented for all function and safety parameters.

In general, descriptive statistics including number of observations, mean, standard deviation, median, minimum, and maximum will be presented for continuous parameters. Categorical parameters will be displayed using counts and percentages within each category.

Additional information is provided in the protocol. Full details of the statistical analysis will be provided in the statistical analysis plan (SAP).

Figure 1: Study Flow Diagram



NOTE: Patients will receive ongoing AUD relapse prevention psychotherapy throughout the study.

SCHEDULE OF EVENTS

TABLE 1: SCHEDULE OF EVENTS

Assessments/Procedures	Screening[1]	Psychedelic Preparation[2] (*In clinic or video call*)			Dosing[3]	Follow-up												
	Day -28 to -14	**Day -12**	**Day -7**	**Day -3**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Day 63**	**Day 72**	**Day 77**	**Day 84**
		(± 5 days)		+2days		**(± 2 days)**			**(± 4 days)**									
General																		
Informed consent	X																	
Confirm eligibility	X				X													
Medical history	X																	
Demographics	X																	
Height/weight	X				X													X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X									X				X				X
Vital signs (HR, BP, and temperature)[4]	X				X	X												X
ECG[7]	X				X	X												X
Cardiac telemetry[23]					X													

Assessments/Procedures	Screening[1]	Psychedelic Preparation[2] (*In clinic or video call*)			Dosing[3]	Follow-up												
	Day -28 to -14	**Day -12**	**Day -7**	**Day -3**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Day 63**	**Day 72**	**Day 77**	**Day 84**
		(± 5 days)		+2days		**(± 2 days)**			**(± 4 days)**									
Urine pregnancy (or serum FSH) test[5]	X				X													
SETS[20]		X																
Diagnosis																		
Alcohol and drug use history[6]	X																	
Biomarkers of Alcohol Use																		
Haematology including MCV and coagulation[16]	X			X		X				X								X
Clinical biochemistry[16]	X			X		X				X								X
Drug screening[16]	X				X													
CDT[16, 24]	X			X						X								X
PK					X[18]													
Urine EtG	X					X				X				X				X
Alcohol breath test					X													
Severity																		
Alcohol TLFB	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
SIP	X			X						X				X				X

Assessments/Procedures	Screening[1]	Psychedelic Preparation[2] (*In clinic or video call*)			Dosing[3]	Follow-up												
	Day -28 to -14	**Day -12**	**Day -7**	**Day -3**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Day 63**	**Day 72**	**Day 77**	**Day 84**
		(± 5 days)		+2days		**(± 2 days)**			**(± 4 days)**									
Craving																		
ACQ					X	X	X			X				X				X
VAS craving					X[19]													
Withdrawal																		
Withdrawal CIWA-Ar					X													
Psychiatric Disorders and Depression																		
MADRS (SIGMA)	X				X					X				X				X
MINI	X																	X[17]
C-SSRS	X				X[21]	X	X											X
CGIS	X					X				X				X				X
PGIC						X				X				X				X
Drug Experience																		
BPL-003 administration					X													
Nasal site reaction[8]					X													
EDI					X[9]													
MEQ30					X[9]													
Readiness for discharge checklist[10]					X													

Assessments/Procedures	Screening[1]	Psychedelic Preparation[2] (*In clinic or video call*)			Dosing[3]	Follow-up												
	Day -28 to -14	**Day -12**	**Day -7**	**Day -3**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Day 63**	**Day 72**	**Day 77**	**Day 84**
		(± 5 days)		+2days		**(± 2 days)**			**(± 4 days)**									
Psychotherapy																		
Psychedelic preparation		X	X	X														
Psychedelic integration[11]						X	X	X										
Qualitative interview[13]					X													
Semi-structured interview[12]						X												X
Psychological change measures[12]				X		X				X								X
Relapse prevention psychotherapy [14]		X[15]	X[15]	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Status and QoL																		
EQ-5D-5L	X									X								X
Treatment Model Feedback[22]											X							
Adverse Events																		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reactivation Questionnaire							X			X								X

Abbreviations: ACQ = Alcohol Craving Questionnaire; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUD = alcohol use disorder; BP = blood pressure; CDT = carbohydrate deficient transferrin; CGIS = Clinical Global Impression of Severity; CIWA-Ar = Clinical Institute Withdrawal Assessment-Alcohol revised; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDI = Ego Dissolution Inventory; EQ-5D-5L = 5-level EuroQol-5 Dimension; EtG = ethylglucuronide; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HR = heart rate; MADRS SIGMA = Montgomery–Asberg Depression Rating Scale, SIGMA version; MCV = mean corpuscular volume; MEQ30 = Mystical Experience Questionnaire; MINI = Mini-International Neuropsychiatric Interview; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; QoL = quality of life;; SETS = Stanford Expectation of Treatment Scale; SIP = Short Inventory of Problems; TLFB = Timeline Follow-Back.
Notes:

1. Screening will occur from Day -28. The maximum time to complete Screening and Psychedelic Preparation will be 28 days.
2. The Psychedelic Preparation sessions may be completed in less than 12 days if the therapist has a good rapport with the patient, with a window of +/-5 days for Day -12 & Day -7, however they should not fall on the same day. The final preparation visit has a window of +2 days and should be Day -3 to Day -1 only. It is preferable that visits be face to face, but if necessary, visits can be completed remotely with the exception of Screening, Day -3, Day 0, Day 1, Day 28, Day 56, Day 84.
3. Unless otherwise indicated, ALL assessments, testing, and blood samples for haematology and clinical chemistry are to be performed PRIOR to dosing.
4. Vital signs (HR, BP, and temperature) at baseline will be measured in triplicate within 30 min (+/- 5mins) before dosing (Triplicate measurements should be obtained as closely as possible in succession, and no more than 2 min apart (temperature does not need to be repeated in triplicate). Predose BP must be within normal range pre dose on dosing day and if not repeated ~ 1 h later. If still not in range then it is considered a Screen fail. Vital signs also to be taken in triplicate within 30 min (+/- 5mins) before dosing Then single measurements at 10, 20, 30, 40 & 60 mins, and then every 30 min (+/- 5mins) until 4 h postdose; and when the patient is assessed as ready to be discharged on Day 0, if later than 4h postdose (as per the readiness for discharge questionnaire). Vital signs from 90 min post-dose onwards will form part of the readiness for discharge questionnaire. A note should be taken of any movement of the participant during Blood Pressure measurements. If systolic Blood pressure is > 160 mmHg then repeat the Blood Pressure measurement.
5. Pregnancy tests will only be done in women of childbearing potential. Urine pregnancy tests in women of childbearing potential will be done only at Screening and before dosing on Day 0. Serum FSH tests in postmenopausal women will be done at Screening only.
6. Including previous abstinence attempts.
7. ECG to be performed in triplicate at Screening (2 minutes apart), single at other visits.
8. A physician will examine the nostrils for any evidence of irritation or reaction after dosing with BPL-003.
9. EDI & MEQ30 To be completed after the qualitative interview, if done.
10. Readiness for discharge assessment to be completed every 30 minutes (+/- 5mins) starting 90 minutes after dosing before discharge from clinic up to 4 hours post dose. If the patient is not ready for discharge at 4 hours post dose then the questionnaire will be repeated again at the point Investigator believes patient may be ready for discharge.
11. The Psychedelic Integration Visit should be held in the clinic but may be done via video call at the discretion of the Investigator or for logistical reasons. The psychedelic integration on Days 1 and 7 should be started after all questionnaires/scales have been completed.
12. See Section 9.7.
13. Patients will be asked to take part in an optional qualitative interview. If they agree, the interview will commence on cessation of the psychedelic experience and before any postdose questionnaires are completed. The therapist will remain with the patient until the cessation of the psychedelic experience.
14. This can be either face to face or remote.
15. AUD relapse prevention psychotherapy (see Appendix 4) will begin during Psychedelic Preparation sessions.
16. Patients will fast (no food or drink, except water) for at least 8 hours before blood draws at the Screening visit

17. Only section I (AUD section) of the MINI to be completed at Day 84.
18. The PK blood sample will be taken three times after dosing at 5, 15 and 60 minutes post dose (+5 minutes for all timepoints) Details concerning the blood draw are provided in the Study Manual.
19. Craving VAS scale to be completed on admission and before discharge on dosing (Day 0). If greater at discharge than admission, then talk down and repeat scale and repeat until no higher than admission before discharging.
20. SETS will be administered prior to beginning the first psychedelic preparation session.
21. On Day 0 the C-SSRS will be done as part of discharge safety check at the end of Day 0.
22. Therapists may complete the Treatment Model feedback questions once from Day 15 to Day 42.
23. Cardiac Telemetry will be performed on Day 0 starting approximately 30 minutes before dosing up to 90 minutes post dose and any anomalies reported
24. CDT to be assessed in blood sample.

1. INTRODUCTION

1.1. Alcohol Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) integrates 2 DSM-IV disorders—alcohol abuse and alcohol dependence—into a single disorder called alcohol use disorder (AUD) with mild, moderate, and severe subclassifications. The key feature of AUD is the impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. Severity is based on the number of criteria a person meets based on their symptoms—mild (2 to 3 criteria), moderate (4 to 5 criteria), or severe (6 or more criteria). DSM-5 lists the following criteria (American Psychiatric Association, 2013):

In the past year, have you

- Had times when you ended up drinking more, or longer, than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over other aftereffects?
- Wanted a drink so badly you couldn't think of anything else?
- Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unprotected sex)?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

According to the World Health Organization (WHO), in 2018 there were 380 million people with AUD worldwide (5.1% of the population over 15 years of age, representing 7.1% and 2.2% of the global burden of disease for males and females, respectively). Alcohol is the leading risk factor for premature mortality and disability among those aged 15 to 49 years, accounting for 10% of all deaths in this age group. Disadvantaged and especially vulnerable populations have higher rates of alcohol-related death and hospitalization. Globally, alcohol is directly responsible for about 3 million deaths per year (about 5.3% of all deaths) in addition to disabilities and poor health (WHO, 2018). Harmful use of alcohol causes a range of mental and behavioural disorders and is associated with the incidence of infectious diseases such as tuberculosis as well as the

course of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), other noncommunicable conditions, and injuries. Beyond individual problems, alcohol abuse leads to significant social and economic losses to society at large. Both acute and chronic heavy drinking can contribute to a wide range of social problems, including domestic violence and marital breakdown, child abuse and neglect, absenteeism, and job loss (Meloni, 2004). In fact, according to a multicriteria decision analysis of drug harm in the United Kingdom (UK), alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places, driven by the overwhelmingly high harm to other people resulting from an individual's alcohol misuse (Nutt, 2010).

According to The National Institute for Health and Care Excellence (NICE) guidelines, treatment for AUD includes brief interventions to facilitate more healthy behaviours; specialised treatment like motivational enhancement therapy to address ambivalence about changing their drinking behaviour or dealing with their problems; detoxification to address withdrawal symptoms; cognitive-behavioural therapies to avoid relapses; and several drugs to diminish cravings or discourage relapses (National Institute for Health and Care Excellence, 2019). For people with severe alcohol dependence and/or significant physical or psychiatric comorbidity, this may require medication-assisted alcohol withdrawal in an inpatient or residential setting (Specialist Clinical Addiction Network, 2006). Current United States (US) Food and Drug Administration (FDA)-approved pharmacological treatments include acamprosate, naltrexone, and disulfiram. Scientific evidence demonstrates the benefits of combining approved drugs for treating AUD with evidence-based behavioural therapy, and the outcomes are generally better when medication and therapy are combined (Mason, 2021). Other emerging and off-label pharmacotherapies include nalmefene, which was approved in Europe and Australia for the purpose of controlling drinking, baclofen, topiramate, and gabapentin (Morley, 2021).

Peer-support group counselling is an approach used to facilitate relapse prevention. Alcoholics Anonymous is one of the earliest organizations formed to provide peer support and it is still the largest; other organisations exist for those who do not agree with the Alcoholics Anonymous philosophy (Kelly, 2020). Yet, despite all the harms and a variety of treatment options, only 19.8% of individuals with lifetime prevalence of AUD have sought treatment (Grant, 2015). Most studies examining the outcomes of people attending alcohol treatment find that 70% to 80% will relapse in the year following treatment, with the highest rate of relapse taking place in the first 3 months after completing treatment (Schuckit, 2009). Poor treatment response is typically associated with greater baseline alcohol use severity indicators (Davis, 2018a; Saitz, 2010), suggesting an unmet intervention need in heavy users.

1.2. Psychedelic-Assisted Psychotherapy

Psychedelic-assisted psychotherapy has been used for the treatment of depression and other psychiatric diseases since the 1920s, initially with mescaline and later, in the 1950s and 1960s, with lysergic acid diethylamide (LSD) and other psychedelics (Jay, 2019). Meta-analyses of these early studies suggest broadly positive clinical effects, although the methods used at that time do not meet currently accepted standards (Fuentes, 2020; Krebs, 2012; Rucker, 2016). Before LSD was controlled, the United States (US) National Institutes of Health funded more than 130 studies exploring its clinical utility, involving thousands of participants, with positive results in a range of disorders, including anxiety, depression, and alcoholism (Hintzen, 2010; Jay, 2019). LSD was used extensively for the treatment of substance use disorders (SUD) (Dyck,

2006). Psychedelics were placed in Schedule 1, initially in the US (US Drug Enforcement Administration, 1970) and then globally by the 1971 United Nations (UN) Convention on Narcotics, and clinical research with these compounds ceased for almost 3 decades (United Nations, 1971). Over the past 20 years, clinical studies of psychedelics for a wide range of psychiatric disorders have been initiated (Johnson, 2018; Nichols, 2016; Nutt, 2021; Rucker, 2016).

Epidemiological studies surveying cases where classic psychedelics were used, often without therapeutic intention, indicate that psychedelics aid addiction recovery across a variety of substances, including alcohol, tobacco, opioids, cocaine, methamphetamine, and cannabis (Garcia-Romeu, 2019; Garcia-Romeu, 2020; Johnson, 2017). Specifically for AUD, a recent survey study found that out of 343 respondents, 83% no longer met AUD criteria after their classic psychedelic experience (the majority used LSD [38%] or psilocybin [36%]) (Garcia-Romeu, 2019). Similarly, observational ethnographic studies of syncretic religions which use psychedelic-containing plants as sacraments also support a role for the classic psychedelics mescaline and ayahuasca in recovery from AUD (Albaugh, 1974; Bergman, 1971; Blum, 1977; de Rios, 2002; Fábregas, 2010; Halpern, 2008; Thomas, 2013) and report significantly lower rates of AUD among members of these religious groups (Fábregas, 2010; Lu, 2009).

Several studies of psychedelic-assisted psychotherapy for the treatment of mood disorders have been completed. Although other drugs which are sometimes considered together with psychedelics have demonstrated benefits for addictions, including AUD—notably ibogaine (Brown, 2013), 3,4-methylenedioxy-methamphetamine (MDMA) (Sessa, 2021), and ketamine (Jones, 2018; Worrell, 2021)—we focus this overview on the "classic" serotonergic psychedelics, such as psilocybin, LSD, mescaline, and dimethyltryptamine (DMT), as well as the DMT-containing admixture ayahuasca. Although modern published studies on classic psychedelics in the treatment of addictions have so far been small open-label studies, they have demonstrated considerable therapeutic potential in a variety of SUDs, including tobacco, alcohol, opioids, and cocaine dependence (Bogenschutz, 2015; Johnson, 2014; Krebs, 2012; Savage, 1973); clinicaltrials.gov: NCT02037126 (Psilocybin-facilitated Treatment for Cocaine Use: A Pilot Study).

Krebs and Johansen (Krebs, 2012) performed a meta-analysis of the 6 randomized, controlled studies of LSD for AUD conducted between 1966 and 1970 (Bowen, 1970; Hollister, 1969; Ludwig, 1969; Pahnke, 1970; Smart, 1966; Tomsovic, 1970). Pooled data included 536 participants with a median LSD dose of 500 µg and showed significant declines in alcohol misuse (59% of AUD patients treated with LSD showed improvements compared to 38% of individuals receiving a non-LSD control treatment).

Bogenschutz and colleagues assessed psilocybin for the treatment of alcohol dependence in a single-arm open-label study. Ten participants with AUD (with a mean 15.1 years of dependence) were followed for 36 weeks. A significant decrease in the percentage of drinking and heavy drinking days (compared to baseline) was found at all follow-up points (Bogenschutz, 2015). One more open-label study of psilocybin for the treatment of AUD (NCT04718792) and several larger, double-blind randomised clinical studies of psilocybin-assisted treatment for AUD are currently underway (clinicaltrials.gov: NCT02061293, NCT04141501, and NCT04410913), as well as one for co-occurring major depressive disorder and AUD (NCT04620759).

The prevalent model for clinical studies in depression assessing psychedelics is that of drug-enhanced psychotherapy. There are well-established guidelines for safety in psychedelic studies (Johnson, 2008). The treatment model involves a 4-stage process: assessment, preparation, experience, and integration. The first phase, assessment, involves careful selection of study participants for their suitability, from both the physical and mental perspectives, to take part in the study. Preparation for the session is designed to build rapport with the facilitators who will be with the participant during the drug session, as well as providing explanations about the drug effects. Integration involves a series of in-depth conversations about the experience, its meaning for the participant, and ways of integrating the experience into everyday life. Emotional support is provided if necessary. The extent of preparation and emotional support have been shown to correlate with the frequency of adverse events (Johnson, 2008). The importance of "set" and "setting" for the safety of participants in clinical studies is emphasised. "Set" refers to the emotional, cognitive, behavioural state, mindset, expectations, and intention of the participants just before psychedelic exposure. "Setting" refers to the physical environment where the psychedelic session takes place. With the appropriate set and setting, the safety of the clinical study participants is greatly increased, including a reduction in risks for psychological and emotional distress and/or physical injury (Carhart-Harris, 2018; Hartogsohn, 2016; Lyons, 2018).

The principle of psychedelic-assisted psychotherapy is that an efficacious dose of mind-altering substance is given only once or twice, accompanied by psychotherapy. The acute effects of psychedelics, coupled with salient and meaningful subjective experiences, open a therapeutic window of plasticity that facilitates insights. Those insights can be consolidated during the subsequent psychotherapy sessions for application in everyday life, resulting in changes in outlook and lifestyle (Carhart-Harris, 2017b).

A common mechanism of action—agonism at different serotoninergic (5-hydroxytryptamine; 5-HT) receptors (especially 5-HT_{2A})—is thought to mediate the therapeutic effects of psychedelics (Nichols, 2016). At the neural level, the long-term effects of psychedelics are likely underpinned by the ability of psychedelics to promote neuroplasticity in key neural circuits relevant to treating neuropsychiatric disorders (Ly, 2018). The plasticity-promoting properties of these substances may contribute to their rapid and enduring antidepressant and anxiolytic effects. Acutely, psychedelics work through 5-HT_{2A} receptors to reset neural networks, especially the default mode network (Carhart-Harris, 2017c). The dysregulation of neural circuits and networks and recalibration may facilitate reductions in habitual thoughts and behaviours associated with depressive disorders.

Additional effects that may be relevant in treatment include increases in emotional empathy (Pokorny, 2017) and other reward and emotion-processing changes (Bershad, 2019; Dolder, 2016; Kometer, 2012; Kraehenmann, 2015; Mueller, 2017; Roseman, 2018), increases in creative divergent thinking (Kuypers, 2016), enhanced mindfulness-related capacities (Sampedro, 2017; Soler, 2016), increased insightfulness (Davis, 2021; Kometer, 2015), reduced avoidance and increases in acceptance and connectedness (Watts, 2017), long-term increases in the personality trait openness (Lebedev, 2016; MacLean, 2011), feelings of awe (Hendricks, 2018), psychological flexibility (Watts, 2020), and emotional breakthrough experiences (Roseman, 2019). Classical psychedelics are also known to induce mystical-type experiences (Griffiths, 2006), which are significantly correlated with positive therapeutic outcomes (Johnson, 2019). Even the use of classic psychedelics across a user's lifespan outside of a clinical setting is associated with reduced odds of past-month psychological distress, past-year suicidal thinking,

and suicide planning and attempt, whereas lifetime use of other illicit drugs is largely associated with the opposite outcomes (Hendricks, 2015).

Historically, psychoactive substances were used, among other reasons, to facilitate mystical/peak experiences in ceremonial settings in different cultures (Schultes, 2001). These experiences are characterised by a sense of unity, sacredness, ineffability, transcendence of time and space, and deeply felt positive mood (Johnson, 2019). Drug-occasioned mystical experiences are hypothesised to be a mediating mechanism underlying the therapeutic effects of psychedelics, and there is robust research evidence that the occurrence of a mystical experience while under the effects of a psychedelic is one of the most reliable predictors of treatment outcomes (Griffiths, 2016; Johnson, 2019; Richards, 1977; Ross, 2016), most notably improvements in SUDs (Bogenschutz, 2015; Garcia-Romeu, 2014; Johnson, 2014; Krebs, 2012; Savage, 1973). In a smoking cessation study (Johnson, 2017), the strength of mystical experiences during psilocybin sessions correlated with clinical change in addictive behaviour. Similarly, in a study of psilocybin for alcohol dependence (Bogenschutz, 2015), ratings of mystical experiences correlated strongly with reductions in drinking behaviour. Links between the strength of mystical experience and therapeutic outcomes in treatment-resistant depression (TRD) were noted in a small open-label study by Carhart-Harris et al (Carhart-Harris, 2017a; Carhart-Harris, 2016; Carhart-Harris, 2018), but also in larger, controlled studies of anxiety and depression associated with life-threatening illness (Grob, 2011; Ross, 2016). The occurrence of mystical experience during a psychedelic session predicted positive outcomes for individuals more than a year later (Griffiths, 2008; Schmid, 2018), and its importance for long-term outcomes occurs regardless of the genesis of the experience (Griffiths, 2011; Russ, 2019).

1.3. 5-Methoxy-N,N-dimethyltryptamine

5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a tryptamine that falls into the category of "classic" psychedelics (Nichols, 2004; 2016). It is endogenously produced in humans, although its biological function, if any, is not known (Barker, 2012; Guchhait, 1976; Narasimhachari, 1971).

5-MeO-DMT binds to several serotonin (5-HT) and other receptor subtypes, with modest selectivity as an agonist at the 5-HT_{1A} receptor vs the 5-HT_{2A} subtype (Halberstadt, 2012; Ray, 2010). It has a higher affinity for the serotonin 5-HT_{1A} receptor (inhibition constant [K_i] <10 nM) than for the 5-HT_{2A} or 5-HT_{2C} receptors (K_i >1000 nM) or other 5-HT receptors (Halberstadt, 2012). Additional activity is mediated through the inhibition of serotonin reuptake. 5-MeO-DMT had almost no effect on monoamine release and dopamine release and reuptake (Nagai, 2007). 5-MeO-DMT shows strong binding to 5-HT receptors (50% effective concentration of 100 nM), being 115% more "sticky" than serotonin (Nonaka, 2007). 5-MeO-DMT is also an agonist of σ-1 receptors (Szabo, 2014) and trace amine-associated receptors (TAARs) (Wallach, 2009).

5-MeO-DMT is extensively metabolised through oxidative deamination mediated by monoamine oxidase A (MAO-A). O-demethylation, N-demethylation, and N-oxygenation are involved to a much smaller extent (Shen, 2011; Sitaram, 1990; Sitaram, 1987).

For a full list of pharmacology studies, please refer to the current version of the Investigator's Brochure (IB).

Historically, snuffs from 5-MeO-DMT–containing plants such as *Virola* spp. or *Anadenanthera peregrina* have been used for centuries by indigenous people of South America (Schultes, 2001;

Schultes, 1984). Recently, a 5-MeO-DMT–rich gland extract of toad *Incilius* (*Bufo*) *alvarius* and synthetic 5-MeO-DMT have gained popularity for spiritual or recreational use, although use in the general population remains low, accounting for only 1.6% of the 0.12% reporting use of novel psychoactive substances in a large annual cross-sectional population survey in the USA, the National Survey on Drug Use and Health (Palamar, 2019; Sexton, 2019). There is no specific mention of this compound or global use statistics in the 2019 World Drug Report (United Nations, 2020) or European Drug Report (EMCDDA, 2021). Doses reported for spiritual/recreational use range from a threshold dose of 1 mg to a dose of 20 mg when smoked and a threshold dose of 3 mg to a dose of 25 mg when insufflated (Erowid, 2021). In an epidemiological survey, the dose ranges for 284 people who used synthetic 5-MeO-DMT were reported as follows: 25% did not know how much they used, 34% used up to 10 mg, 37% used 11 to 50 mg, and 5% used doses greater than 50 mg (Davis, 2018b). An observational study in a naturalistic setting lists individual doses ranging from 6 to 21 mg, with some participants redosing up to 4 times in the same session, bringing the cumulative dose to a range from 18 to 61 mg (Uthaug, 2020a).

5-MeO-DMT was included in Schedule 1 of the Controlled Substances Act in the United States in 2009 (US Drug Enforcement Administration, 2010), and is a controlled substance in some countries in Europe and the UK (Erowid, 2021; UK Home Office, 2019).

1.4. Review of Investigational Medicinal Product

BPL-003 is the benzoate salt of 5-MeO-DMT being developed by Beckley Psytech Ltd. (BPL) as a therapy for treatment-resistant depression (TRD) and AUD. BPL-003 will be administered intranasally as a dry powder.

1.4.1. Nonclinical Data

1.4.1.1. Nonclinical Pharmacology

5-MeO-DMT induces behavioural responses in rats and mice which are predominantly mediated through the 5-HT_{1A} receptor, although 5-HT_{2A} receptor activation is also involved (Berendsen, 1989; Eison, 1992; Halberstadt, 2011; Krebs-Thomson, 2006; Lucki, 1984; Smith, 1986; Tricklebank, 1985). 5-MeO-DMT has also been shown to induce aggressive responses in cats and submissive gestures, hyperactivity, distancing, checking, and reduction in social grooming in monkeys (Benington, 1965; Schlemmer, 1981; 1986; Schlemmer, 1977).

In vitro receptor profiling has shown that 5-MeO-DMT has the greatest affinity for the serotonin receptor 5-HT_{1A} (K_i of 1.9 nM, several orders of magnitude higher than that for other serotonergic receptors) (Halberstadt, 2012). 5-MeO-DMT also has significant affinity for other receptors, such as dopamine (D_1 and D_3), norepinephrine (α_2), and the norepinephrine transporter (Nagai, 2007; Ray, 2010). 5-MeO-DMT has almost no effect on monoamine release and dopamine release and reuptake (Nagai, 2007).

Serotonin receptors are widely expressed across the vascular system (Ullmer, 1995), and psychedelics are known to increase breath rate, heart rate (HR), and blood pressure (BP) (Nichols, 2016). Specifically, DMT has been demonstrated to increase HR and BP in human and animal studies (Carbonaro, 2016b; Strassman, 1994). A cardiovascular study in cats (Lalley, 1982) reported that 20 to 200 µg/kg 5-MeO-DMT inhibited phrenic and sympathetic neural discharges and depressed BP within seconds after injection, with complete recovery noted after

20 minutes. Interestingly, phrenic inhibition induced by 5-MeO-DMT could be overcome by ambient heat (Lalley, 1982). That observation could be explained by the high affinity of 5-MeO-DMT for 5-HT_{1A} receptors: 5-HT_{1A} agonists decrease BP and HR via a central mechanism, by inducing peripheral vasodilation and stimulating the vagus nerve (Dabiré, 1991; Kaumann, 2006). However, it is possible that at higher doses, 5-HT_{2A} and other 5-HT receptor–mediated effects will be apparent.

1.4.1.2. Nonclinical Pharmacokinetics (Published Data)

Absorption and terminal elimination of 5-MeO-DMT (the active moiety) are rapid: maximum plasma concentration (C_{max}) is 5 to 6 minutes and terminal elimination half life ($t_{½}$) is 12 to 19 minutes after intraperitoneal (IP) administration in mice (Sitaram, 1990), with similar results in rats (Sitaram, 1987).

5-MeO-DMT distributes to the liver, kidneys, and brain in rabbit, rat, and mouse models (Berger, 1978; Sitaram, 1990; Sitaram, 1987). After IP administration, 5-MeO-DMT concentrations were 1.7-fold higher in rat brain than in plasma (Sitaram, 1987).

5-MeO-DMT is primarily metabolised through oxidative deamination mediated by MAO-A (Sitaram, 1990; Sitaram, 1987). Studies in the rat showed that the main urinary metabolite of 5-MeO-DMT is 5-methoxyindoleacetic acid (5-MIAA; 54%), followed by 5-hydroxy-N,N-dimethyltryptamine glucuronide (23%), 5-hydroxyindoleacetic acid (5-HIAA; 14%), and bufotenine (9%) (Agurell, 1969; Sitaram, 1987; Squires, 1975; Suzuki, 1981; Yu, 2003). A 50% decrease in systemic clearance is observed at higher doses of 5-MeO-DMT (10 or 20 mg/kg intravenous [IV] or IP in mice), indicating that MAO-A-mediated metabolism becomes saturated. This nonlinearity is also reflected in the corresponding increase in brain concentration of 5-MeO-DMT (Shen et al., 2010; Shen, Jiang and Yu, 2011).
O-demethylation of 5-MeO-DMT, results in the production of the active metabolite bufotenine (itself a potent psychedelic). The extent to which 5-MeO-DMT is O-demethylated is dependent on the genetic cytochrome P2D6 (CYP2D6) polymorphism. As such, variations in CYP2D6 genotype (from poor to ultra-rapid metabolisers) may contribute to variability in the metabolism (Shen et al., 2010).
MAO inhibitors can modulate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of 5-MeO-DMT. Co-administration of 5-MeO-DMT and a MAO inhibitor significantly increases and extends the systemic and cerebral exposure to 5-MeO-DMT in rodents (Halberstadt et al., 2008; Halberstadt, Nichols and Geyer, 2012; Halberstadt, 2016; Jiang, Shen and Yu, 2016), by promoting its accumulation in the brain (Halberstadt, 2016). MOA inhibition also enhances the hallucinogenic effect of 5-MeO-DMT through conversion to bufotenine, which binds the 5-HT_{2A} receptor with a 5 to 10-fold greater affinity, and about 3-fold higher potency, than the parent molecule (Spencer, Glaser and Traber, 1987; Glennon et al., 1994; Roth et al., 1997). This can result in hyper-serotonergic effects or serotonin toxicity. However, unlike 5-MeO-DMT, bufotenine does not readily cross the blood-brain barrier (Migliaccio et al., 1981).

1.4.1.3. Summary of BPL non-clinical toxicology studies

BPL-sponsored toxicology program has characterised the test item as part of a series of studies, including maximum tolerated dose and a pivotal 14-day repeat dose toxicity study in two species. The test item used in the pivotal repeat dose nonclinical toxicology studies showed a very short half-life in both rats and dogs, and there was no evidence of bioaccumulation in either

species following 14 days of repeated administration. There was generally no evidence of gross systemic or organ toxicity associated with the test item at pharmacologically relevant dose ranges in the nonclinical species.

In a 14-day intranasal toxicology non-clinical study in male and female rats (ITR report 700041), plasma concentrations of 5-MeO-DMT increased as a function of the dose administered. Peak (Cmax) concentrations were reached within 2 to 5 min post dosing (tmax) with apparent elimination half-lives (t½) ranging from 6.8 to 9.4 min. Values trended lower on Day 14 compared to Day 1. There was no apparent sex difference and no evidence of accumulation with repeated dosing.

In a 14-day intranasal toxicology study in male and female dogs (ITR report 62959), plasma concentration of 5-MeO-DMT increased as a function of the dose administered. Peak concentrations were reached within 3 to 14 min (tmax), post dosing with apparent elimination half-lives ranging from 19 to 95 min. The values were not markedly different on Day 1 and Day 14. There was no apparent sex difference and no evidence of accumulation with repeated dosing.

Furthermore, as part of the dose confirmation phase (phase II) of a Maximum Tolerated Dose study in the dog (ITR 62958), the test item was administered to one male and one female dog, once per day at 2.5mg/kg for 5 days, followed by twice-per-day administration at 5mg/kg/day (2.5mg/kg on each administration), 4 hours apart on days 6 and 7. There was no effect on mortality, body weight, food consumption, or a severe adverse reaction, and also no apparent exacerbation of clinical signs or evidence of bioaccumulation following this administration paradigm in the dogs (total human equivalent dose of 167 mg per day). Clinical signs and symptoms following administration of 2.5mg/kg/day or 5mg/kg/day included, but not limited to, salivation, vocalization, sensitivity to touch, shaking and tremors, dilated pupils, muscle stiffness, decrease in activity, uncoordination, and lying on cage floor. Generally, these signs were of slight to moderate intensity, transient in duration, and followed the plasma concentrations of the active substance.

Therefore, toxicology studies in both rats and dogs characterised a compound with a short duration of action, which induced transient serotonergic stereotypes in the nonclinical species.

1.4.1.4. Safety

For a full list of non-clinical studies please refer to the current version of the IB.

1.4.1.5. Toxicology

For a full list of non-clinical studies please refer to the current version of the IB.

1.4.2. Previous Experience in Humans

1.4.2.1. Clinical Studies

BPL is currently evaluating 5-MeO-DMT in six clinical studies summarised in Table 2.

TABLE 2. SUMMARY OF 5-MEO-DMT CLINICAL TRIALS

IMP	Study Number	Phase	Study Title	No. of Subjects	Doses Tested	Status
BPL-002	BPL-5MEO-101 (NCT05032833)	1	A Double-Blind, Randomized, Phase 1, First-in-Human, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of Intranasal 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in Healthy Subjects	36 dosed	2.5 to 14 mg or placebo	Clinical conduct complete; report pending
BPL-003 and BPL-003S	BPL-003-103 (NCT05347849)	1	A Two-Part, Phase 1, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of Intranasal BPL-003 (5-Methoxy-N,N-dimethyltryptamine benzoate) in Healthy Subjects	Part A: 44 dosed Part B: 30 planned 11 dosed	Part A: 1 to 12 mg or placebo Part B: 0.3 to 16 mg in 1 or 2 sprays	Part A: complete Part B: ongoing
BPL-003	BPL-003-204 (NCT05660642)	2a	An Open-Label, Phase 2a, Single Dose Study to Evaluate the Safety Tolerability and Pharmacodynamics of BPL-003 in Patients with Treatment Resistant Depression	12 planned 2 dosed	10 or 12 mg	Ongoing
BPL-003	BPL-003-203 (NCT05674929)	2a	An Open-Label, Phase 2a Single Dose Study in Patients With Alcohol Use Disorder	12 planned	10 mg	Ongoing
BPL-003	BPL-003-201 (NCT05870540)	2b	A Quadruple Masked, Dose-Finding Study to Evaluate the Efficacy and Safety of Intranasal BPL-003, with Open Label Extension, in Patients with Treatment-Resistant Depression	225 planned	0.3, 8 or 12 mg	In set-up

BPL-003	BPL-003-205	2a	An Exploratory Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intranasal BPL-003 in Patients with Difficult-to-Treat Major Depressive Disorder	16 planned	1 or 2 doses in a single day Doses of 12 mg or 16 mg, in 2 sprays	Planned

1.4.2.2. Clinical Experience with BPL-002

BPL-5MEO-101 (5-MeO-DMT intranasal liquid): Phase 1 placebo-controlled, single-ascending dose study in healthy, psychedelic-naïve subjects (UK) – clinical conduct complete. A total of 24 healthy subjects received single doses of up to 14 mg of BPL-002 (5-MeO-DMT-HCl) and 12 received placebo. No serious adverse events (SAEs) were reported, and all treatment-emergent adverse events (TEAEs) were mild (84%) or moderate (16%). The most frequently reported events were blood pressure systolic increased (15.7%), throat irritation (14.5%) and heart rate increased (8.4%). Overall, the tolerability of up to 14 mg of BPL-002 was considered good by the Safety Review Committee (SRC). The PK of BPL-002 was not linear; exposure did not increase with dose. The highest Cmax measured in any subject was 13.9 ng/ml and the geometric mean Cmax of the highest dose group (14 mg) was 2.49 ng/ml.

1.4.2.3. Clinical Experience with BPL-003

BPL-003-103: Phase 1 randomized, single-center study in healthy volunteers (clinicaltrials.gov #NCT05347849) to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single intranasal doses of BPL-003 (5-MeO-DMT.benzoate) in healthy, psychedelic-naïve subjects.

BPL-003-103 is divided into two-parts (Part A double blind, placebo controlled and Part B open label) with planned enrolment of up to 65 healthy male or female subjects (aged 25 to 55 years), in up to 11 cohorts of: 6 subjects (Cohorts 1-4), 7 subjects (Cohorts 5-7), and 5 subjects (Cohorts 8-11) as follows.

- The clinical conduct of Part A (Cohorts 1-7) is complete, and 44 healthy volunteers planned to receive single doses of up to 12 mg of BPL-003 or placebo at a ratio of either 4 active:2 placebo (Cohorts 1-4) or 5 active:2 placebo (Cohorts 5-7). Doses were administered as a single spray in 1 nostril.

- In Part B (Cohorts 8-11), which is ongoing, subjects will receive a single intranasal dose of BPL-003, however doses may be administered as a single spray in 1 nostril, or as 2 sprays. Increasing dose levels may be administered if deemed safe by the SRC and are predicted to lead to exposure below the safety limit determined in preclinical dog studies (C_{max} 421 ng/mL or AUC 220 h.ng/mL).

1.4.2.3.1. BPL-003-103 Part A Results

31 healthy volunteers received single doses of up to 12 mg of BPL-003 and 13 received placebo. 21 out of 44 subjects (48%) reported a total of 38 treatment emergent adverse events (TEAEs), of which 2 (15%) were with placebo. The most frequently reported TEAEs were: nasal discomfort (26% of all TEAEs), nausea (18%), vomiting (13%) and headache (11%) (Table 3).

The majority of TEAEs (89%, [34/38] were mild, while 11% [4/38] were moderate in severity. The moderate TEAEs were pyrexia (placebo), back pain (4 mg), chest discomfort (8 mg) and tremor (8 mg). 32 of the 38 TEAEs were classified as related to study medication in the Investigator's opinion. The duration of most of the probably related TEAEs was short (minutes to 1-2 hours) occurring during the duration of the PD / psychedelic / consciousness altering effect of the study drug.

Study BPL-003-103 resulted in no deaths or serious adverse events. In addition, no subjects experienced AEs leading to study discontinuation after BPL-003 administration. No suicidal ideation or suicidal behavior were reported. There were no nasal findings on examination post drug administration and no clinically important changes in vital signs, ECG, telemetry, or laboratory safety tests. The tolerability of up to 12 mg of BPL-003 was considered good by the SRC.

TABLE 3: SUMMARY OF BPL-003-103 TEAES BY PREFERRED TERM

TEAE Coded PT	Placebo N=13	1 mg N=4	2.5 mg N=4	4 mg N=4	6 mg N=4	8 mg N=5	10 mg N=5	12 mg N=5	Total N=44
Number of Participants with TEAE, N (%)	2 (15%)	1 (25%)	1 (25%)	4 (100%)	3 (75%)	4 (80%)	2 (40%)	4 (80%)	21 (48%)
TEAE by Event, n (%)									
Nasal discomfort			1	2	2	2		3	10 (26%)
Nausea				2	1	2	1	1	7 (18%)
Vomiting				2		1		2	5 (13%)
Headache	1			1		2			4 (11%)
Other (<2 total events)	1	1		1	2	3	2	2	12 (32%)
Total	**2**	**1**	**1**	**8**	**5**	**10**	**3**	**8**	**38 (100%)**

Abbreviations: N = sample size; TEAE = treatment-emergent adverse events; PT = preferred term

The PK parameters of BPL-003 were approximately dose linear. That is the C_{max} and AUC of 5-MeO-DMT approximately increased with dose over the range 2.5 mg – 12 mg. The median T_{max} ranged from 4 to 15 to min over the doses tested (average of 8.7 min). The arithmetic, mean $T_{1/2}$ ranged from 15 to 27 min (average of 20.9 min). No dose exceeded the maximum exposure limits defined by the preclinical safety in the dog (C_{max} 421 ng/mL or AUC 220 h.ng/mL).

The active metabolite, bufotenine, was only detected at very low levels (1.46ng/mL), at the 6 mg dose level 16 min timepoint in one study participant.

In this study assessments were made of PD endpoints that were thought to be predictive of efficacy outcomes in TRD subjects. Literature data indicate that the 30-item Mystical Experience Questionnaire (MEQ-30) data may be used as a surrogate marker of potential future psychiatric efficacy (Hirschfield, 2021; Griffiths, 2011), and so was the key PD outcome measure conducted. A score of ≥3 was defined to be the threshold to elicit a significant experience. A score of ≥3 in all 4 subdomains of the MEQ-30 was defined as a complete mystical experience (Barrett, 2015).

The mean subject MEQ-30 scores generally increased with BPL-003 dose, with levels ≥3 being observed at doses of 6 mg and above in at least one sub-domain or total MEQ-30 score. The highest MEQ-30 scores were attained with 12 mg BPL-003, and 3 of 5 subjects (60%) achieved a complete mystical experience at 10 mg and 12 mg doses.

1.4.2.4. Literature Data of 5-MeO-DMT

Safety and Effects on Symptoms of Depression

Epidemiological Studies and Case Reports

There is documented modern use of 5-MeO-DMT, both as pure synthesised molecule and as a gland secretion of the toad *Incilius alvarius*. Several case studies and many epidemiological assessments of 5-MeO-DMT have been made, as summarised below.

Safety and Tolerability

Epidemiological studies and case reports list the following acute adverse effects of 5-MeO-DMT administration: fear, sadness, anxiety, confusion, feeling like dying, crying, paranoia, shaking/trembling, vomiting, nausea, transient headache, pressure or weight in their chest or abdomen, loss of body perception, and dissociative experience with memory loss (blackout). Delayed adverse effects (up to 1 week after dosing), including somatic tension in muscles, difficulties sleeping, and "flashbacks" or "reactivation" (re-experiencing some of the effects felt during the drug session), are described in the IB.

Preliminary evidence from naturalistic studies shows that psychological AEs from the psychedelic experience, occurring in 37% of 5-MeO-DMT users, are tolerable but challenging (Davis, 2018b). However, it is likely that in a clinical setting, these adverse effects can be reduced by providing appropriate psychological support before, during, and after the session. Similarly, it has been noted that AEs associated with other psychedelics, such as psilocybin-containing fungi, are much more frequent during recreational use than during controlled experimental or therapeutic sessions (Carbonaro, 2016a).

Epidemiological studies of 5-MeO-DMT demonstrate that it has a safe profile of use; however, co-administration of 5-MeO-DMT with MAO inhibitors (MAO-I) or drugs of abuse can be dangerous. There have been 2 reported deaths, 1 associated with use of 5-MeO-DMT and beta-carbolines (which have MAO-inhibiting effects), and 1 following the use of 5-MeO-DMT with cannabis and cocaine (Brush, 2004; Sklerov, 2005). Further details on published toxicity reports and the associated AEs are described in the IB.

Observational Studies and Reported Outcomes Following 5-MeO-DMT Administration

5-MeO-DMT has gained popularity in naturalistic settings as a means for spiritual exploration or personal growth or as a way to improve well-being or relieve problems associated with mental health (Davis, 2018b; Davis, 2019). Recreationally or ceremonially, 5-MeO-DMT has a safe profile of use and low potential for psychiatric or biomedical consequences, and it might have psychotherapeutic effects, although these studies have low evidential standards (Davis, 2018b; Uthaug, 2019; Uthaug, 2020b). Moreover, when 5-MeO-DMT is used ceremonially, ratings of mystical experiences, well-being, and other positive effects were higher compared with its use in nonstructured recreational settings (Sepeda, 2020). Several countries in which 5-MeO-DMT is not illegal offer retreats and treatment programs. A survey from one such retreat found beneficial effects of 5-MeO-DMT and ibogaine treatments in 51 US Special Operations Forces veterans. Those patients indicated, via self-reported questionnaires, that these substances helped them with their traumatic experiences, suicidal ideation, depression, and anxiety, although clinical studies in controlled settings need to determine if this is indeed the case (Davis, 2020).

A recent study (Uthaug, 2019) assessed the effect of inhaling vapor from dried toad secretion containing 5-MeO-DMT in 42 participants. Participants reported higher levels of life satisfaction as well as lower levels of depression, stress, and anxiety. However, it should be noted that only approximately 25% to 30% of the dried secretion consisted of the primary component 5-MeO-DMT. Other tryptamines such as bufotenine and DMT were present in the inhaled vapor. Uthaug

et al examined the effects of synthetic 5-MeO-DMT in a prospective study (Uthaug, 2020b). Similar to the previous study with toad secretions, they reported increased ratings of mindfulness and decreased ratings of depression and anxiety.

In one study of 20 individuals, mystical experiences were reported by 75% of 5-MeO-DMT users and were comparable in quality to those occasioned by high doses of psilocybin (Barsuglia, 2018). This suggests potential therapeutic effects of 5-MeO-DMT, as mystical experiences (occasioned by psilocybin and LSD) have been identified as the strongest predictors of treatment outcomes for a variety of psychiatric conditions, from TRD to addiction (Bogenschutz, 2015; Carhart-Harris, 2016; Griffiths, 2016).

Clinical studies in controlled settings are needed to determine if this is indeed the case. Limited clinical study data are available for 5-MeO-DMT, as the inhaled formulation GH001.

- In a Phase 1 open-label, single ascending dose and individualized multiple-dose study (NCT04698603 GH001-HV-101; Reckweg, 2021), GH001 was administered through inhalation as single doses of 2, 6, 12, and 18 mg or as an individualized dose regimen (IDR) in 22 healthy volunteers. Prominent psychedelic effects were observed with single doses of 6, 12, and 18 mg, with maximal effects evident after the IDR dosing. No SAEs were reported. AEs were mild (n=25) or moderate (n=2) and resolved spontaneously. The most frequently reported AEs were nausea and headache. All doses were considered safe and well tolerated by the Study Safety Group.
- In a Phase 1/2 open-label, single and individualized multiple-dose study of up to 3 doses of 5-MeO-DMT were administered to 8 patients with TRD (GH001-TRD-102; NCT04698603). There were no reported clinically significant changes in any safety assessments (psychiatric safety, cognitive function, ECG, vital signs, safety laboratory analysis) post dose compared to baseline. There were three AEs of moderate intensity (2 x nausea, 1 x depressive symptom) with all others being mild; no SAEs. Topline data reported 7 of 8 patients (87.5%) in remission (Montgomery-Asberg Depression Rating Scale [MADRS] score ≤10) at Day 7 after IDR dosing, with a mean change from baseline in MADRS at Day 7 of -24.4 points (-76%) (Reckweg, 2023).

1.5. Rationale for the Proposed Study

The mechanisms underlying the therapeutic efficacy of classic psychedelics in AUD are yet to be conclusively elucidated (Rieser, 2021) (see Figure 2); however, given that preliminary evidence indicates the efficacy of psychedelics across a variety of SUDs, it is likely that nonspecific mechanisms shared across all addictions or more widely across internalising mental health disorders are being targeted (Nutt, 2020). The ubiquitous expression of 5-HT receptors throughout the CNS makes them central to a multitude of higher neurophysiological processes, including modulating mood, cognition, reward, learning, memory, cognitive flexibility, sleep, and many other vital functions.

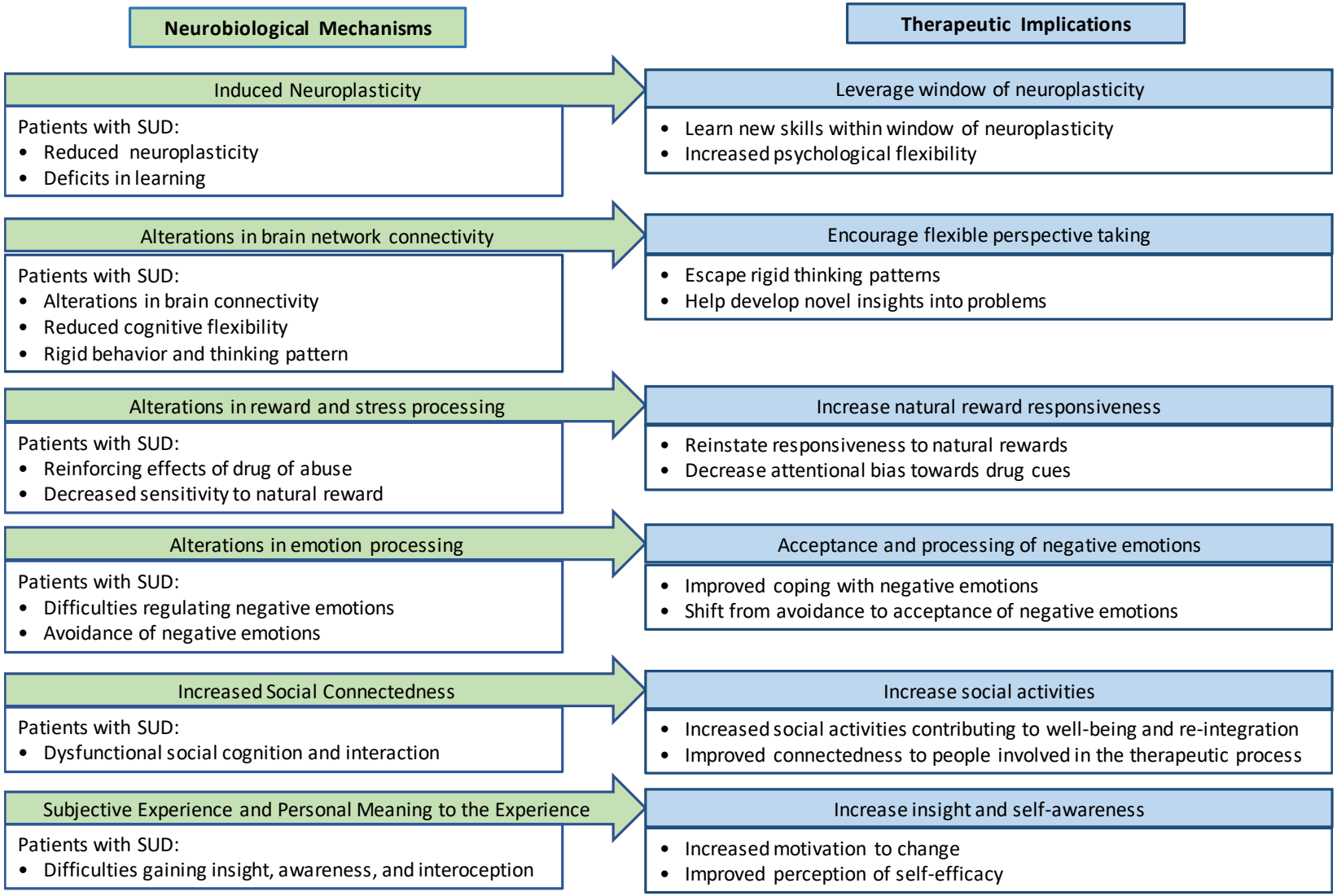
Psychedelics, including 5-MeO-DMT–containing preparations, have been used for centuries by indigenous people. Epidemiological studies of current spiritual/recreational use indicate that many people report beneficial outcomes, including alleviation of symptoms of addiction (Davis, 2018b; Davis, 2019). Clinical trials with defined doses and purity of the psychedelic substance,

and appropriate care, set, and setting are required to evaluate the safety and efficacy of psychedelics. Most clinical trials with psychedelics have been conducted with long-lasting substances like psilocybin or LSD. However, short-lasting compounds like 5-MeO-DMT produce similar effects on the brain networks and reliably induce mystical experiences (Barsuglia, 2018).

5-MeO-DMT lacks pharmacological activity when taken orally. In order to bypass first-pass metabolism, parenteral routes of administration have been explored. An intranasal route of administration has been selected for ease of administration and to enhance bioavailability. Intranasal administration of 5-MeO-DMT has been explored previously and showed feasibility and pharmacological activity via this route (Ott, 2001).

This open-label study will generate safety and tolerability data and evaluate the feasibility of delivery for BPL003-assisted relapse prevention psychotherapy in the treatment of AUD.

Figure 2: Overview of Neurobiological Mechanisms and Their Therapeutic Implications



Abbreviations: SUD = substance abuse disorder
Reproduced from Figure 1 of Rieser et al, 2021.

1.6. Risk-Benefit Profile

Steps taken to mitigate risk in the present study are described in Section 4.5.

Potential Risks:

- Adverse events related to the serotonergic system, including tachycardia and raised blood pressure
- Adverse events during the psychedelic experience, including anxiety, confusion, paranoia, and dissociation
- Psychological adverse events following the psychedelic experience
- Nasal and/or pharyngeal irritation postdose

Potential Benefits:

Alleviation of the symptoms of addiction following administration of 5-MeO-DMT has been reported anecdotally and in epidemiological studies.

The overall risk-benefit ratio is considered acceptable.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives:

- To assess the safety and tolerability of single intranasal dose of BPL-003 (5-MeO-DMT) in patients with AUD

2.2. Secondary Objectives:

- To assess the PD (including psychological effects) of single intranasal doses of BPL-003 in patients with AUD
- To assess the feasibility of the treatment model for BPL-003 combined with relapse prevention psychotherapy in patients with AUD

2.3. Exploratory Objectives:

- To explore the effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy in patients with AUD on alcohol use and related symptoms
- To explore the effects of BPL-003 combined with relapse prevention psychotherapy on health-related quality of life (QOL) in patients with AUD
- To assess the correlation of PD effects with alcohol use and related symptoms
- To explore exposure levels after a single intranasal dose of BPL-003 in patients with AUD

3. STUDY ENDPOINTS

3.1. Primary Endpoints

Safety Endpoints

- Percentage of patients with treatment-emergent adverse events (TEAEs)
- Percentage of patients with clinically significant postdose abnormal laboratory tests
- Percentage of patients with clinically significant abnormal postdose vital sign measurements (HR, BP, and body temperature)
- Percentage of patients with postdose suicidal ideation as determined by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Change in C-SSRS score compared to Baseline at Days 7 and 84
- Readiness for discharge questionnaire
- Measure the frequency, emotional valence and functional impact of any re-activation events in the study through the Reactivation Questionnaire (ReAQ)

3.2. Secondary Endpoints

Pharmacodynamic Endpoints:

- Percentage (%) of patients experiencing a complete mystical experience, as assessed by the MEQ30on Day 0
- Description of the BPL-003 subjective experience data (from the qualitative interview)
- The effects of BPL-003 as determined by the MEQ30 and EDI
- Psychological change as measured with a questionnaire and semi-structured interview

Treatment Model:

- Treatment model, feedback from therapists on
  - Frequency and duration of psychotherapy sessions
  - Implementation of therapy manuals
  - Overall therapy model

3.3. Exploratory Endpoints

Pharmacokinetic:

- Blood samples to determine 5-MeO-DMT and its metabolites (including bufotenine) plasma concentrations will be taken after dosing on Day 0.

Drinking Craving:

- Change in alcohol craving as measured by Alcohol Craving Questionnaire (ACQ) at Days 1, 7, 28, 56, and 84 compared to Baseline (pre-dose on Day 0)
- Alcohol cravings as measured by Craving Visual Analogue Scale (VAS)
- Alcohol withdrawal symptoms as measured by Clinical Institute Withdrawal Assessment (CIWA-Ar)
- Consequences of alcohol use as measured by Short Inventory of Problems (SIP)

Alcohol Use:

Using the Timeline Follow-Back (TLFB) interview, the following parameters of alcohol use in the 90 days before dosing and endpoint will be recorded:

- Percentage of Heavy Drinking Days (PHDD) in 85d prior D-3 (or start of detox) vs PHDD post-dosing measured on d14, d28, d56, d84.
- Percentage of drinking days (PDD) in 85d prior D-3 (or start of detox) vs PDD post-dosing measured on d14, d28, d56, d84.
- Mean Units per day (UPD): In 85d prior D-3 (or start of detox) vs UPD post-dosing measured on d14, d28, d56, d84.
- Abstinence: Percentage of Abstinent days (PAD) in 85d prior D-3 (or start of detox) vs PAD on d14, d28, d56, d84 (with biomarker verification).
- Longest duration (days) of continuous abstinence
- Number of days after BPL-003 dosing to first drink
- Number of days after BPL-003 dosing to first HDD (defined by UK government as >7 units a day for a woman and >9 units per day for a man)
- Average number of standard units of alcohol consumed per week in 85d prior D-3 (or start of detox) vs post-dosing measured on d14, d28, d56, d84 (and reported referencing UK risk levels)
- Maximum number of standard units of alcohol consumed on any one day

Correlation of PD effects with alcohol use and related symptoms

The correlation of the occurrence of a “complete mystical experience” and “ego dissolution”,” measured by the MEQ30 and EDI, with improvement in alcohol use and craving (measured by AQC, TLFB, EtG, CDT)

Biomarkers

- Alcohol use as measured by EtG in urine at Days 1, 28, 56, 84 compared to Screening
- Alcohol use as measured by CDT in blood at Days 28 & 84 compared to Screening

Wellbeing

- Change in Montgomery–Asberg Depression Rating Scale (MADRS) at Days 28, 56, and 84 compared to Baseline
- Change in Clinical Global Impression Severity (CGIS) at Days 1, 28, 56, and 84 compared to Baseline

- Patient Global Impression Change (PGIC) at Days 1, 28, 56, and 84
- Change in 5-level EuroQol-5 Dimension (EQ-5D-5L) at Days 28 and 84 compared to Baseline

Expectation

- Assess positive and negative expectations as measured by Stanford Expectations of Treatment Scale (SETS)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Study BPL-003-203 is an open-label, dual-centre, Phase 2a study to evaluate the safety, tolerability, and PD effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy to assess the treatment model and explore the potential effects on alcohol use and related symptoms. This study will assess a dry powder benzoate formulation of 5-MeO-DMT (BPL-003). Enrolment of up to 12 patients with AUD is planned in up to 2 cohorts (Cohorts 1 and 2). Patients will receive a single dose of 10mg (Cohort 1) or 12mg (Cohort 2) BPL-003.

After completing the screening period, those patients who are confirmed as eligible will participate in a minimum of 3 preparatory sessions over approximately 2 weeks before the BPL-003 treatment session. These psychological support sessions will be conducted by a therapist with psychedelic knowledge and the alcohol use disorder therapist. The last of the 3 sessions will be conducted at the clinic where the dosing will occur so that patients can become familiar with the dosing room, clinic staff and a practice run with the nasal delivery system can be completed. Baseline assessments will be completed on the BPL-003 treatment day, before BPL 003 administration. BPL-003 will be administered on the treatment day in accordance with established safety practices for psychedelic research. A minimum of 3 integration sessions will occur over approximately 2 weeks after the treatment session, together with AUD relapse prevention psychotherapy (Appendix 4 for details) that will guide the patient through the 12-week, post-dose follow-up period.

4.1.1. Confirmation of AUD

Confirmation of AUD will be based on the following assessments: alcohol and drug use history and the MINI to confirm AUD according to DSM-5.

4.2. Number of Patients

Enrolment of patients with AUD is planned until up to 12 evaluable patients in up to 2 Cohorts have completed (dosed and completed Day 0) the study. Although this study is exploratory and there is no formal sample size calculation, the sample size is estimated to be able to detect common drug-induced safety events in this patient population (Shen, 2019).

4.3. Dose Selection

The doses of 10 mg and 12 mg selected for this study are based on a review of the safety, tolerability, pharmacokinetic (PK), and PD data from the dose levels tested to date in study BPL-003-103 (a single ascending-dose study in healthy volunteers).

Single escalating doses of 1 mg, 2.5 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12mg BPL-003 or placebo were dosed intranasally in a total of 44 healthy subjects (31 with active and 13 with placebo).

The overall tolerability of up to 12 mg of BPL-003 was considered good by the Safety Review Committee. 21 out of 44 subjects (48%) reported a total of 38 treatment-emergent adverse events (TEAEs). No SAEs were reported, and all TEAEs were mild or moderate in severity; 3 (11%)

moderate TEAEs. The most frequently reported TEAEs were nasal discomfort (26% of all TEAEs), nausea (18%), headache (11%) and vomiting (13%). There were no important clinical changes in vital signs, ECG, telemetry, or laboratory safety tests.

The PK parameters of BPL-003 were approximately dose linear. That is the Cmax and AUC of 5-MeO-DMT approximately increased with dose over the range 2.5 mg – 12 mg. The median Tmax ranged from 4 to 15 to min over the doses tested (average of 8.7min). The arithmetic mean $t_{1/2}$ ranged from 15 to 27 min (average of 20.9 min). No dose exceeded the maximum exposure limits defined by the preclinical safety in the dog (Cmax 421 ng/mL or AUC 220 h.ng/mL).

The MEQ30 data, which is used as a "surrogate marker" of potential future psychiatric efficacy, indicate that 60% of healthy subjects had a "peak experience" at BPL-003 doses of 10 mg or 12 mg, and that these doses have the potential to be efficacious to investigate further in patient populations.

In conclusion, based on this data analysis, that the risk / benefit profile of the 10 mg and 12 mg doses of BPL-003 are favourable: both doses of BPL-003 were generally well tolerated, had predictable PK parameters and the potential to be efficacious in patient populations.

In this study, patients will receive a single dose of 10 mg BPL-003 in Cohort 1. As this is the first study of BPL-003 in this patient population, it is unknown how the pharmacodynamic effects in patients with AUD may compare to those seen in healthy volunteers. Data from a pilot study of psilocybin for patients AUD suggested a lower level of acute subjective response (as measured by the MEQ) compared to the response seen in healthy volunteers with comparable doses (Bogenschultz, 2015). Therefore, a potential optional second cohort has been included to provide the option of studying a 12 mg dose should the SRC consider this to be appropriate.

The sponsor may trigger an SRC to evaluate continuation of the study at the 10 mg dose or dose escalation to 12 mg (Cohort 2). The SRC will comprise, as a minimum, of one Investigator [or delegate], the Sponsor's medical monitor and the Chief Medical Officer [or delegate]. The SRC will review, as a minimum, safety, tolerability, PK and PD data up to Day 1 from at least 3 patients dosed with 10 mg BPL-003 in Cohort 1. The dose will be escalated to 12 mg only if the safety, tolerability, PK and PD at 10 mg are acceptable. Dose decisions will be documented before further dosing. Additional SRC meetings may be scheduled as required.

4.4. Criteria for Study Termination

BPL reserves the right to terminate the study or a clinical study site at any time (see Section 12.11 for details). Conditions that may warrant termination of the study include, but are not limited to

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of BPL to suspend or discontinue testing or the treatment with the study drug
- Failure of the Investigator to comply with Good Clinical Practice (GCP)
- Submission of knowingly false information from the clinical study site to BPL or designee or to regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, BPL or designee and the Investigator(s) will ensure that adequate consideration is given to the protection of patients' interests.

4.5. Risk Mitigation

The design of this Phase 2a study is based on the European Medicines Agency Guideline on strategies to identify and mitigate risks for early clinical studies with IMPs (European Medicines Agency, 2017).

This study has been designed to mitigate the known risks associated with classic psychedelics and the 5-HT_{2A} receptor agonist class, and the potential risks based on nonclinical toxicity data, epidemiological studies of the use of 5-MeO-DMT for spiritual/recreational purposes, and safety data obtained from studies of 5-MeO-DMT in healthy volunteers. The key risk mitigation plans include definition of the patient population via the eligibility criteria; adherence to the guidelines for the safe use of psychedelics (Johnson, 2008), with particular attention paid to the set and setting parameters; observation of participants for 24 hours following drug administration; and provision of psychological support during and after the study.

Additional safety risk to study participants is mitigated by the following considerations:

- The available clinical and preclinical toxicity data indicate an acceptable safety profile for BPL-003. For a full list of studies, please refer to the current version of the IB.
- The doses selected for this study have been evaluated in a Phase 1 study with healthy volunteers (BPL-003-103).
- Concomitant medications with known or suspected PK or PD interactions with 5-MeO-DMT have been excluded; notably MAO-Is are prohibited.
- Patients must have a breath alcohol level of zero prior to dosing.
- The psychedelic experience may result in adverse psychological reactions, such as increased levels of anxiety, hallucinations, or flashbacks. The Investigator and therapists will provide psychological support throughout the study to manage any adverse psychological reactions. This will be done through the preparatory visits, during dosing, and the integration visits. Furthermore, only those persons with disposition judged by the Investigator to be compatible with establishment of rapport with study team and/or safe exposure to BPL-003 will be included in the study.
- Patients will be briefed on what to expect during BPL-003 dosing through preparatory meetings and familiarised with the dosing procedure and setting, as recommended by published guidelines (Johnson, 2008).
- Patients will receive the dose and spend their dosing experience in a safe, comfortable, and relaxing physical session environment.
- A physician must be present in the room for the 90 minutes immediately after drug administration in order to closely observe each patient.
- Vital signs including temperature will be measured after dosing.
- The clinic is experienced with trials of psychedelic compounds similar to BPL-003 and will follow its standard operating procedures (SOPs).

- The study site will be suitably prepared to deal with any medical emergencies. A medical emergency is an acute, unplanned event that has the potential for serious harm or death, including anaphylaxis and cardiorespiratory arrest. Resuscitation trolleys are to be located in nearby areas. Trolleys are to be checked on a regular basis to ensure that all drugs and equipment are in-date and functional. Study site staff will be suitably trained and an appropriate number of trained staff will be with the patients during and after dosing to ensure any emergencies can be dealt with safely.
- For safeguarding purposes, the dosing session will be video recorded, and all preparation sessions and integration sessions will be audio only recorded. These recordings will only be reviewed on an ad-hoc basis for safety and adherence purposes. In addition, subject to specific consent by participants, the audio and video recording of the sessions may be used for other purposes. These are for therapy optimisation, with the purpose of improving further training manuals and procedures, or for Sponsor (or delegate) training purposes. Additional consent will be sought for these activities. Participants who do not consent to the use of recordings for therapy optimisation or training purposes will not be excluded from the study. The audio and video recordings will be stored securely with restricted access, in compliance with UK data protection law (including General Data Protection Regulation or GDPR). Benzodiazepines, including oromucosal midazolam, and other suitable tranquilising treatment will be available as a rescue medication, if needed.

4.5.1. COVID-19

The Investigator and BPL have reviewed the risks of conducting the study in light of the current COVID-19 pandemic. The first priority is the safety of study patients and staff; however, the Investigator and BPL also have an ethical duty to preserve the scientific integrity of the study as far as possible.

Exposure to BPL-003 is unlikely to increase the risk of contracting COVID-19 infection or to worsen the severity of an infection.

There is no interaction with BPL-003 that might affect any aspect of vaccination, such as timing or efficacy. However, to enable a clearer determination of relationship between BPL-003 and any adverse events, it would be advisable, where possible, for the vaccination to be given 7 days before or 7 days after the single dose of BPL-003.

The study will be run at two sites, Clerkenwell Health and the NIHR Wellcome King's Clinical Research Facility which fall under the King's College Hospital NHS Trust and the Lorraine Hewitt House which falls under the South London and Maudsley NHS Trust, in collaboration with King's Health Partners. To keep patients and site staff safe, the study will be run in line with the Trust's policies for managing studies during the pandemic. This includes strict infection prevention control measures, such as reducing site traffic, maintaining social distancing, facility decontamination, and screening.

The Investigator is responsible for ensuring patient and staff safety, and that study procedures are conducted in accordance with the protocol and Good Clinical Practice (GCP). Any deviations from the protocol that result from the COVID-19 pandemic, and COVID-19–related AEs or SAEs will be documented.

The study team will follow the guidance outlined in their site SOP for managing studies during COVID-19. The risk to patients will be re-evaluated by BPL throughout the COVID-19 pandemic, if deemed necessary by emerging events. BPL's own Risk Management Plan will also provide oversight of the potential impact of COVID-19 on the study.

4.6. Definition of the End of the Study

The end of the study is defined as the final follow-up visit by the last patient. If the sponsor does not choose to trigger an SRC, the study may complete after cohort 1. If the study is terminated prematurely, the study ends when the Sponsor notifies the Investigator in writing that the study has finished, or when the last patient attends the final follow-up visit, whichever is later.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Number of Patients

Up to twelve evaluable patients with AUD (see Section 4.2) in up to 2 cohorts (Cohorts 1 and 2)
.

5.2. Patient Inclusion and Exclusion Criteria

5.2.1. Diagnosis and Main Criteria for Inclusion

To be eligible to participate in this study, patients must meet the following criteria:

1. Willing and able to give informed consent
2. Age 18 to 64 years at Screening
3. Diagnosed with moderate to severe AUD (based on DSM-5)
4. Minimum of 4 HDD in the 28 days before Screening
5. No more than 14 days after the last HDD or completion of detoxification (at point of screening), with no HDD in the 72 hours prior to dosing, and no alcohol at all in the 24 hours prior to dosing
6. Willing to abstain from using recreational drugs from Screening until end of the study
7. Willing to abstain from smoking during their time in the clinic on the day of drug administration as instructed by clinical staff
8. Willing to refrain from psychedelic drug use (excluding the study drug) from Screening until the end of the study
9. Able (in the Investigator's opinion) and willing to undertake and comply with all study requirement, with the ability to complete all protocol-required assessment tools and to comply with all study visits
10. Willing to allow their own general practitioner, and consultant if appropriate, to be informed of study participation
11. Living in stable/secure accommodation in the community
12. In possession of a personal mobile phone and able to nominate at least one locator individual (e.g., a family member, friend, or recovery mentor) with a verifiable address and a telephone number to assist with the arrangement of follow-up appointments

5.2.2. Exclusion Criteria:

5.2.2.1. General Medical Exclusion Criteria

1. History of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure (BP) and heart rate (HR). This includes, but is not limited to, severe coronary artery disease, history of myocardial infarction, unstable angina, cerebrovascular accident, aneurysm or revascularization procedure

within 12 months before Screening, significant valvular heart disease, heart failure of any etiology, history of a stroke or transient ischemic attack.

2. History of uncontrolled hypertension despite adequate therapy or any history of a hypertensive crisis or ongoing evidence of uncontrolled hypertension (defined as repeated supine systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg). Patients with well-controlled hypertension that has been successfully treated with anti-hypertensive medicines may
3. Uncontrolled or insulin-dependent diabetes
4. History of seizures (including febrile and withdrawal seizures)
5. Any other clinically significant neurological, cardiovascular, pulmonary, gastrointestinal, hepatic, renal, or any other major concurrent illness that, in the opinion of the Investigator, may interfere with the interpretation of the study results or constitute a health risk for a patient if they take part in the study
6. Abnormal and, in the opinion of the Investigator, clinically significant results on the physical examination, vital signs, electrocardiogram (ECG), or laboratory tests at Screening (Visit 1)
7. Patients who are exhibiting any signs of alcohol withdrawal at Day 0 as assessed by Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA Ar)
8. Positive for alcohol at Day 0
9. Positive urine drug screen for illicit drugs or drugs of abuse
10. Currently receiving monoamime oxidase inhibitors (MAO-I), tramadol, opioids, antiviral medication, cytochrome P4502D6 inhibitors, antidepressant medication, including selective serotonin reuptake inhibitors be enrolled if they pass additional screening to rule out underlying cardiovascular disease.
11. (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, lithium, antipsychotic medications, triptans, tramadol, 5 hydroxytryptophan (5-HTP), herbal preparations containing 5-HTP, St John's Wort, or any other medications or supplements that may affect serotonergic function or may interfere with the study drug (see Section 6.2.1)
12. History of intolerance to 5-MeO-DMT, dimethyltryptamine (DMT), or related compounds
13. Any nasal obstruction, blockage, or symptoms of congestion
14. Any personal or family history of malignant hyperthermia
15. Disposition judged by the Investigator (or delegate) to be incompatible with establishment of rapport with study team and/or safe exposure to BPL-003
16. Presence of acute or chronic illness or infection or history of chronic illness or infection sufficient to invalidate the patient's participation in the study or make it unnecessarily hazardous
17. Presence or history of severe adverse reaction to any drug or drug excipient
18. Female patients who are pregnant or lactating or of childbearing potential and not willing to use adequate forms of contraception during the study and for 1 month after completion of the study, as described in Section 6.2.4
19. Male patients who are sexually active and not willing to use adequate forms of contraception during the study and for 1 month after completion of the study, as described in Section 6.2.4

20. Patients who have taken part in a clinical research study in the last 4 weeks, whether or not they received an investigational medicinal product as part of that research study
21. Current criminal justice involvement with legal proceedings, which in the opinion of the Investigator means the participant may fail to complete the study protocol due to re-incarceration or relocation from the clinic's catchment area
22. Unable to communicate in English to a level required to accept standard care and psychosocial intervention
23. Patients who, in the opinion of the Investigator, are not suitable to participate in the study for any other reason not mentioned in the entry criteria

5.2.2.2. Psychiatric Exclusion Criteria:

1. Personal or first-degree family history of schizophrenia, bipolar disorder, psychotic disorder (unless substance induced or due to a medical condition), delusional disorder, paranoid disorder, or schizoaffective disorder, as defined by DSM-5. Personal history determined by medical records and positive diagnoses on the Mini-International Neuropsychiatric Interview (MINI version 7.02) to be confirmed by the Investigator
2. Any major psychiatric disorders, with the exception of mild or moderate anxiety and/or depression, as determined by a MINI and confirmed by the Investigator
3. A clinical diagnosis of post-traumatic stress disorder (as determined by MINI)
4. Psychological therapies other than those planned per protocol that are initiated or terminated within 21 days of baseline and for the duration of the study
5. Has suicidal ideation with some intent to act within the 12 months before Screening, per the Investigator's clinical judgment or based on the Columbia-Suicide Rating Scale (C-SSRS), corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behaviour within the 12 months before Screening. Suicidal ideation with intent to act or suicidal behaviour as assessed on Day –3 should also be excluded
6. Suicide attempts and/or self-injurious behavior within 12 months before Screening.
7. Regular use of or dependence on other drugs other than caffeine or nicotine. Presence or history of SUD (not including AUD) as defined by the DSM-5. The Investigator will evaluate the patient's ability to abstain from using this substance during the study. The patient must have a negative recreational drug test on Day 0, before dosing
8. Any self-reported use of psychedelic compounds (phenethylamines, tryptamines, or dissociatives) in the past 6 months

5.3. Patient Withdrawal Criteria

Patients are free to withdraw from the study at any time without giving reasons. Furthermore, the Investigator may withdraw a patient for reasons such as intolerance to study drug, intercurrent illness, need for medication which is contraindicated, significant noncompliance with the

requirements of the study, or withdrawal of consent. The Investigator will assess the reasons for withdrawal as far as possible and will fully record the circumstances and medical details.

Patients will be informed before they agree to take part in the study that if they withdraw or are withdrawn:

- The Investigator will stop collecting information about them; and
- They can ask the Investigator to destroy any identifiable samples taken from them.

The Investigator will ask withdrawn patients to have a follow-up examination, to check that they have come to no harm as a result of taking part in the study. Provided that the patient agrees, they will undergo, at withdrawal from the study (or as soon as possible afterwards), all assessments scheduled for the final Follow-up Visit. If patients withdraw after dosing but before completing the scheduled assessments, they will also be required to complete a psychological assessment before discharge from the clinic. The Investigator will record in the case report form (CRF) the results of the follow-up examination of withdrawn patients.

Withdrawn patients will be replaced at the discretion of the Sponsor and Investigator.

6. TREATMENT OF PATIENTS

6.1. Description of Study Drug

Patients will receive a single intranasal dose of BPL-003. The dose selected will be based on the PK, PD, safety, and tolerability data from the completed study BPL-003-103.

Doses will be delivered using the Aptar Unidose (UDS) intranasal dry powder delivery system. Each dose is preloaded into the delivery device. Further details may be found in Section 7.1.

All doses will be administered by a trained member of the study team, in the presence of a psychiatrist and therapist.

6.2. Concomitant Medications

6.2.1. Prohibited Medications

A list of medications prohibited during the study is provided in Appendix 1.

6.2.2. Previous and Concomitant Treatment

Previous and current treatment restrictions are described in Section 5.2.2.

During the study, concomitant medication may be given if the patient's personal physician believes it to be necessary. In addition, paracetamol (acetaminophen) will be allowed each day for mild analgesia. It should be given in line with package label/instructions. Administration of COVID-19 vaccination will also be allowed (see Section 4.5.1). Any other concomitant treatment will be given only if deemed strictly necessary by the Investigator. In any case, all concomitant treatments will be reported in the eCRF along with their daily dosage, duration, and reasons for administration. Patients who have received any concomitant treatment may be withdrawn from the study at the discretion of an Investigator.

6.2.3. Rescue Medication

Benzodiazepines, including oromucosal midazolam, and other suitable tranquilising treatment will be available as rescue medication, if needed. Oromucosal midazolam 2.5 to 5 mg by mouth (PO) or lorazepam injection 0.5 to 2 mg intramuscular (IM) will be offered as a first-line treatment. Risperidone 2 to 4 mg PO or aripiprazole 9.75 mg IM will be offered as a second-line treatment. These treatments will be given under the supervision of a psychiatrist.

6.2.4. Contraception and Pregnancy

At screening, the Investigator (or designee) will confirm that the patient has selected/is using an appropriate method of contraception. The Investigator will also confirm that the patient has been instructed in the consistent and correct use of that contraception, and will document the conversation and the patient's affirmation in the patient's records. In addition, the Investigator or designee will instruct the patient to call the clinic immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient (pregnancy reporting is described in Section 10.2.6).

Patients must use a reliable method of contraception during the study, as follows.

Men

During the study and for 1 month after the final follow-up visit, male patients must not have sex without using a condom if their partner is a woman of childbearing potential. They do not need to use any contraception if their partner is not of childbearing potential. Partners who are not of childbearing potential are defined as men; postmenopausal women (no menstrual periods for at least 12 months); or women who have no uterus, ovaries, or fallopian tubes.

Patients must not plan to father a child or donate sperm during the study and for 1 month after their final follow-up visit.

Women

All female patients who are of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 30 days after their follow-up visit. They must have been using that method for at least 28 days before the start of the study.

Highly effective methods of contraception are those that result in a failure rate of less than 1% per year when used consistently and correctly and include the following:

1. Combined or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal, injections or implants)
2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. Bilateral tubal occlusion
5. Vasectomised partner (with surgical success)

A woman is considered to be of non-child-bearing potential if she meets one of the following criteria:

- Is postmenopausal (no menses for least 12 months without alternative medical cause; FSH at screening confirms postmenopausal status)
- Has no uterus, ovaries, or fallopian tubes

Women who are taking hormone replacement therapy can continue to do so during the study, but they must use contraception (as described above).

Patients who practice true abstinence or who only have same-sex relationships need not use contraception, provided it is in line with their preferred and usual lifestyle. Note: periodic abstinence [e.g., calendar, ovulation, symptothermal, and post-ovulation methods] and withdrawal are not acceptable methods of contraception). Should any such patient stop practising true abstinence, they must use contraception as described above.

6.3. Treatment Compliance

Patients will be dosed at the research site under the supervision of at least 1 physician, in the presence of a psychiatrist and therapist.

6.4. Patient Numbers

Patients will be assigned a patient number at screening, after they have signed the informed consent form (ICF). This patient number will be the primary patient identifier throughout the duration of the study. Each patient will be assigned a unique number in the order in which they are entered into the study. Once a patient number has been allocated, it must not be reassigned to another patient. If a patient does not meet the entry criteria (screen failure), they may be rescreened at the discretion of the Investigator and medical monitor. Rescreened patients will be assigned a new patient number.

6.5. Randomization and Blinding

This in an open-label study; all patients will receive BPL-003.

6.6. Study Visits

The study visits are outlined below. Study visits and procedures are also detailed in the Schedule of Events in Table 1.

- **Screening:** Patients will be screened up to 14 days before their psychedelic preparation session to confirm their eligibility for the study.
- **Abstinence:** Patients will be expected to have no HDD at least 72 hours prior to dosing and no alcohol at all in the 24 hours prior to dosing. If breath alcohol is not zero on dosing day, patients may reschedule once if they are deemed not to have completely relapsed; however, if they fail the second time, they will be excluded from the study.
- **Psychedelic Preparation Sessions:** Following the initial Screening Visit, all patients will participate in 3 preparatory sessions over approximately 2 weeks before being dosed (patients should not undertake preparation sessions if intoxicated, as recommended by published guidance on the conduct of studies of psychedelic compounds) (Johnson, 2008). Investigator discretion to be applied where patient has some alcohol in their system, but is still able to absorb the information and build a therapeutic alliance. The aim will be to establish a therapeutic alliance during the preparatory sessions so that patients will be well prepared for the BPL-003 treatment session and receive ongoing AUD relapse prevention psychotherapy. The psychedelic preparation session will be audio recorded for safety and quality assurance purposes.
- **Dosing Visit:** After completion of the 3 preparatory sessions, patients will attend the clinical study facility for their dosing visit. Patients will be resident at the clinic from the morning of Day 0 (dosing day) until approximately 4 hours postdose.

- BPL-003 will be administered to patients in the designated setting, in accordance with published guidelines for clinical trials of psychedelic compounds (Johnson, Richards and Griffiths, 2008), with particular emphasis on 'set' (the subject's mental state prior to dosing) and 'setting' (the dosing environment). The psychedelic therapist will remain with patients while patients are in an altered state of consciousness.
- During the dosing session, the therapist will be supportive and non-directive, and not attempt to influence the patient's psychedelic experience. Site staff will be trained to maximise patients' psychological welfare during dosing and the subsequent psychedelic experience (e.g., assessments will be performed with as minimal interruption as possible;

patients will be encouraged to lie down during dosing). All psychological support providers will be trained in accordance with the therapy manual.
- All dosing sessions will be audio/video recorded for safety and quality assurance purposes
- After return to a usual state of consciousness after dosing, patients will be asked to have a one-to-one guided qualitative interview with independent researchers trained in microphenomenology methods to discuss their psychedelic experience (as detailed in the Qualitative Interview Study Manual). This will be done either face to face at the clinic or via video call. Clinical research measures will then be administered to provide quantitative measures of the patient's psychedelic experience.
- After dosing, the patients will have to remain at site for at least 4 h. Patients may be discharged 4 h after dosing, provided the Investigator or psychiatrist determines that it is safe for the patient to leave, having assessed their individual psychological wellbeing. All patients will have their "readiness for discharge" (see Appendix) assessed every 30 min starting 90 min after dosing. If the patient is not ready for discharge at 4 h post dose, then the questionnaire will be repeated when the Investigator believes the patient may be ready for discharge.
- If the study team considers that a patient may pose a risk to themselves or others, they may be prevented from leaving the site. Patients will be informed of that possibility, and consent to it, at Screening. Any actions taken to minimise a participant's risk to themselves or others and/or prevent them from leaving the site will be undertaken in accordance with appropriate legislation.
- In the event of extreme distress unresponsive to any intervention, or in the event of threatened or actual violence, rescue medication will be given in liaison with medical staff at the site. The medication of choice is a short acting benzodiazepine given orally and therefore follows established National Institute for Health and Care Excellence (NICE) guidelines for rapid tranquilisation. Oromucosal midazolam or lorazepam injection will be given as a first line treatment. Any further treatment will follow NICE guidelines. Rescue medication will be given under the supervision of a psychiatrist. . If rescue medication is given, patients may need to stay at the site for longer than scheduled, for additional observation. The necessity of continued observation will be constantly reviewed by the Investigator, and the event will be reported to the Sponsor's pharmacovigilance group, or delegate.

- **Follow-up Visits (for 12 weeks postdose):**

- **Psychedelic Integration Sessions:** Patients will have at least 3 integration sessions over the 2 weeks following their dose to discuss their experience with the therapists. The psychedelic integration sessions will be audio recorded for safety and quality assurance purposes.

- **Relapse Prevention Psychotherapy:** Patients will have weekly sessions following the dose of BPL-003 as defined in the AUD Therapy manual (can be either face to face or remote) with an AUD therapist (see Appendix 4 for details).

The following timing deviations will **not** be regarded as protocol deviations.

TABLE 4: ACCEPTABLE DEVIATION TIMES

Procedure	Timepoint	Acceptable deviation
Preparation Visit	Days -12 & -7	+/- 5 days
Preparation visit	Day -3	+ 2 days
PK blood sampling	Day 0 – Postdose	+5 min of the scheduled time
Vital signs	Day 0 – Predose	before dosing
	Day 0 – Postdose	±5 min of the scheduled time
Readiness for Discharge questionnaire	Day 0 – Postdose	±5 min of the scheduled time
Integration visit	Follow up days 1, 7, 14	+/- 2 days
Follow up visit	Follow up days 21 - 84	+/- 4 days

6.7. Patient Lifestyle Restrictions

Patients will fast (no food or drink, except water) for at least 8 hours before laboratory blood safety at Screening. On Day 0, patients should be given a light, low-fat breakfast (such as water and fruit) at least 2 hours before dosing.

No food or drink containing poppy seeds will be allowed from 2 weeks before dosing until the Follow-up Visit.

No HDD will be allowed from 72 hours before dosing, and no alcohol at all in the 24 hours prior to dosing.

No recreational drugs will be allowed from Screening until the final Follow-up Visit.

Patient contraceptive requirements are described in Section 6.2.4.

Patients must abstain from smoking, if applicable, while resident on the ward on the day of drug administration as instructed by clinical staff. When permitted, a patient wishing to smoke will be accompanied by clinic staff.

Patients should be accompanied by a responsible adult when released from the clinical study site.

Patients must not drive a car or work with machines for 24 h after dosing.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

BPL-003 will be administered intranasally using the Aptar Unidose (UDS) dry powder delivery system.

Full details of BPL-003 are included in the BPL-003 IB and investigational medicinal product dossier (IMPD).

7.2. Study Drug Packaging and Labeling

BPL-003 has been synthesised by Sterling Pharma Solutions (Dudley, UK) to Good Manufacturing Practice (GMP) standards and prefilled into the Aptar Unidose (UDS) intranasal dry powder delivery device. The device allows a single fixed dose of BPL-003 to be administered intranasally. The dry powder is prefilled into and administered using a standard single unit dose nasal pump device.

Upperton Pharma Solutions (Nottingham, UK) will load the study drug into the Aptar Unidose (UDS) device. Eramol (UK) Ltd (Horley, UK) will label and Qualified Person certify the final patient specific doses, in accordance with GMP and with Eramol (UK) Ltd Manufacturing Authorisation for IMPs (MIA[IMP]).

The fully packaged and labelled BPL-003 will be provided to the study site pharmacy.

7.3. Study Drug Storage

BPL-003 will be stored according to GMP, site SOPs, and a Home Office UK controlled drug licence which is required to possess and supply Schedule 1 drugs.

Details on storage conditions and temperature will be included in the pharmacy manual.

7.4. Administration

BPL-003 will be administered to patients by a trained member of the study team using a single unit dose pump spray. The unit contains only 1 spray, so it should not be tested before use. While the patient is sitting down, he/she should be asked to blow his/her nose to clear the nasal passages. Once the tip of the device is placed into the nostril, the clinic staff will press the plunger to release the dose. Details for administering the dose will be described in a separate study procedures manual.

Dummy UDS devices will be available for demonstration of dosing.

7.5. Study Drug Accountability

It is the responsibility of the Investigator to ensure that a current record of study drug inventory and disposition is maintained at the study site throughout the study. The Investigator, pharmacist, or designee, must keep an accurate record of the quantities of the study drug received, which should match the total quantities of used and unused study drug.

Pursuant to requirements under the Home Office UK Schedule 1 controlled drug licence, a strict audit trail of drug dispensing and usage will be kept. If a patient elects not to take the treatment

on the Dosing Visit, then the study team will return the dose to the site pharmacy, who will arrange quarantine and/or secure destruction in accordance with regulations.

7.6. Study Drug Handling and Disposal

Unused study drug will be destroyed locally per site SOPs or returned to a location designated by BPL or designee. Destruction of study drug should not occur until the end of the study, unless otherwise authorised by BPL or designee. If the study drug is to be destroyed locally, it is the Investigator's responsibility to ensure that arrangements have been made for disposal; that destruction certificates are filed; and that the applicable local regulations, guidelines, and institutional procedures are followed.

At the end of the study, all unused BPL-003 supplies will be returned to the Sponsor or destroyed in accordance with the Sponsor's instructions.

8. PHARMACOKINETIC ASSESSMENTS

There will be three blood draws after dosing on Day 0 to determine the plasma concentration of 5MeO-DMT and its metabolites. The blood draw will be done at 5, 15 and 60 minutes post dose (+5 minutes at each timepoint). The blood will be drawn from the venous catheter previously inserted for the predosing draws for the other laboratory assessments.

Plasma samples will be separated into a primary and backup aliquot and frozen at about –70°C (or below) within 2 hours after collection, and stored until dispatched to Analytical Services International (ASI), St George's Hospital Medical School, University of London, London.

All samples will be analysed at the end of the study as a single batch.

Sample collection, processing and shipping instructions will be included in a separate Study Manual.

9. PHARMACODYNAMIC ASSESSMENTS

PD assessment time points are given in the Schedule of Events (Table 1).

Patients will also be asked to take part in an optional one-to-one guided interview after their dose to discuss their dosing experience in their own words to gather qualitative information.

Patients will self-complete the PD assessments using the Electronic Patient Reported Outcome system (ePRO) system, unless otherwise indicated.

9.1. Stanford Expectation of Treatment Scale

As a patient's response to treatment may be influenced by the expectations that the patient has before initiating treatment, the influence of participant expectancy may reduce statistical power in a clinical study. The Stanford Expectations of Treatment Scale (SETS) (Younger, 2012) is a 6-item scale for measuring positive and negative treatment expectancies. SETS is used to improve statistical sensitivity for detecting treatment differences in clinical studies. The SETS will be administered prior to the first psychedelic preparation session on Day –7.

9.2. Mystical Experience Questionnaire

The extent of a patient's mystical experience after receiving BPL-003 will be assessed using the Mystical Experience Questionnaire (MEQ30) that was developed and validated through factor analysis of retrospective accounts of experiences with psilocybin-containing mushrooms (Maclean, 2012). That analysis provided a 4-factor structure of the MEQ30: mystical, positive mood, transcendence of time and space, and ineffability. The questionnaire comprises a list of 30 phenomena. Patients will rate the degree to which they experienced each phenomenon using the following scale:

- 0 = none; not at all
- 1 = so slight cannot decide
- 2 = slight
- 3 = moderate
- 4 = strong (equivalent in degree to any other strong experience)
- 5 = extreme (more than any other time in my life and stronger than 4)

9.3. Ego Dissolution Inventory

The extent of a patient's dissolution of ego after receiving BPL-003 will be assessed using the EDI (Nour, 2016).

The inventory comprises 8 statements. Patients will rate their agreement with each statement by marking on a visual analogue scale (VAS) from 0 ("No, not more than usually") to 100 ("Yes, entirely or completely").

9.4. 5-Level EuroQol 5-Dimension

The 5-level EQ-5D version (EQ-5D-5L) consists of 2 parts: the EQ-5D descriptive system and the EQ-VAS.

The EQ-5D-5L is a self-assessed, health-related quality of life questionnaire. The scale measures quality of life on a 5-component scale, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a scale that describes the degree of problems in that area (eg, I have no problems walking about, slight problems, moderate problems, severe problems, or unable to walk). This tool also has an overall health scale (EQ-VAS), where the rater selects a number between 1 and 100 to describe the condition of their health, 100 being the best imaginable. Convergent validity was demonstrated by a correlation between EQ-5D-5L and the dimensions of WHO-5 ($r=0.43$, $p<0.001$) (Janssen, 2013). The EuroQol approach is reliable, with average test-retest reliability using interclass coefficients with mean of 0.78 and 0.73 (Brooks, 1996).

9.5. Timeline Follow-Back

The alcohol Timeline Follow-Back (TLFB; calendar prompt interview) originally developed by Sobell and Sobell (Sobell, 1992) was adapted from the Form 90 structured interview (Miller, 1996) to indicate "active" recording of each day in the recall period (i.e., "abstinent" or "alcohol consumed") with standard and high-strength beverage types typically consumed by the study clinical population before treatment to assist the interviewer record units consumed on a drinking day from the participant's verbatim report.

The TLFB has been shown to have good psychometric characteristics with a variety of drinker groups, and it can generate variables that provide a wide range of information about an individual's drinking (e.g., pattern, variability, and magnitude of drinking). The method is recommended for use when relatively precise estimates of drinking are necessary, especially when a complete picture of drinking days (i.e., high- and low-risk days) is needed. Although TLFB summary data have been found to be generally reliable, as with all drinking assessment methods, exact day-by-day precision cannot be assumed or necessarily expected. Overall, the TLFB method provides a relatively accurate portrayal of drinking and has both clinical and research utility.

9.6. Qualitative Interview

After dosing, patients will be asked to take part in an optional qualitative interview. If they agree, they will have a one-to-one guided interview with independent researchers trained in microphenomenology methods to discuss their psychedelic experience. This will be done either face to face at the clinic or via video call. The qualitative interview will provide a more nuanced understanding of the phenomenology of BPL-003 effects compared with the questionnaires used in this study. Data from this interview will help inform future clinical studies of this compound.

The interview will

- Provide a holistic phenomenological description of the experience during the entire drug session
- Identify, within the holistic description, one or more phases or moments of interest, e.g., peak or mystical experience (if present), experience of ego dissolution, or otherwise salient aspects of the experience
- Outline the general structure of BPL-003 experience and identify unique and common features between individual experiences

- Characterise, describe, or determine potential therapeutic mechanisms, effects, and processes resulting from the BPL-003 experience
- Identify possible risks and their mitigation

Details of the methodology and interview structure to be used can be found in the Qualitative Interview Study Manual.

9.7. Optional Semi-Structured Interview & Psychological Change Measures

The optional semi-structured interviews will take place on Days 1 and 84. These interviews will be topic-guided, audio-recorded, qualitative interviews to understand a patient's psychological changes from shortly after dosing (Day 1) until Day 84.

Patients will be invited to complete an optional online psychological change questionnaire on Days -3, 1, 28, and 84. The questionnaire will consist of validated scales measuring psychological changes such as personality traits, anxiety traits and avoidance, beliefs about self, others and environment, suggestibility, absorption, expectations about the treatment, and wellbeing and resilience pre- and postdosing, to understand the potential effect of BPL-003 dosing combined with relapse prevention psychotherapy.

Details of the methodology, interview structure and psychological changes measures can be found in the Psychological Change Study Manual.

9.8. Montgomery–Asberg Depression Rating Scale

The Montgomery–Åsberg Depression Rating Scale (MADRS) will be completed at the visits outlined in Table 1.

Via the electronic Clinical Outcome Assessment (eCOA), an appropriately trained member of the study team will use the Structured Interview Guide for the MADRS (SIGMA) to interview the subject moving from broad questions about symptoms to more detailed ones which allow the precise rating of symptom severity. The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders (Williams, 2008). A higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60. The questionnaire includes questions on the following symptoms: (1) apparent sadness, (2) reported sadness, (3) inner tension, (4) reduced sleep, (5) reduced appetite, (6) concentration difficulties, (7) lassitude, (8) inability to feel, (9) pessimistic thoughts, and (10) suicidal thoughts. The usual cutoff points are:

- 0 to 6 = normal/symptom absent
- 7 to 19 = mild depression
- 20 to 34 = moderate depression
- >34 = severe depression.

9.9. Alcohol Craving Questionnaire

The Alcohol Craving Questionnaire Short Form Revised (ACQ-SF-R) (Singleton, 1997) will be completed at Baseline (pre-dose on Day 0) and at the visits on Days 1, 7, 28, 56, and 84.

9.10. Craving Visual Analogue Scale

A Craving VAS will be used on dosing day to assess the relative craving status of the patient before discharge on Day 0 dosing compared to prior to dosing. The scale will be completed on admission (A) and again at the point of discharge (B). If the rating at B is greater than at A, then an additional craving talk down procedure will be implemented and VAS B repeated. Patients will be discharged only when their VAS rating at B is the same or lower than at A.

9.11. Clinical Global Impression of Severity

A brief Clinical Global Impression of Severity (CGIS) (Busner, 2007) questionnaire of the patient's condition will be completed at the visits outlined in Table 1. The CGIS uses a 7-item scale to rate total severity whether or not, in the Investigator's judgment, it is due entirely to drug treatment. This rating is based upon observed and reported symptoms, behaviour, and function. The Investigator will compare the patient's current condition to that at Screening and determine how much the patient has changed on the following scale:

- 0 = not assessed
- 1 = normal, not at all ill
- 2 = borderline ill
- 3 = mildly ill
- 4 = moderately ill
- 5 = markedly ill
- 6 = severely ill
- 7 = among the most extremely ill patients

9.12. Patient Global Impression of Change

A brief PGIC will be completed at the visits outlined in Table 1. The PGIC uses a 7-item scale to rate total improvement reported by patient whether or not it is due to drug treatment. The patient will report their own current condition compared to that at Screening on the following scale:

- 0 = Not assessed
- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

9.13. Clinical Institute Withdrawal Assessment for Alcohol-Revised

The Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) (Saitz, 1994; Sullivan, 1989) is a 10-item scale used in the assessment and management of alcohol withdrawal. Each item on the scale is scored independently, and the summation of the scores yields an aggregate value that correlates to the severity of alcohol withdrawal. The ranges of scores are designed to prompt specific management decisions such as the administration of benzodiazepines. The maximum score is 67; mild alcohol withdrawal is defined by a score ≤10, moderate by scores 11 to 15, and severe by any score ≥16.

9.14. Short Inventory of Problems

The Drinker Inventory of Consequences (DrInC) was developed to assess consequences of alcohol use; it contains 50 items, 45 of which measure consequences in 5 domains: interpersonal, intrapersonal, physical, impulse control, and social. In the briefer 15-item version of this measure, the Short Inventory of Problems (SIP), 3 items from each of the 5 domains based on the strongest item–subscale correlations were selected. Revised versions use the 15 items with the strongest item–total correlations (Blanchard, 2003). The version used in this study is the SIP-2R developed by the Center on Alcohol, Substance use, And Addictions (CASAA) at the University of New Mexico. A sample of the SIP-2R questionnaire is provided in Appendix 2.

9.15. Readiness for discharge questionnaire

An appropriately trained member of the site team will complete the readiness to discharge questionnaire to determine the earliest timepoint the patient is able to leave the clinical study site safely. The postdose vital signs (HR, BP and temperature), done every 30 min, are included as part of this questionnaire. Patients will have their readiness for discharge assessed every 30 min starting 90 min after dosing, up to the point the patient has been deemed safe to leave the clinical study site. The final readiness to discharge questionnaire will be verified by a suitable physician. If the final readiness to discharge is before the 4 h postdose timepoint the patient will remain until 4 h postdose as per this protocol. Completion of the readiness to discharge questionnaire can stop once the patient has been deemed safe to leave the clinical study site as per the questionnaire. If the patient is not ready for discharge at 4 hours postdose then the questionnaire will be repeated again at the point Investigator believes patient may be ready for discharge.

9.16. Treatment model Feedback

Feedback on the treatment model will be sought from therapists on the frequency and duration of psychotherapy sessions, implementation of therapy manual and overall therapy model. Feedback will be obtained in a qualitative interview to be conducted by the Beckley Medical Monitor or delegate individually with each therapist following completion of each patient's integration sessions. It will be completed once per patient, and occur between Day 15 to Day 42.

9.17. Biomarkers

9.17.1. Ethyl Glucuronide

Ethanol is excreted from the body in a variety of ways, including

- Direct excretion of ethanol (5%-10%) in urine, sweat, and breath
- Metabolic excretion by conversion to acetaldehyde or acetic acid (>90%)
- Metabolic excretion by conversion to ethyl glucuronide (EtG) and ethyl sulfate (<0.1%), both of which are readily eliminated through urination

While most of these excretory products are detectable in urine for very short periods of time (<24 hours), EtG has a longer half-life and may be detectable in urine for up to 72 hours after consumption, depending on the dose taken prior to specimen collection. Although higher amounts of EtG might indicate greater alcohol consumption, the exact EtG number is influenced by several factors, including how recently alcohol was consumed. The presence of EtG in urine indicates only that the individual was exposed to ethanol at some point in the recent past before testing, typically within the preceding 72 hours.

There are some limitations to this test. It can produce a positive test from the mere exposure to alcohol that is present in many daily-use products, e.g., mouthwashes, breath sprays, foods prepared with or flavored with alcohol, and hand sanitizers. Therefore, a positive test should be confirmed either with another test or with verification from the patient that he or she did indeed drink alcohol. However, the EtG test accurately detects a person who recently consumed alcohol 70% or more of the time. One study showed that for moderate to heavy drinking, this value increases to 85% (Shukla, 2017).

9.17.2. Carbohydrate Deficient Transferrin

Chronic alcohol use causes a transient change in the glycosylation pattern of transferrin, where the relative amounts of disialo- and asialotransferrin (carbohydrate deficient transferrin [CDT]) are increased over the amount of normally glycosylated tetrasialotransferrin. CDT can be used to detect whether someone is a binge drinker or a daily heavy drinker (4 or more drinks a day) (Fleming, 2004). It can even be used to determine AUD relapse (Mitchell, 1997). Generally, CDT levels will return to normal within several weeks of abstinence of alcohol use. CDT testing alone is not recommended for general screening for AUD; however, when combined with other assessments (e.g.: gamma-glutamyl transpeptidase [GGT], alanine aminotransferase [ALT], aspartate aminotransferase [AST], mean corpuscular volume [MCV], EtG, and patient self-reporting), clinicians can expect to identify the majority of patients with AUD (Gough, 2015).

9.17.3. Haematology and Clinical Chemistry

Changes in the reported values of MCV, ALT, AST, and GGT will also be used to monitor for signs of relapse.

10. ASSESSMENT OF SAFETY

Patient safety will be assessed by laboratory assessments (routine haematology, clinical biochemistry, and coagulation), physical examinations, 12-lead ECGs and cardiac telemetry, vital signs (BP, HR, and temperature), and the C-SSRS. AEs and concomitant medications will be recorded from Screening until the patient's last visit. Nasal site reaction will be assessed after dosing.

10.1. Safety Parameters

10.1.1. Demographic/Medical History

A detailed medical history, including concomitant medication, will be obtained at the Screening Visit.

10.1.2. Vital Signs

Vital sign measurements (HR, systolic and diastolic BP) and temperature must be collected at each visit outlined in the Schedule of Events (Table 1). The baseline will be measured in triplicate within 30 min (+/- 5mins) before dosing, (Triplicate measurements should be obtained as closely as possible in succession, and no more than 2 min apart; temperature does not need to be repeated in triplicate). Predose BP must be within normal range pre dose on dosing day and if not then repeated ~ 1 h later .

Vital signs then taken as single measurements at 10, 20, 30, 40 mins, and then every 30 min (+/- 5mins) from 1 hour post-dose until 4 hours post dose: and when the patient is assessed as ready to be discharged on Day 0, if later than 4 h post dose. BP should be measured in the supine position under standardised conditions. A note should be taken of any movement of the participant during blood pressure measurements. If systolic blood pressure is > 160 mmHg then repeat the measurement. Vital signs from 90 min post-dose onwards will form part of the readiness for discharge questionnaire and can be stopped once the patients are confirmed ready for discharge as per the questionnaire.

10.1.3. Weight and Height

Weight and height must be collected at Screening, Day 0, and Day 84.

10.1.4. Physical Examination

A physical examination will be performed at the Screening Visit and at Days 28, 56, and 84.

Any physical examination findings that qualify as AEs or SAEs must be documented on the appropriate CRF pages.

10.1.5. Electrocardiogram

A 12-lead ECG will be obtained (in triplicate, 2 minutes apart) at Screening to assess eligibility and at the visits outlined in Table 1. Recordings will be made with patients in a supine position; patients will remain in that position for at least 10 min before the ECG is recorded. PR, RR, QRS and QT intervals will be captured. QT interval will be corrected using Fridericia's formula (QTcF). The ECG may be repeated as clinically indicated during the study at the discretion of the Investigator.

10.1.6. Cardiac Telemetry

Cardiac telemetry will be conducted on Day 0 starting approximately 30 minutes before dosing up to 90 minutes post dose and any anomalies reported. The cardiac telemetry may be repeated as clinically indicated during the study at the discretion of the Investigator. Recordings will be stored securely electronically or printed in compressed format on A4 pages; any important abnormalities will be printed in uncompressed form, and commented upon by the Investigator.

10.1.7. Mini-International Neuropsychiatric Interview

A Mini-International Neuropsychiatric Interview (MINI) (Sheehan, 1998) will be performed for each patient at the Screening Visit.

Positive diagnoses on the MINI will be subject to confirmation by a psychiatrist at a clinical interview.

10.1.8. Columbia-Suicide Severity Rating Scale

Patient suicidal ideation will be assessed at the visits outlined in Table 1 using the C-SSRS (Posner, 2011). The questionnaire will be administered by the Investigator or an appropriate delegate. The "baseline" questionnaire will be used at Screening, considering activity from the last 12 months, and the "since last visit" questionnaire will be used for subsequent visits.

10.1.9. Reactivation Questionnaire

Epidemiological data and anecdotal reports indicate that the use of 5-MeO-DMT is associated with the potential occurrence of a complex and not well understood phenomenon that has been termed "reactivation" (Ortiz Bernal et al, 2022). Anecdotal reports online do seem to suggest that reactivations tend to occur mainly at night as people are drifting off to sleep, and generally tend to dissipate the longer the time has elapsed from the time they took 5-MeO-DMT. In a broad sense, it appears that reactivations are experienced as transient but intense (Type 1 Hallucinogen Persisting Perception Disorder [HPPD]) and tend to subside days or weeks after 5-MeO-DMT use in most cases, as opposed to persisting over longer periods of time as is the case with HPPD Type 2. More data are needed, therefore the ReAQ was developed for study teams to measure the occurrence, context and emotional valence of potential reactivations. The questionnaire will be completed by a psychiatrist or study physician on paper (Appendix 5 Reactivation questionnaire).

10.1.10. Laboratory Assessments

Blood samples will be collected at the Screening Visit and at the visits outlined in Table 1. Clinical laboratory evaluations will be performed locally. Additional laboratory tests should be performed per standard of care, and significant findings should be reported in the CRF.

10.1.10.1. Haematology

- Haemoglobin
- White blood cell count
- Red blood cell count
- Differential count
- Platelet count
- Mean corpuscular volume (MCV)

10.1.10.2. Clinical Chemistry

- Potassium
- Sodium
- Creatinine
- Gamma-glutamyl transpeptidase (GGT)
- Urea
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Total bilirubin

10.1.10.3. Coagulation

Coagulation variables to be assessed during the study are prothrombin time, activated partial thromboplastin time, and international normalized ratio.

The results of all local laboratory tests required by this protocol will be provided as a report and included in the patient's medical notes.

Any abnormal laboratory test result considered clinically significant by the site Investigator must be recorded on the appropriate AE page of the CRF and should be followed up as adequate until it has returned to normal or a satisfactory explanation has been provided.

10.1.10.4. Drug Screen

Urine will be tested for drugs of abuse during the Screening Period and before dosing on Day 0 according to the laboratory's SOP. Tests will include amphetamines, cocaine, opiates, cannabis, barbiturates, benzodiazepines, MDMA. Drug testing kits will be used. An Alcohol Breath Test will also be performed pre-dose at D0, and CDT and EtG are performed at screening. The results must be obtained before dosing.

10.1.10.5. Pregnancy Screen

A urine pregnancy test (human chorionic gonadotrophin) will be performed during Screening for WOCBP. Pregnancy testing is also to be performed and results obtained before dosing on Day 0. The results must be negative for the patient to continue in the study.

For female patients whose postmenopausal status is unconfirmed, a blood sample for serum FSH will be obtained at Screening to document postmenopausal status.

10.1.10.6. Nasal Site Reaction

A physician will examine the nostrils for evidence of any local site reaction after dosing.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse and Serious Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each patient will be instructed to contact the Investigator immediately should they manifest any signs or symptoms they perceive as serious.

10.2.1.1. Adverse Event

An AE is any untoward or unfavourable medical occurrence, including abnormal sign (eg, abnormal physical examination or laboratory finding), symptom, or disease related to the patient's participation in the study, which does not necessarily have a causal relationship with the study drug. AEs should be reported throughout the study, any time after consent until 30 days after dosing, whichever is latest.

Examples of an AE include:

- A new condition detected or diagnosed after participation in the study even though it may have been present prior to the start of the study
- Signs, symptoms, or clinical sequelae of a suspected overdose of a concurrent medication (an overdose per se should not be reported as an AE/SAE)
- Signs or symptoms temporally associated with study participation.

Examples that are NOT an AE include:

- A medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Investigators should consider an event that leads to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy, as an AE.

Clinically significant changes in the findings of physical examination, and clinically significant abnormalities in the results of objective tests (e.g. laboratory variables, ECG) may also be considered as AEs. The investigator will use the following criteria when deciding whether to report an abnormal result as an AE. If any of these criteria are met, the investigator will report the result as an AE.

1. The test result is associated with accompanying symptoms.
2. Results of additional diagnostic tests cause concern or necessitate medical intervention.
3. As a consequence of the test result, or the subject is given concomitant treatment.
4. The investigator considers the result to constitute an AE.

10.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, or follow-up) that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect in the offspring of a study patient

- Other important medical events

NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.*

NOTE: *In general, "hospitalization" signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.*

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization by at least 1 overnight stay or fulfils any other serious criteria, the event is serious.

When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

NOTE: *The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.*

NOTE: *Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. These should also be considered serious.*

Examples of such events are second primary cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, and blood dyscrasias or convulsions that do not result in hospitalization.

All SAEs that occur after any patient has consented to the study, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by BPL and reported to the Sponsor or its designee within 24 hours of the Investigator becoming aware of the incident.

10.2.2. Relationship to Study Drug

The Investigator should make an assessment of whether the AE is likely to be related to study drug according to the following definitions, taking into consideration temporal relationship of the event to the study procedure and alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors.

- **Not Related:** An AE for which there is no reasonable temporal association between its onset and administration of the study drug or that can reasonably be explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.

- **Unlikely Related:** An AE with a temporal relationship to study drug administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
- **Possibly Related:** An AE for which there is a reasonable temporal association between its onset and study drug administration and for which other causal factors may not be excluded.
- **Probably Related:** An AE for which there is a reasonable temporal association between its onset and study drug administration and that is at least more likely to be explained by the study drug administration than by any other cause (e.g., underlying disease, complications, concomitant drugs, or concurrent treatment).

There may be situations when an SAE has occurred but the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality for every event on the initial submission of the SAE. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For expedited regulatory reporting purposes, the classification of "Not Related" or "Unlikely Related" will be considered "Unrelated", meaning that no valid reason exists for suggesting a relationship; classification of "Possibly Related" or "Probably Related" will be considered "Related", meaning that there is a valid reason, even undetermined, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE.

10.2.3. Assessment of Severity

The severity of AEs will be graded on a 3-point scale using the following definitions:

- **Mild:** Discomfort noticed but no disruption of normal activity
- **Moderate:** Discomfort sufficient to reduce or affect normal daily activity
- **Severe:** Inability to work or perform normal daily activity

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterised as intermittent require documentation of onset and duration of each episode.

10.2.4. Recording AEs and SAEs

All SAEs/AEs will be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well-being at study visits. The questioning about SAEs/AEs will cover the current visit as well as the time between the previous and the current visit. All SAEs/AEs occurring after the patient signs the ICF until the end of the Follow-up Visit, or 30 days after dosing the last dose (whichever is latest) must be recorded on the relevant SAE/AE page in the patient's eCRF, irrespective of severity or whether or not they are considered related to the treatment.

All SAEs/AEs observed by the Investigator or one of his/her clinical collaborators or reported by the patient spontaneously or in response to a direct question will be evaluated by the Investigator.

The nature of each event, date and time (where appropriate) of onset, outcome, severity, and relationship to study procedure should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF.

Concomitant medication administered for the treatment of an SAE, at any time, must also be recorded on the SAE report form.

As a consistent method of soliciting AEs, the patient should be asked a nonleading question such as: "How have you felt since participating in the study or since the previous visit?"

Note: The Investigator should record only those SAE or AEs having occurred within the time frame defined above.

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relative to the event. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

The Investigator or designee will then record all relevant information regarding the AE/SAE in the eCRF. Note that the eCRF should not be used to report SAEs. This should be done using the paper SAE Report form, to the sponsor or designee within the required 24 hours of becoming aware of the incident.

10.2.5. Follow-up of AEs and SAEs and Assessment of Outcome

After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts.

Investigators will follow up patients

- With at least 1 SAE or patients withdrawn from the study due to an AE, until the event has resolved, subsided, or stabilised; the event is otherwise explained; or the patient is lost to follow-up
- In the case of other nonserious AEs, patients will be followed until they complete the study or are lost to follow-up
- The Investigator should not conclude that the patient is lost to follow-up earlier than 30 days after discontinuation of study drug

Clinically significant laboratory abnormalities will be followed up until they have returned to normal or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any patient must be made available to the Investigator. If a clinically significant laboratory abnormality is reported as an AE, the Investigator will determine the severity and relatedness of the event.

The outcome of any nonserious AE or any SAE reported during the entire study will be assessed as follows:

- Recovered/resolved

- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only)

10.2.6. Pregnancy and Pregnancy Follow-up

If, during the study, the Investigator becomes aware of a pregnancy in a patient or their partner, it must be reported to the Sponsor's pharmacovigilance delegate details below using the paper pregnancy form, immediately (within 24 hours of the Investigator's awareness). Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Provided the patient (or their partner) consents, the Investigator will follow the pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs.

Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

10.2.7. Adverse Events of Special Situations

The following AESS events should be reported in an expedited manner (within 24 hours of the Investigator's awareness) to the Sponsor's pharmacovigilance delegate, using the SAE process, regardless of severity.

- Any exposure to study drug through breastfeeding
- AEs associated with study drug overdose or medication error
- AEs associated with study drug abuse, misuse, overuse

10.2.8. AEs of Special Interest (AESI)

An AE of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to study medication, for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required. Such AESIs may require further investigation to characterize and understand them. AESIs should be reported to the Sponsor's pharmacovigilance delegate as per the SAE reporting process for the study (see Section 10.3).

The AESIs indicative of the below will be monitored for this study.

- AEs indicative of abuse potential,
- Significant suicidality ideation, defined as a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS or suicidal behaviour.

AEs indicative of abuse potential include the following for events, unless they are observed before dosing:

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness
- Abnormal thinking
- Hallucinations
- Inappropriate affect
- Somnolence
- Mood disorders and disturbances
- Psychosis
- Aggression
- Confusion and disorientation

10.3. Reporting Serious Adverse Events

All SAEs, from the time of written consent to participate in the study until the final follow-up assessment, regardless of study drug relationship, must be reported to the Sponsor's pharmacovigilance delegate and Beckley generic safety email address with as much information as possible within 24 hours of the Investigator becoming aware of the event. To make the report, the Investigator will complete the study specific paper SAE form and send it by email. Contact details of the Sponsor's pharmacovigilance group and delegate and Sponsors safety email address are as follows.

SAE Reporting

Worldwide Clinical Trials Drug Safety:

Email (preferred): drugsafety@worldwide.com

In cases where the email system is unavailable, site staff will transmit the back-up paper SAE Report Form by fax to:

Worldwide Clinical Trials Drug Safety:

Fax: +44 208 043 4813

The Sponsor (or designee) will notify the Research Ethics Committee (REC) of SAEs that occur during this study, if applicable, in accordance with the SOPs issued by the Research Ethics Service (RES).

The Sponsor will notify the Medicines Division of the Medicines and Healthcare products Regulatory Agency (MHRA) of all SAEs, and will be responsible for ensuring that the main REC is notified of suspected unexpected serious adverse drug reactions (SUSARs), if applicable.

SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the Sponsor has learned of them. Other SUSARs must be reported to the MHRA and REC within 15 days after the Sponsor has learned of them.

Follow-up information related to SAEs must be submitted to the Sponsor's pharmacovigilance group or delegate and Sponsors safety email address as soon as relevant data are available.

The Sponsor is responsible for determining the expectedness of the event, using the reference safety information in the IB. must be notified to the MHRA and REC

10.4. Device Events

Any issue, concern, or malfunction with the dosing device must be reported to the Sponsor's pharmacovigilance delegate (World Wide Clinical Trials), in an expedited manner following the SAE process (as above) within 24 hours, with as much information as possible, including accompanying pictures if available (as detailed in the current study specific safety management plan).

11. STATISTICS

Full details of the statistical analysis will be provided in the statistical analysis plan (SAP).

11.1. Statistical Hypothesis

The study is an exploratory one, and there are no null hypotheses to be tested.

11.2. Sample Size Estimation

Enrolment of patients with AUD is planned until up to 12 evaluable patients have completed the study. An evaluable patient is defined as a patient who has been dosed and completed Day 0.

As this is a pilot study, no formal sample size determination is appropriate.

11.3. Analysis Populations

The following populations will be identified:

Safety Population: All patients who received the dose of study drug

PD Population: All patients who received the study drug and a PD measure is available

PK concentration population: All subjects who received the study drug and for whom a pharmacokinetic sample has been analysed

The primary endpoints will be analysed using the Safety Population.

11.4. Interim Analysis

There will be no interim analyses.

11.5. Final Analysis

Final statistical analysis will be done by a Sponsor-appointed statistician. The SAP will be finalised after completion of the final protocol and before database lock.

All statistical analysis and reporting will be done using SAS software v9.4 or higher.

11.6. General Considerations

The minimum set of summary statistics for numeric variables will be number (n), mean, standard deviation (SD; or standard error [SE]), median, minimum, and maximum. Where appropriate for data interpretation, 95% confidence intervals will be presented.

Categorical data will be summarised in frequency tables with number and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented to the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters). The mean, median, and percentiles (e.g., Q1 and Q3) will be presented to one additional decimal place. The SD and SE will be presented to 2 additional decimal places.

"Baseline" will be the latest value obtained before BPL-003 administration (before dosing on Day 0, or Screening if not recorded at predose on Day 0 or Day -3[e.g., weight]). Out-of-range laboratory tests may be repeated. If a test is out of range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

11.6.1. Disposition of Patients

The disposition of all patients in all analysis populations will be summarised, including number completing the study and number discontinued from the study.

All patients who withdraw or are withdrawn from the study will be listed with the reason for withdrawal.

11.6.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics (e.g., vital signs and ECGs) will be summarised.

All concomitant medications taken by patients will be listed. All nonstudy medication will be coded using the version of the WHO Drug Global dictionary current at the time of database lock.

11.6.3. Treatment Compliance

Dates and times of dosing will be listed.

11.7. Analysis of Clinical Endpoints

11.7.1. PD Endpoints

PD data will be summarised using the PD Population.

PD data will be listed by treatment and time point and summarised by treatment and time point. Changes from baseline questionnaires will be summarised by time point.

Patients who completed the qualitative interview will be listed.

Detailed additional analysis will be described in the SAP.

11.7.1.1. Adverse Events and Serious Adverse Events

AEs will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) current at the time of database lock.

All AEs will be listed.

A TEAE is an AE that emerges during treatment (having been absent before treatment) or that worsens after treatment (International Council for Harmonisation, 1998). The number of patients with at least one TEAE will be tabulated by actual treatment and MedDRA system organ class and preferred term. For each of the following, the number of TEAEs and the number of patients with TEAEs will be summarised as follows:

- TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class and preferred term

Patients with more than one TEAE will be counted only once, at the maximum causality, for each system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and possibly related, respectively.

AEs leading to withdrawal, deaths, and other SAEs will be listed separately (fatal events will be listed separately from nonfatal events).

11.7.1.2. Clinical Laboratory Evaluations

Data from haematology, clinical biochemistry, and coagulation sampling will be summarised. Changes from baseline will be summarised by timepoint.

Any laboratory value outside the reference interval for that variable will be flagged with an 'H' if it is higher than the reference interval and with an 'L' if it is lower. Additionally, if, during the course of the study, a variable changes from baseline by more than a predetermined amount (as defined by the Principal Investigator), that value will receive a flag 'I' if increased or 'D' if decreased. Therefore, if a value both falls outside the reference interval and changes from the baseline value by more than the predetermined amount, it will be double flagged and considered to be of potential clinical importance (PCI).

All laboratory values of PCI will be listed. In a separate listing, laboratory values of PCI will be listed with all related laboratory results (i.e., haematology, clinical biochemistry, or coagulation). Frequencies of laboratory values of PCI and clinically significant laboratory values of PCI will be summarised.

11.7.1.3. Other Safety Measures

Vital signs at each planned assessment and change in vital signs from baseline at each planned post-Baseline assessment will be summarised.

Vital signs outside the normal ranges in will be considered of PCI and listed and summarised separately. Frequency of clinically significant vital signs will be summarised.

QT interval will be corrected using Fridericia's (QTcF) formula.

ECG variables will be summarised by treatment and timepoint. Changes from baseline will be summarised by timepoint.

QTcF >450 ms and increases in QTcF from baseline (Day 0 predose) of >30 ms will be considered to be of PCI. The number of patients with QTcF of PCI will be summarised by actual treatment and timepoint, giving the numbers of patients with QTcF >450 ms, >480 ms, and >500 ms, and the numbers of patients with increases in QTcF from baseline of >30 ms and >60 ms. A supporting listing of all patients with an QTcF value of PCI and a separate listing of ECG findings classified as abnormal by the Investigator will also be provided.

The frequency of clinically significant ECG values will be summarised.

Abnormal physical examination findings will be listed.

11.7.1.4. Concomitant Medication

Concomitant medication will be listed.

11.7.1.5. Concentration data

PK concentration data will be summarised using the PK concentration population. Plasma concentrations will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically.

12. STUDY ADMINISTRATION

12.1. Ethical Conduct of the Study

This study is to be performed in accordance with the protocol, appropriate sections of The Medicines for Human Use (Clinical Trials) Regulations and current amendments, the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), which has its origins in the Declaration of Helsinki, and all applicable local rules and regulatory requirements of the country. Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements.

12.2. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favourable opinion in writing by a suitably recognised REC as appropriate and by the MHRA. The study will not proceed unless BPL obtains from the MHRA a clinical trial authorisation (CTA), and the REC approves the study. The Investigator must submit the written REC approval to BPL or designee before he or she can enrol any patient into the study.

The Investigator is responsible for informing the REC of any amendment to the protocol in accordance with local requirements. In addition, the REC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the REC upon receipt of amendments as local regulations require.

The Investigator is also responsible for providing the REC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. BPL or designee will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the REC according to local regulations and guidelines.

12.3. Written Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

In obtaining and documenting informed consent, the Investigator should comply with applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the 2013 Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the REC's written approval/favourable opinion of the written ICF and any other written information to be provided to patients.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the REC.

An Investigator or designee will describe the protocol to potential patients face to face. The ICF may be read to the patients, but the Investigator or designee shall give the patients ample opportunity to inquire about details of the study and ask any questions before the patient dates and signs the ICF.

Although informed consent information can be presented to groups at an initial information session, each patient must be given the opportunity to individually pose questions to the Investigator or designee prior to the patient dating and signing the ICF.

The ICF must be in a language fully comprehensible to the prospective patients. Informed consent shall be documented by the use of a written consent form approved by the REC and signed and dated by the patients and by the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been understood.

Each patient's signed ICF must be kept on file by the Investigator for possible inspection by Regulatory Authorities and/or Site Monitor and Regulatory Compliance persons. The patients should receive a copy of the signed and dated written ICF and any other written information and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to patients.

Both the informed consent discussion and the written ICF and any other written information to be provided to the patients should include explanations of the following:

- That the study involves research
- The purpose of the study
- The study procedures to be followed, including all invasive procedures
- The patient's responsibilities
- Those aspects of the study that are experimental
- The reasonably foreseeable risks or inconveniences to the patients and, when applicable, to an embryo, foetus, or nursing infant
- The reasonable expected benefits
- The anticipated prorated payment, if any, to patients for participating in the study
- The anticipated expenses, if any, for patients for participating in the study
- That a patient's participation in the study is voluntary and the patient may refuse to participate in or withdraw from the study, at any time, without penalty or loss of benefits to which patients are otherwise entitled
- Those records identifying patients will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, patients' identities will remain confidential
- That the patients will be informed in a timely manner if information becomes available that may be relevant to the patients' willingness for continued participation in the study

- The person(s) to contact for further information regarding the study and the rights of study patients, and who to contact in the event of study-related injury
- The foreseeable circumstances and/or reasons under which a patient's participation in the study may be terminated
- The expected duration of a patient's participation in the study
- The approximate number of patients involved in the study

The Investigator has the final responsibility for final presentation of the ICF, respecting the mandatory requirements of local regulations.

12.4. Patient Confidentiality

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by BPL or designee or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that, for data verification purposes, authorised representatives of BPL or designee or the regulatory authority may require direct access to parts of the study site or clinic records relevant to the study that include the patient's medical history.

The Investigator must ensure that the patient's privacy is maintained. A patient should be identified only by his/her assigned patient number on the eCRFs or other documents submitted to BPL or designee. The Investigator should keep documents that are not submitted to BPL or designee (e.g., signed ICFs) in a strictly confidential file.

12.5. Research Ethics Committee

The final study protocol, including the final version of the ICF, must be approved or given a favourable opinion in writing by a suitable recognised REC. The Investigator must submit written approval to BPL or designee before he or she can enrol any patient into the study.

Progress reports and notifications of SAEs will be provided to the REC according to regulations and guidelines.

The REC must be constituted according to the local laws/customs of the country in which the participating institution/Investigator is carrying out the study, and in accordance with the ICH Harmonized Tripartite Guideline for GCP recommendations.

12.6. Case Report Forms and Source Documents

The Investigator or designee will record data on all observations, tests, and assessments specified in the protocol on the eCRFs provided by BPL or designee. Data collected in source documents will be transcribed into the eCRF. Any data reported in the eCRF, which is derived from the site's source documents, should be consistent with the source documents. Before the start of the study, the Sponsor and Investigator will sign an agreement listing the source documents to be used in this study. Source documents will be securely stored within the clinic.

12.7. Data Collection

Certain data may be entered directly into ePRO. Other data will be collected in the eCRF, which means that patient information will be entered into a computer at the investigational site. The site will be capable of modifying the data to ensure accuracy with the medical records.

Data collection for the qualitative interview (including audio data) is outlined in the Qualitative Interview Manual.

Clinical data (including AEs, concomitant medication, etc.) will be entered into a 21 CFR Part 11-compliant Medrio M-1 database. The Medrio M-1 system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data reported in the eCRF, derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Where the data violate data validation checks, queries will be generated for resolution by clinical staff. All edits made to the database upon resolution of queries will be recorded in an electronic audit trail.

The database will be locked after the following have been completed: all expected eCRF data have been entered and accounted for; all discrepancies have been resolved; data have been coded as appropriate; SAEs have been reconciled; all site audit findings impacting the database have been closed; and quality control inspection has been completed.

All new/updated information will be reviewed and verified by a designated site monitor according to the monitoring guidelines. This information will finally be stored in a central database maintained by a designated study data coordinating centre. At the conclusion of the study, the designated study data coordinating centre will archive the study data in accordance with internal procedures. In addition, the Investigator will be provided with a CD-ROM or download link of the final version of the data generated at the investigational site.

Specific instructions for data entry into the eCRF will be included in the training material provided to the investigational site.

12.8. Study Monitoring

Before the study site can enter a patient into the study, a representative of the BPL or designee will:

- Determine the adequacy of the site facilities
- Discuss with the site Investigator and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the BPL or designee or its representatives. This will be documented in a Clinical Study Agreement between BPL and the Investigator.

During the study, a monitor from BPL or designee will have regular contacts with the study site for the following:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the study team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed

- Perform source data verification
- Record and report any protocol deviations not previously sent to BPL or designee
- Confirm that AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to BPL or designee and that those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The monitor will be available between visits if the Investigator or other staff needs information or advice.

12.9. Quality Assurance Audits and Inspections

In compliance with GCP and regulatory requirements, authorised representatives of BPL or designee, or regulatory agencies, may visit the site to conduct quality assurance audits or inspections, including source data verification, at any time during or following a study. BPL or designee or a regulatory authority may perform audits. The purpose of a BPL or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported, according to the protocol, ICH GCP Harmonized Tripartite Guidelines, and any applicable regulatory requirements. The Investigator must agree to allow auditors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors to discuss findings and issues. The Investigator should contact BPL or designee immediately if contacted by a regulatory agency about an inspection.

12.10. Investigator Compliance

The Investigator will conduct the study in compliance with the protocol provided by BPL and approved by the REC and the appropriate regulatory authority. Modifications to the protocol will not be made without agreement of BPL. The regulatory authority and REC do not need to approve any substantial change to the protocol that needs to be implemented urgently to eliminate an immediate hazard to the patient. In this event, the Investigator will contact BPL or designee to discuss the planned course of action. Any deviation from the protocol must be documented.

The REC and/or regulatory authority must approve substantial amendments before they are implemented.

12.11. Study or Clinical Site Termination

BPL reserves the right to terminate the study or the clinical study site at any time. Conditions that may warrant termination of the study include but are not limited to

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of BPL to suspend or discontinue testing or the treatment with the study drug
- Failure of the Investigator to comply with GCP

- Submission of knowingly false information from the clinical study site to BPL or designee or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, BPL and the Investigator will ensure that adequate consideration is given to the protection of patients' interests.

BPL will promptly inform, via written communication, the Investigator and/or the institution conducting the study if the study is suspended or terminated, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the REC promptly and provide the reason for the suspension or termination.

12.12. Expected Duration of Patient Participation

Patients will participate in the study for approximately 16 weeks, including screening and psychedelic preparation (up to 4 weeks), and ongoing AUD relapse prevention psychotherapy over 12 weeks.

12.13. Data Handling and Recordkeeping (Records Retention)

12.13.1. Inspection of Records

BPL or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts or records and study source documents, and other records related to study conduct.

12.13.2. Retention of Records

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, drug inventory, and REC and BPL or designee correspondence pertaining to the study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for BPL-003, or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. There may be other circumstances in which BPL or designee is required to maintain study records; therefore, BPL or designee should be contacted before removing study records for any reason.

12.14. Publication Policy

A description of this clinical study will be available on http://www.ClinicalTrials.gov and other national registries of clinical studies, as required by local regulations.

It is anticipated that BPL will publish the results of this clinical study in medical/scientific journals and/or present the results in a variety of forums.

Publication by the clinical study site(s) of any data from this study must be carried out in accordance with the Clinical Study Agreement.

13. LIST OF REFERENCES

Agurell S, Holmstedt, B, Lindgren, JE. Metabolism of 5-methoxy-N,-N dimethyltryptamine-14 C in the rat. Biochemical Pharmacology. 1969;18(10):2771-2781.

Albaugh BJ, Anderson, PO. Peyote in the treatment of alcoholism among American Indians. The American Journal of Psychiatry. 1974;131(11):1247-1250.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). 5 ed. Arlington, VA: American Psychiatric Association; 2013.

Barker SA, McIlhenny, EH, Strassman, R. A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955-2010. Drug Test Anal. 2012;4(7-8):617-635.

Barsuglia J, Davis, AK, Palmer, R. Intensity of mystical experiences occasioned by 5-MeO-DMT and comparison with a prior psilocybin study. Frontiers in Psychology. 2018;9:2459.

Benington F, Morin, RD, Clark, LC. 5-methoxy-N, N-dimethyltryptamine, a possible endogenous psychotoxin. The Alabama Journal of Medical Sciences. 1965;2(4):397-403.

Berendsen HHG, Jenck, F, Broekkamp, CLE. Selective activation of 5HT1A receptors induces lower lip retraction in the rat. Pharmacology, Biochemistry, and Behavior. 1989;33(4):821-827.

Berger G, Mazière, M, Marazano, C, Comar, D. Carbon 11 labeling of the psychoactive drug o-methyl-bufotenine and its distribution in the animal organism. European Journal of Nuclear Medicine. 1978;3(2):101-104.

Bergman RL. Navajo peyote use: its apparent safety. The American Journal of Psychiatry. 1971;128(6):695-699.

Bershad AK, Schepers, ST, Bremmer, MP, Lee, R, de Wit, H. Acute subjective and behavioral effects of microdoses of lysergic acid diethylamide in healthy human volunteers. Biological Psychiatry. 2019;86(10):792-800.

Blanchard KA, Morgenstern, J, Morgan, TJ, Lobouvie, EW, Bux, DA. Assessing consequences of substance use: psychometric properties of the inventory of drug use consequences. Psychology of Addictive Behaviors. 2003;17(4):328-331.

Blum K, Futterman, SL, Pascarosa, P. Peyote, a potential ethnopharmacologic agent for alcoholism and other drug dependencies: possible biochemical rationale. Clinical Toxicology. 1977;11(4):459-472.

Bogenschutz MP, Forcehimes, AA, Pommy, JA, Wilcox, CE, Barbosa, PCR, Strassman, RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. Journal of Psychopharmacology (Oxford, England). 2015;29(3):289-299.

Bowen WT, Soskin, RA, Chotlos, JW. Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism: a follow-up study. The Journal of Nervous and Mental Disease. 1970;150(2):111-118.

Brooks R. EuroQol: the current state of play. Health Policy (Amsterdam). 1996;37(1):53-72.

Brown TK. Ibogaine in the treatment of substance dependence. Current Drug Abuse Reviews. 2013;6(1):3-16.

Brush DE, Bird, SB, Boyer, EW. Monoamine oxidase inhibitor poisoning resulting from Internet misinformation on illicit substances. Journal of Toxicology Clinical Toxicology. 2004;42(2):191-195.

Busner J, Targum, SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont, Pa). 2007;4(7):28-37.

Carbonaro TM, Gatch, MB. Neuropharmacology of N,N-dimethyltryptamine. Brain Research Bulletin. 2016a;126(Pt 1):74-88.

Carbonaro TM, Bradstreet, MP, Barrett, FS. Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. Journal of Psychopharmacology (Oxford, England). 2016b;30(12):1268-1278.

Carhart-Harris RL, Nutt, DJ. Serotonin and brain function: a tale of two receptors. Journal of Psychopharmacology (Oxford, England). 2017a;31(9):1091-1120.

Carhart-Harris RL, Goodwin, GM. The therapeutic potential of psychedelic drugs: past, present, and future. Neuropsychopharmacology. 2017b;42(11):2105-2113.

Carhart-Harris RL, Bolstridge, M, Rucker, J. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry. 2016;3(7):619-627.

Carhart-Harris RL, Roseman, L, Bolstridge, M. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Scientific Reports. 2017c;7(1):13187.

Carhart-Harris RL, Bolstridge, M, Day, CMJ. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology. 2018;235(2):399-408.

Dabiré H. Central 5-hydroxytryptamine (5-HT) receptors in blood pressure regulation. Therapie. 1991;46(6):421-429.

Davis AK, Arterberry, BJ, Bonar, EE. Predictors of positive drinking outcomes among youth receiving an alcohol brief intervention in the emergency department. Drug and Alcohol Dependence. 2018a;188:102-108.

Davis AK, Barsuglia, JP, Lancelotta, R, Grant, RM, Renn, E. The epidemiology of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) use: benefits, consequences, patterns of use, subjective effects, and reasons for consumption. Journal of Psychopharmacology (Oxford, England). 2018b;32(7):779-792.

Davis AK, So, S, Lancelotta, R, Barsuglia, JP, Griffiths, RR. 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. The American Journal of Drug and Alcohol Abuse. 2019;45(2):161-169.

Davis AK, Averill, LA, Sepeda, ND, Barsuglia, JP, Amoroso, T. Psychedelic treatment for trauma-related psychological and cognitive impairment among US Special Operations Forces veterans. Chronic Stress (Thousand Oaks, Calif). 2020;4:2470547020939564.

Davis AK, Barrett, FS, So, S, Gukasyan, N, Swift, TC, Griffiths, RR. Development of the Psychological Insight Questionnaire among a sample of people who have consumed psilocybin or LSD. Journal of Psychopharmacology (Oxford, England). 2021;35(4):437-446.

de Rios MD, Grob, CS, Baker, JR. Hallucinogens and redemption. Journal of Psychoactive Drugs. 2002;34(3):239-248.

Dolder PC, Schmid, Y, Müller, F, Borgwardt, S, Liechti, ME. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. Neuropsychopharmacology. 2016;41(11):2638-2646.

Drobes DJ, Thomas, SE. Assessing craving for alcohol. Alcohol Research & Health. 1999;23(3):179-186.

Dyck E. 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Social History of Medicine. 2006;19(2):313-329.

Edwards G, Gross, MM. Alcohol dependence: provisional description of a clinical syndrome. British Medical Journal. 1976;1(6017):1058-1061.

Eison AS, Wright, RN. 5-HT1A and 5-HT2 receptors mediate discrete behaviors in the Mongolian gerbil. Pharmacology, Biochemistry, and Behavior. 1992;43(1):131-137.

EMCDDA. European Drug Report: Trends and Developments: European Monitoring Centre For Drugs And Drug Addiction; 2021 [Available from: https://www.emcdda.europa.eu/publications/edr/trends-developments/2021_en.

Erowid. 5-MeO-DMT Reports: Erowid Experience Vaults; 2021 [cited 2021. Available from: https://erowid.org/experiences/subs/exp_5MeODMT.shtml.

European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. European Medicines Agency; 2017.

Fábregas JM, González, D, Fondevila, S. Assessment of addiction severity among ritual users of ayahuasca. Drug and Alcohol Dependence. 2010;111(3):257-261.

Fleming M, Mundt, M. Carbohydrate-deficient transferrin: validity of a new alcohol biomarker in a sample of patients with diabetes and hypertension. The Journal of the American Board of Family Practice. 2004;17(4):247-255.

Fuentes JJ, Fonseca, F, Elices, M, Farré, M, Torrens, M. Therapeutic use of LSD in psychiatry: a systematic review of randomized-controlled clinical trials. Frontiers in Psychiatry. 2020;10:943.

Garcia-Romeu A, Griffiths, RR, Johnson, MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Current Drug Abuse Reviews. 2014;7(3):157-164.

Garcia-Romeu A, Davis, AK, Erowid, F, Erowid, E, Griffiths, RR, Johnson, MW. Cessation and reduction in alcohol consumption and misuse after psychedelic use. Journal of Psychopharmacology (Oxford, England). 2019;33(9):1088-1101.

Garcia-Romeu A, Davis, AK, Erowid, E, Erowid, F, Griffiths, RR, Johnson, MW. Persisting reductions in cannabis, opioid, and stimulant misuse after naturalistic psychedelic use: an online survey. Frontiers in Psychiatry. 2020;10:955.

Gough G, Heathers, L, Puckett, D. The utility of commonly used laboratory tests to screen for excessive alcohol use in clinical practice. Alcoholism, Clinical and Experimental Research. 2015;39(8):1493-1500.

Grant BF, Goldstein, RB, Saha, TD. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015;72(8):757-766.

Griffiths R, Richards, W, Johnson, M, McCann, U, Jesse, R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. Journal of Psychopharmacology (Oxford, England). 2008;22(6):621-632.

Griffiths RR, Johnson, MW, Carducci, MA. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of Psychopharmacology (Oxford, England). 2016;30(12):1181-1197.

Griffiths RR, Richards, WA, McCann, U, Jesse, R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology. 2006;187(3):268-283.

Griffiths RR, Johnson, MW, Richards, WA, Richards, BD, McCann, U, Jesse, R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology. 2011;218(4):649-665.

Grob CS, Danforth, AL, Chopra, GS. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of General Psychiatry. 2011;68(1):71-78.

Guchhait RB. Biogenesis of 5-methoxy-N,N-dimethyltryptamine in human pineal gland. Journal of Neurochemistry. 1976;26(1):187-190.

Halberstadt AL, Geyer, MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. Neuropharmacology. 2011;61(3):364-381.

Halberstadt AL, Nichols, DE, Geyer, MA. Behavioral effects of α,α,β,β-tetradeutero-5-MeO-DMT in rats: comparison with 5-MeO-DMT administered in combination with a monoamine oxidase inhibitor. Psychopharmacology. 2012;221(4):709-718.

Halpern JH, Sherwood, AR, Passie, T, Blackwell, KC, Ruttenber, AJ. Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. Medical Science Monitor. 2008;14(8):SR15-SR22.

Hartogsohn I. Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. Journal of Psychopharmacology (Oxford, England). 2016;30(12):1259-1267.

Hendricks PS. Awe: a putative mechanism underlying the effects of classic psychedelic-assisted psychotherapy. International Review of Psychiatry (Abingdon, England). 2018;30(4):331-342.

Hendricks PS, Thorne, CB, Clark, CB, Coombs, DW, Johnson, MW. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. Journal of Psychopharmacology (Oxford, England). 2015;29(3):280-288.

Hintzen A, Passie, T. The Pharmacology of LSD: A Critical Review: OUP/Beckley Foundation Press; 2010.

Hollister LE, Shelton, J, Krieger, G. A controlled comparison of lysergic acid diethylamide (LSD) and dextroamphetmine in alcoholics. The American Journal of Psychiatry. 1969;125(10):1352-1357.

International Council for Harmonisation. Statistical principles for clinical trials. ICH Harmonised Tripartite Guideline: International Council for Harmonisation; 1998.

Janssen MF, Pickard, AS, Golicki, D. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation. 2013;22(7):1717-1727.

Jay M. Mescaline: A Global History of the First Psychedelic:: Yale University Press; 2019.

Johnson M, Richards, W, Griffiths, R. Human hallucinogen research: guidelines for safety. Journal of Psychopharmacology (Oxford, England). 2008;22(6):603-620.

Johnson MW, Garcia-Romeu, A, Griffiths, RR. Long-term follow-up of psilocybin-facilitated smoking cessation. The American Journal of Drug and Alcohol Abuse. 2017;43(1):55-60.

Johnson MW, Garcia-Romeu, A, Cosimano, MP, Griffiths, RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of Psychopharmacology (Oxford, England). 2014;28(11):983-992.

Johnson MW, Griffiths, RR, Hendricks, PS, Henningfield, JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018;142:143-166.

Johnson MW, Hendricks, PS, Barrett, FS, Griffiths, RR. Classic psychedelics: an integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacology & Therapeutics. 2019;197:83-102.

Jones JL, Mateus, CF, Malcolm, RJ, Brady, KT, Back, SE. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. Frontiers in Psychiatry. 2018;9:277.

Kaumann AJ, Levy, FO. 5-hydroxytryptamine receptors in the human cardiovascular system. Pharmacology & Therapeutics. 2006;111(3):674-706.

Kelly JF, Humphreys, K, Ferri, M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. Cochrane Database of Systematic Reviews. 2020;3(3).

Kometer M, Pokorny, T, Seifritz, E, Volleinweider, FX. Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. Psychopharmacology. 2015;232(19):3663-3676.

Kometer M, Schmidt, A, Bachmann, R, Studerus, E, Seifritz, E, Vollenweider, FX. Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. Biological Psychiatry. 2012;72(11):898-906.

Kraehenmann R, Preller, KH, Scheidegger, M. Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biological Psychiatry. 2015;78(8):572-581.

Krebs-Thomson K, Ruiz, EM, Masten, V, Buell, M, Geyer, MA. The roles of 5-HT1A and 5-HT2 receptors in the effects of 5-MeO-DMT on locomotor activity and prepulse inhibition in rats. Psychopharmacology. 2006;189(3):319-329.

Krebs TS, Johansen, PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. Journal of Psychopharmacology (Oxford, England). 2012;26(7):994-1002.

Kuypers KPC, Riba, J, de la Fuente Revenga, M, Barker, S, Theunissen, EL, Ramaekers, JG. Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. Psychopharmacology. 2016;233(18):3395-3403.

Lalley PM. Inhibition of phrenic and sympathetic vasomotor neurons in cats by the serotonin analog 5-methoxy-N,N-dimethyltryptamine. The Journal of Pharmacology and Experimental Therapeutics. 1982;220(1):39-48.

Lebedev AV, Kaelen, M, Lövdén, M. LSD-induced entropic brain activity predicts subsequent personality change. Human Brain Mapping. 2016;37(9):3203-3213.

Lu L, Liu, Y, Zhu, W. Traditional medicine in the treatment of drug addiction. The American Journal of Drug and Alcohol Abuse. 2009;35(1):1-11.

Lucki I, Nobler, MS, Frazer, A. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. The Journal of Pharmacology and Experimental Therapeutics. 1984;228(1):133-139.

Ludwig A, Levine, J, Stark, L, Lazar, R. A clinical study of LSD treatment in alcoholism. The American Journal of Psychiatry. 1969;126(1):59-69.

Ly C, Greb, AC, Cameron, LP. Psychedelics promote structural and functional neural plasticity. Cell Reports. 2018;23(11):3170-3182.

Lyons T, Carhart-Harris, RL. Increased nature relatedness and decreased authoritarian political views after psilocybin for treatment-resistant depression. Journal of Psychopharmacology (Oxford, England). 2018;32(7):811-819.

MacLean KA, Johnson, MW, Griffiths, RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. Journal of Psychopharmacology (Oxford, England). 2011;25(11):1453-1461.

Maclean KA, Leoutsakos, JM, Johnson, MW, Griffiths, RR. Factor analysis of the Mystical Experience Questionnaire: a study of experiences occasioned by the hallucinogen psilocybin. Journal for the Scientific Study of Religion. 2012;51(4):721-737.

Marlatt GA, Donovan, D M. Relapse prevention: Maintenance strategies in the treatment of addictive behaviors. 2nd ed. New York, NY: The Guilford Press; 2005.

Mason BJ, Heyser, CJ. Alcohol use disorder: the role of medication in recovery. Alcohol Research : Current Reviews. 2021;41(1):07.

Meloni JN, Laranjeira, R. [The social and health burden of alcohol abuse]. Rev Bras Psiquiatr. 2004;26:S7-S10.

Miller W. FORM 90: A Structured Assessment Interview for Drinking and Related Behaviors Test Manual. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; 1996.

Miller W, Rollnick, S. Motivational interviewing: Preparing people for change. 2nd ed. New York, NY: Guilford Press; 2002.

Mitchell C, Simpson, D, Chick, J. Carbohydrate deficient transferrin in detecting relapse in alcohol dependence. Drug and Alcohol Dependence. 1997;48(2):97-103.

Morley KC, Perry, CJ, Watt, J. New approved and emerging pharmacological approaches to alcohol use disorder: a review of clinical studies. Expert Opinion on Pharmacotherapy. 2021;22(10):1291-1303.

Mueller F, Lenz, C, Dolder, PC. Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. Translational Psychiatry. 2017;7(4):e1084.

Nagai F, Nonaka, R, Satoh Hisashi Kamimura, K. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. European Journal of Pharmacology. 2007;559(2-3):132-137.

Narasimhachari N, Heller, B, Spaide, J. Urinary studies of schizophrenics and controls. Biological Psychiatry. 1971;3(1):9-20.

National Institute for Health and Care Excellence Alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence. The British Psychological Society and The Royal College of Psychiatrists; 2011. Contract No.: Clinical Guideline CG115.

National Institute for Health and Care Excellence. Guidance. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. Leicester (UK): British Psychological Society and The Royal College of Psychiatrists.; 2019.

Nichols DE. Hallucinogens. Pharmacology & Therapeutics. 2004;101(2):131-181.

Nichols DE. Psychedelics. Pharmacological Reviews. 2016;68(2):264-355.

Nonaka R, Nagai, F, Ogata, A, Satoh, K. In vitro screening of psychoactive drugs by [(35)S]GTPgammaS binding in rat brain membranes. Biological & Pharmaceutical Bulletin. 2007;30(12):2328-2333.

Nour MM, Evans, L, Nutt, D, Carhart-Harris, RL. Ego-dissolution and psychedelics: validation of the Ego-Dissolution Inventory (EDI). Frontiers in Human Neuroscience. 2016;10:269.

Nutt D, Carhart-Harris, R. The current status of psychedelics in psychiatry. JAMA Psychiatry. 2021;78(2):121-122.

Nutt D, Erritzoe, D, Carhart-Harris, R. Psychedelic psychiatry's brave new world. Cell. 2020;181(1):24-28.

Nutt DJ, King, LA, Phillips, LD, Independent Scientific Committee on, D. Drug harms in the UK: a multicriteria decision analysis. Lancet. 2010;376(9752):1558-1565.

Ortiz Bernal, A. M., Raison, C. L, Lancelotta, R. L., & Davis, A. K. Reactivations after 5-methoxy-N,N-dimethyltryptamine use in naturalistic settings: An initial exploratory analysis of the phenomenon's predictors and its emotional valence. Front. Psychiatry 2022 13:1049643.

Ott J. Pharmañopo-psychonautics: human intranasal, sublingual, intrarectal, pulmonary and oral pharmacology of bufotenine. Journal of Psychoactive Drugs. 2001;33(3):273-281.

Pahnke WN, Kurland, AA, Unger, S, Savage, C, Grof, S. The experimental use of psychedelic (LSD) psychotherapy. Journal of the American Medical Association. 1970;212(11):1856-1863.

Palamar JJ, Le, A. Use of new and uncommon synthetic psychoactive drugs among a nationally representative sample in the United States, 2005-2017. Human Psychopharmacology. 2019;34(2):e2690.

Pokorny T, Preller, KH, Kometer, M, Dziobek, I, Vollenweider, FX. Effect of psilocybin on empathy and moral decision-making. The International Journal of Neuropsychopharmacology. 2017;20(9):747-757.

Posner K, Brown, GK, Stanley, B. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. The American Journal of Psychiatry. 2011;168(12):1266-1277.

Potgieter AS, Deckers, F, Geerlings, P. Craving and relapse measurement in alcoholism. Alcohol and Alcoholism (Oxford, Oxfordshire). 1999;34(2):254-260.

Ray TS. Psychedelics and the human receptorome. PLoS One. 2010;5(2):e9019.

Reckweg J, Mason, NL, van Leeuwen, C, Toennes, SW, Terwey, TH, Ramaekers, JG. A phase 1, dose-ranging study to assess safety and psychoactive effects of a vaporized 5-methoxy-N,N-dimethyltryptamine formulation (GH001) in healthy volunteers. Frontiers in Pharmacology. 2021;12:760671.

Richards WA, Rhead, JC, DiLeo, FB, Yensen, R, Kurland, AA. The peak experience variable in DPT-assisted psychotherapy with cancer patients. Journal of Psychedelic Drugs. 1977;9(1):1-10.

Rieser NM, Herdener, M, Preller, KH. Psychedelic-Assisted Therapy for Substance Use Disorders and Potential Mechanisms of Action. Current Topics in Behavioral Neurosciences: Springer Berlin Heidelberg; 2021. 1-25 p.

Roseman L, Demetriou, L, Wall, MB, Nutt, DJ, Carhart-Harris, RL. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology. 2018;142:263-269.

Roseman L, Haijen, E, Idialu-Ikato, K, Kaelen, M, Watts, R, Carhart-Harris, R. Emotional breakthrough and psychedelics: validation of the emotional breakthrough inventory. Journal of Psychopharmacology (Oxford, England). 2019;33(9):1076-1087.

Ross S, Bossis, A, Guss, J. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of Psychopharmacology (Oxford, England). 2016;30(12):1165-1180.

Rucker JJ, Jelen, LA, Flynn, S, Frowde, KD, Young, AH. Psychedelics in the treatment of unipolar mood disorders: a systematic review. Journal of Psychopharmacology (Oxford, England). 2016;30(12):1220-1229.

Russ SL, Carhart-Harris, RL, Maruyama, G, Elliott, MS. States and traits related to the quality and consequences of psychedelic experiences. Psychology of Consciousness. 2019;6(1):1-21.

Saitz R. Alcohol screening and brief intervention in primary care: absence of evidence for efficacy in people with dependence or very heavy drinking. Drug and Alcohol Review. 2010;29(6):631-640.

Saitz R, Mayo-Smith, MF, Roberts, MS, Redmond, HA, Bernard, DR, Calkins, DR. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. Journal of the American Medical Association. 1994;272(7):519-523.

Sampedro F, de la Fuente Revenga, M, Valle, M. Assessing the psychedelic "after-glow" in ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities. The International Journal of Neuropsychopharmacology. 2017;20(9):698-711.

Savage C, McCabe, OL. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. Archives of General Psychiatry. 1973;28(6):808-814.

Schlemmer RF, Davis, JM. Evidence for dopamine mediation of submissive gestures in the stumptail macaque monkey. Pharmacology, Biochemistry, and Behavior. 1981;14:95-102.

Schlemmer RF, Davis, JM. A primate model for the study of hallucinogens. Pharmacology, Biochemistry, and Behavior. 1986;24(2):381-392.

Schlemmer RF, Narasimhachari, N, Thompson, VD, Davis, JM. The effect of a hallucinogen, 5-methoxy N,N-dimethyltryptamine, on primate social behavior. Communications in Psychopharmacology. 1977;1(2):105-118.

Schmid Y, Liechti, ME. Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology. 2018;235(2):535-545.

Schuckit MA. Alcohol-use disorders. Lancet. 2009;373(9662):492-501.

Schultes R, Hofmann, A, Ratsch, C. Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers. 2 ed2001.

Schultes RE. Fifteen years of study of psychoactive snuffs of South America: 1967-1982--a review. Journal of Ethnopharmacology. 1984;11(1):17-32.

Sepeda ND, Clifton, JM, Doyle, LY, Lancelotta, R, Griffiths, RR, Davis, AK. Inhaled 5-methoxy-N,N-dimethyltryptamine: supportive context associated with positive acute and enduring effects. Journal of Psychedelic Studies. 2020;4(2):114-122.

Sessa B, Higbed, L, O'Brien, S. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. Journal of Psychopharmacology (Oxford, England). 2021;35(4):375-383.

Sexton JD, Crawford, MS, Sweat, NW, Varley, A, Green, EE, Hendricks, PS. Prevalence and epidemiological associates of novel psychedelic use in the United States adult population. Journal of Psychopharmacology (Oxford, England). 2019;33(9):1058-1067.

Sheehan DV, Lecrubier, Y, Sheehan, KH. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of Clinical Psychiatry. 1998;59:22-33.

Shen HW, Jiang, XL, Yu, AM. Nonlinear pharmacokinetics of 5-methoxy-N,N-dimethyltryptamine in mice. Drug Metabolism and Disposition: the Biological Fate of Chemicals. 2011;39(7):1227-1234.

Shen J, Swift, B, Mamelok, R, Pine, S, Sinclair, J, Attar, M. Design and conduct considerations for first-in-human trials. Clinical and Translational Science. 2019;12(1):6-19.

Shukla L, Sharma, P, Ganesha, S. Value of ethyl glucuronide and ethyl sulfate in serum as biomarkers of alcohol consumption. Indian Journal of Psychological Medicine. 2017;39(4):481-487.

Singleton EG. Alcohol Craving Questionnaire (ACQ-NOW). Alcohol and Alcoholism (Oxford, Oxfordshire). 1997;32:344.

Singleton EG. A brief version of the Alcohol Craving Questionnaire (ACQ-NOW)? Rockville, MD: National Institute on Drug Abuse; 1999.

Singleton EG, Gorelick, DA. Mechanisms of alcohol craving and their clinical implications. Recent Developments in Alcoholism. 1998;14:177-195.

Sitaram BR, McLeod, WR. Observations on the metabolism of the psychotomimetic indolealkylamines: implications for future clinical studies. Biological Psychiatry. 1990;28(10):841-848.

Sitaram BR, Lockett, L, Talomsin, R, Blackman, GL, McLeod, WR. In vivo metabolism of 5-methoxy-N,N-dimethyltryptamine and N,N-dimethyltryptamine in the rat. Biochemical Pharmacology. 1987;36(9):1509-1512.

Sklerov J, Levine, B, Moore, KA, King, T, Fowler, D. A fatal intoxication following the ingestion of 5-methoxy-N,N-dimethyltryptamine in an ayahuasca preparation. Journal of Analytical Toxicology. 2005;29(8):838-841.

Smart RG, Storm, T, Baker, EF, Solursh, L. A controlled study of lysergide in the treatment of alcoholism. 1. The effects on drinking behavior. Quarterly Journal of Studies on Alcohol. 1966;27(3):469-482.

Smith LM, Peroutka, SJ. Differential effects of 5-hydroxytryptamine1a selective drugs on the 5-HT behavioral syndrome. Pharmacology, Biochemistry, and Behavior. 1986;24(6):1513-1519.

Sobell L, Sobell, M. Timeline Follow-Back: A Technique for Assessing Self-Reported Alcohol Consumption. New York, NY: Springer Science+Business Media LLC; 1992.

Soler J, Elices, M, Franquesa, A. Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities. Psychopharmacology. 2016;233(5):823-829.

Specialist Clinical Addiction Network. Inpatient Treatment of Drug and Alcohol Misusers in the National Health Service London.: Specialist Clinical Addiction Network; 2006.

Squires RF. Evidence that 5-methoxy-N, N-dimethyl tryptamine is a specific substrate for MAO-A in the rat: implications for the indoleamine dependent behavioural syndrome. Journal of Neurochemistry. 1975;24(1):47-50.

Strassman RJ, Qualls, CR. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. Archives of General Psychiatry. 1994;51(2):85-97.

Sullivan JT, Sykora, K, Schneiderman, J, Naranjo, CA, Sellers, EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). British Journal of Addiction. 1989;84(11):1353-1357.

Suzuki O, Katsumata, Y, Oya, M. Characterization of eight biogenic indoleamines as substrates for type A and type B monoamine oxidase. Biochemical Pharmacology. 1981;30(11):1353-1358.

Szabo A, Kovacs, A, Frecska, E, Rajnavolgyi, E, Psychedelic, N. Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. PLoS One. 2014;9(8):e106533.

Thomas G, Lucas, P, Capler, NR, Tupper, KW, Martin, G. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. Current Drug Abuse Reviews. 2013;6(1):30-42.

Tiffany ST, Carter, BL, Singleton, EG. Challenges in the manipulation, assessment and interpretation of craving relevant variables. Addiction (Abingdon, England). 2000;95(8):S177-S187.

Tomsovic M, Edwards, RV. Lysergide treatment of schizophrenic and nonschizophrenic alcoholics: a controlled evaluation. Quarterly Journal of Studies on Alcohol. 1970;31(4):932-949.

Tricklebank MD, Forler, C, Middlemiss, DN, Fozard, JR. Subtypes of the 5-HT receptor mediating the behavioural responses to 5-methoxy-N,N-dimethyltryptamine in the rat. European Journal of Pharmacology. 1985;117(1):15-24.

UK Home Office. List of most commonly encountered drugs currently controlled under the misuse of drugs legislation. In: Office H, editor.: UK Government; 2019.

Ullmer C, Schmuck, K, Kalkman, HO, Lübbert, H. Expression of serotonin receptor mRNAs in blood vessels. FEBS Letters. 1995;370(3):215-221.

United Nations. Final Act of the United Nations Conference for the Adoption of a Protocol on Psychotropic Substances. United Nations; 1971.

United Nations. UN World Drug Report 2020: United Nations Office on Drugs and Crime;; 2020 [Available from: https://wdr.unodc.org/wdr2020/.

Controlled Substances Act, (1970).

US Drug Enforcement Administration. Schedules of controlled substances: placement of 5-methoxy-N,N-dimethyltryptamine into Schedule I of the Controlled Substances Act. Final rule. In: Drug Enforcement Administration, editor. Federal Register2010. p. 79296-79300.

Uthaug MV, Lancelotta, R, van Oorsouw, K. A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of psychopathological symptoms. Psychopharmacology. 2019;236(9):2653-2666.

Uthaug MV, Lancelotta, R, Ortiz Bernal, AM, Davis, AK, Ramaekers, JG. A comparison of reactivation experiences following vaporization and intramuscular injection (IM) of synthetic 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting. Journal of Psychedelic Studies. 2020a;4(2):1-10.

Uthaug MV, Lancelotta, R, Szabo, A, Davis, AK, Riba, J, Ramaekers, JG. Prospective examination of synthetic 5-methoxy-N,N-dimethyltryptamine inhalation: effects on salivary IL-6, cortisol levels, affect, and non-judgment. Psychopharmacology. 2020b;237(3):773-785.

Wallach JV. Endogenous hallucinogens as ligands of the trace amine receptors: a possible role in sensory perception. Medical Hypotheses. 2009;72(1):91-94.

Watts R, Luoma, JB. The use of the psychological flexibility model to support psychedelic assisted therapy. Journal of Contextual Behavioral Science. 2020;15:92-102.

Watts R, Day, C, Krzanowski, J, Nutt, D, Carhart-Harris, R. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. Journal of Humanistic Psychology. 2017;57(5):520-564.

WHO. Global Status Report on Alcohol and Health 2018 Geneva, Switzerland: World Health Organization; 2018 [Available from: https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf?ua=1.

Williams, J. B. W. & Kobak, K. A. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). Brit J Psychiat 192, 52–58 (2008).

Worrell SD, Gould, TJ. Therapeutic potential of ketamine for alcohol use disorder. Neuroscience and Biobehavioral Reviews. 2021;126:573-589.

Younger J, Gandhi, V, Hubbard E, Mackey, S. Development of the Stanford Expectations of Treatment Scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. Clin Trials 9(6):767-76 (2012)

Yu A-M, Idle, J, Herraiz, T, Küpfer, A, Gonzalez, F. Screening for endogenous substrates reveals that CYP2D6 is a 5-methoxyindolethylamine O-demethylase. Pharmacogenetics. 2003;13(6):307-319.

14. APPENDICES

APPENDIX 1: PROHIBITED CONCOMITANT MEDICATIONS WITH BPL-003

This list of medications is **not all-inclusive**; if necessary, please contact the Medical Monitor for any questions regarding a medication(s).

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the administration of intranasal study medication until after the last dose of intranasal study medication.

Note in the following table: N, Prohibited; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

Drug Name or Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
ADHD medications (e.g., atomoxetine, guanfacine)	N	N		Safety
Anorexiants (e.g., phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	N	N	Subjects with seizures are excluded. Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine)	Safety and PD interaction
Antidepressants	N	N		Safety and PD interaction
Antipsychotics	N	N		PD interaction

Drug Name or Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam) and non-benzodiazepine sleeping medication (including zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of intranasal treatment session or cognition testing	Safety and PD interaction
Buspirone (Buspar)	N	N		PD interaction
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	N	N		Safety and PD interaction
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited)	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	N	Intranasally administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration. Pseudoephedrine-containing oral products should not be used within 12 hours prior to an intranasal treatment session.	Safety and PD interaction
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety

Drug Name or Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Ketanserin	N	N		Safety and PD interaction
Linezolid	N	N	Antibiotic with potential interaction	Safety and PK interaction
Lithium	N	N		PD interaction
Memantine	N	N		PD interaction
Methyldopa	N	N		Safety and PD interaction
Mirtazapine (Remeron)	N	N		
Monoamine oxidase-A (MAO-A) inhibitors	N	N	Examples are phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate), moclobemide	Safety (possible risk of serotonin syndrome)
Monoamine oxidase-B (MAO-B) inhibitors	N	N	Examples are selegiline, rasagiline (Azilect)	Safety (possible risk of serotonin syndrome)
Opioids	N	N		PD interaction
Psychostimulants (e.g., amphetamines, methylphenidate, and modafinil, armodafinil)	N	N		Cardiovascular safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction

Drug Name or Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Serotonin agonists	N	N	Drugs that are known serotonin agonists are excluded. Examples are: naronapride, serotonin, vortioxetine, mosapride, urapidil, dihydroergotamine, cabergoline, ziprasidone, flibanserin, rotigotine, cinitapride, brexpiprazole, cariprazine, fenfluramine, pergolide, bromocriptine, lorcaserin, cisapride, metergoline, asenapine, renzapride, aripiprazole, prucalopride	
Triptans	Y	N	Can be taken except around time of dosing	
St. John's Wort	N	N		PD interaction and PK
Substances that work as MAOIs	N	N	BPL-003 is metabolized by MAO; therefore, these drugs are not allowed as concomitant medications and need to be discontinued. Examples are MOAI antidepressants.	PK
Trazodone (Desyrel)	N	N		PD interaction (blockade of 5-HT_{2A})

Abbreviations: 5-HT_{2A} = serotonin receptor 2A; IM = intramuscular; IV = intravenous; MAO = monoamine oxidase, MAOI = monoamine oxidase inhibitor; N = prohibited; PD = pharmacodynamic; PK = pharmacokinetic; Y = permitted (with restrictions; please refer to column labeled Comments for additional guidance).

APPENDIX 2: READINESS FOR DISCHARGE QUESTIONNAIRE – 5-MEO-DMT

Concept:

- Brief assessment scale (checkbox exercise) that will be utilized after dosing with 5-MeO-DMT
- Assessment will be performed every 30 min starting 90 minutes after dose
- Will determine when patients can safely leave the office, patient will need to remain until 4 hours post dose even if discharge confirmed safe before that time.

Assessment:

This questionnaire will assess the readiness of the patients to be discharged from the supervisory care after a 5-MeO-DMT treatment. The healthcare provider will assess several characteristics that indicated that the psychedelic effects of 5-MeO-DMT have subsided to a level where further monitoring is not necessary anymore.

Clinical Assessment (most sensitive feature first):

The assessment will be performed by a study clinician and initially, all the assessments will have to be performed at every time point but after the investigator acknowledges that an item is fulfilled this will no longer need to be asked each time but can be completed based on previously confirmed answer.

Each question must be answered with YES in order to be able to discharge the patient safely from care. Once all items are checked as a YES the last question to confirm that the patient is ready for discharge can be completed and no further reviews every 30 minutes are required. If this occurs before 4 hours post dose the patient will remain until the completion of 4 hours waiting period before actually being discharged. If the patient is not ready to be discharged at 4 hours post dose the every 30 minute assessments will stop but a final questionnaire will be completed once the Investigator is satisfied that the patient is ready prior to discharge.

- The patient is fully responsive, aware of their surroundings, and reacts adequately
- The acute psychedelic effects of the drug have completely subsided
- The patient is fully orientated (name, location, time)
- Blood pressure and pulse rate have returned to normal or only slightly elevated levels. The breathing frequency and body temperature are normal

- The patient has a stable gate and normal muscle coordination and can walk safely
- Potential side effects are mild to moderate in intensity and do not need to be medically monitored
- The patient has no acute suicidal ideations or suicidal intentions
- Possible distress or feelings of being overwhelmed have sufficiently subsided to a degree that the patient themselves feel safe to be discharged

After all prior assessments have been answered with YES the final question can be completed. The last question cannot be ticked as yes until all the proceeding questions are yes.

- **In the opinion of the assessor, the patient is now safe to be discharged**

APPENDIX 3: FACTOR MEANS AND DESCRIPTIVE STATISTICS

Factor	Mean	Confid. -95.000%	Confid. +95.000%	Std.Dev.	Standard Error
COMP_SFR	2.622226	2.406279	2.838174	1.621456	.109568
XPCT_SFR	3.545983	3.382864	3.709103	1.224791	.082764
PURP_SFR	3.859695	3.618971	4.100419	1.807488	.122139
EMOT_SFR	3.754779	3.586491	3.923067	1.263598	.085386

Adapted from (Singleton, 1999).

APPENDIX 4: COGNITIVE BEHAVIOURAL RELAPSE PREVENTION INTERVENTION FOR ALCOHOL USE DISORDER

Patient cognitive behavioural relapse prevention intervention (RPI) will be conducted in line with manual devised by clinicians at Lambeth Addictions Consortium (centre) – a specialist community treatment clinic in the London Borough of Lambeth (operated by South London and Maudsley NHS Mental Health Foundation Trust). In the context of the centre's integrated care pathway for moderate–severe AUD, patients will be invited to receive a structured RPI.

The RPI will align with UK national clinical recommendations (National Institute for Health and Care Excellence 2011) (NICE) for the community/outpatient treatment of adults with moderate and severe alcohol dependence who have successfully completed withdrawal using adaptations of cognitive behavioural therapies. NICE recognises the origins of effective treatment for AUD in Marlatt and Gordon's model of relapse prevention (Marlatt, 2005) and Miller and Rollnick's Motivational Interviewing (Miller, 2002), and the broad international evidence-base that has been summarised in meta-analytic systematic reviews since.

The study RPI will be adapted to integrate with the single session of BPL-003 with the aim of enhancing treatment engagement and effectiveness. It will include the following structural features:

- An empathic (therapeutic alliance building) and change focussed style of communication to encourage self-efficacy
- Linked case management for service users who have had difficulty engaging in treatment or are at risk of dropping out;
- An individualised care plan, developed in collaboration with the service user (and relevant others), that includes a comprehensive assessment of personal needs and goals, and required inter-agency working;
- Collaborative assessment (case formulation) to develop and update a working hypothesis of how alcohol-related problems have been maintained; how they are attenuated and prevented (including a focus on high-risk drinking situations, alcohol-related cognitions, behaviours, and evaluations);
- Modification of maladaptive alcohol-related and general cognitions and beliefs (including cognitive restructuring/reconsolidation, and behavioural experiments to develop coping skills);
- Interventions for common mental health conditions comorbid with AUD (including depression and anxiety, following NICE guidelines)
- Facilitated support to engage in recovery activities (including self-help groups);

During the study, the RPI will be offered to patients as weekly individual (in person and/or via video) sessions with a trained AUD therapist. Following immediately after screening and informed consent, with all sessions including coping strategies (and other homework assignments) to be deployed outside the clinic, the RPI will be structured across the following 3 phases:

Stage 1: Assessment and care planning (Weeks -2 to -1)

Session 1: This session will include a focused clinical history of the development of AUD, the objective will be to build rapport, discuss any previous experience of treatment, previous coping strategies, general expectations for alcohol treatment, social supports and stressors, symptoms of anxiety and depression, and set out treatment goals in the context of the care plan (90 minutes).

Session 2: The objective of this session will be to produce a collaborative testable hypothesis of how the disorder has been maintained. A micro-formulation will be based on recent typical (and unusual) episodes of alcohol use and will include contexts, triggers, physical sensations, elaborated cognition (attention, mental images, beliefs, appraisals, coping strategies, problematic affective and behavioural responses, post-drinking evaluations and problems (together forming vicious cycles of AUD maintenance) (90 minutes).

Stage 2: Early treatment (Weeks 1 to 4)

Sessions 3 to 6: The objective of initial sessions in this stage will be to use (and update) the AUD formulation to cognitively restructure elaborated cognitions, emotions and appraisals, and any unwanted/maladaptive behavioural responses. A basic behavioural activation approach will be used to review and identify mood increasing activities to reinforce recovery. Each session will review the participant's cognitive control over alcohol-related approach (craving) thoughts and decision making. This stage of treatment will aim to support the participant build and deploy cognitive control skills for lapse and relapse prevention.

Stage 3: Middle treatment (Weeks 5 to 8)

Sessions 7 to 10: Building on earlier sessions – and incorporating the experience of exposure to BPL-003 – micro-formulations of high-risk situations, learning examples of virtuous cycles where intrusive/elaborated approach cognitions for drinking have been successfully managed, and shifts/growth in personal values and appraisals, and interpersonal relationships and functioning. With an emphasis on creating, implementing, and reviewing behavioural experiments that test and modify expectations and beliefs. In this stage (approximately Session 6) will include a review of symptoms and the therapeutic process, care plan, and goal attainment, and encouragement to experience self-help and other recovery supports.

Stage 4: Later treatment and blueprint (Weeks 9 to 12)

Sessions 11 to 14: The aim of the final stage of the RPI will be to consolidate treatment, with a review of the participant's decision making and coping with high-risk situations and any lapses. The participant's general and micro-formulations (with the expectation of a transition from vicious to virtuous cycles of cognitions, appraisals, behaviours, and evaluations) will be incorporated with and shifts/growth in personal values and appraisals that flow from the RPI and BPL-003. The final session will focus on the evaluation of treatment goals (including a blueprint summary of the therapy), along with a discussion of further/ongoing needs and continuing care medical and welfare referral.

APPENDIX 5: REACTIVATION QUESTIONNAIRE

Re-Activations Questionnaire (ReAQ)

Epidemiological data and anecdotal reports indicate that the use of 5-MeO-DMT is associated with the potential occurrence of a complex and not well understood phenomenon that has been termed "reactivation" (Ortiz Bernal et al, 2022).

Anecdotal reports online do seem to suggest that reactivations tend to occur mainly at night as people are drifting off to sleep, and generally tend to dissipate the longer the time has elapsed from the time they took 5-MeO-DMT.

In a broad sense, it appears that reactivations are experienced as transient but intense (Type 1 Hallucinogen Persisting Perception Disorder (HPPD)) and tend to subside days or weeks after 5-MeO-DMT use in most cases, as opposed to persisting over longer periods of time as is the case with HPPD Type 2.

More data is needed, therefore the ReActivation Questionnaire (ReAQ) was developed for study teams to measure the occurrence, context and emotional valence of potential reactivations. The questionnaire will be completed by the investigator or study team.

1. **Occurrence:**
   Since study drug dosing or last assessment of this scale (which ever occurred last), have you had a spontaneous re-experience or re-activation of a past study drug experience e.g., a flashback or a feeling as though your study drug experience is happening again?

   a. No (=> End of Assessment)
   b. Yes (=> Continue to questions below)

2. **Frequency:**
   a. When did the first re-experience or re-activation take place?
      Instruction for the assessor: please write down date (DDMMMYYYY) and how many days after the dosing day they first occurred

   b. How many re-experience or re-activation events have you had in total i.e., since study drug dosing?
      Instruction for the assessor: please write down the total number of events

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3. **Emotional Valence:**
Were the re-experience or re-activation events mostly *negative, neutral, or positive experiences?*

Instruction for the assessor: please check the appropriate box

- *Mostly positive* ☐
- *Neutral* ☐
- *Mostly negative* ☐

4. **Functional Impact**
Please rate the impact of the reactivation symptoms on the following domains (None, Mild, Moderate, Severe).

Instruction for the assessor: please check the appropriate box for each domain (a, b and c)

	None	Mild	Moderate	Severe
a. Work	☐	☐	☐	☐
b. Social Life	☐	☐	☐	☐
c. Family Life	☐	☐	☐	☐

5. **Narrative:**
Please provide more details on any re-activations or re-experiences e.g., how did they evolve, any comments on emotional valence?

Instruction for the assessor: please summarise the participant's narrative as free text (free text)

Ortiz Bernal, A. M., Raison, C. L., Lancelotta, R. L., & Davis, A. K. (2022, November 9). *Reactivations after 5-methoxy-N,N-dimethyltryptamine use in naturalistic settings: An initial exploratory analysis of the phenomenon's predictors and its emotional valence.*
Frontiers. https://doi.org/10.3389/fpsyt.2022.1049643