STUDY SYNOPSIS

Protocol Title:	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
Study Number:	BPL-003-201
Compound:	BPL-003
Clinical Phase:	Phase 2b
Investigator(s)/ Study Center(s):	This study will be conducted in approximately 40 study centers, located globally. Worldwide Clinical Trials (Worldwide), a contract research organization (CRO), will oversee operational aspects of this study on behalf of Beckley Psytech, Ltd. (BPL), the Sponsor of the study.

OBJECTIVES AND ENDPOINTS:

Objectives	Endpoints
CORE Primary	
To determine the efficacy of 12 mg of BPL-003 given with psychological support to participants with treatment-resistant depression (TRD)	Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) for 12 mg compared to 0.3 mg of BPL-003 at Day 29
CORE Secondary	
Key Secondary: To determine the efficacy, including early onset, of BPL-003 given with psychological support to participants with TRD	Change from baseline in MADRS for 12 mg compared to 0.3 mg of BPL-003 at Day 8 Change from baseline in MADRS for 8 mg compared to 0.3 mg of BPL-003 at Day 29 Change from baseline in MADRS for 8 mg compared to 0.3 mg of BPL-003 at Day 8
To determine the safety of 0.3 mg, 8 mg, or 12 mg of BPL-003 given with psychological support to participants with TRD	Number of events and percentage of participants with treatment -emergent adverse events (TEAEs)

	Percentage of participants with clinically significant abnormal laboratory tests compared to baseline Percentage of participants with clinically significant abnormal vital sign measurements (heart rate, blood pressure, and body temperature) compared to baseline Percentage of participants with clinically significant electrocardiogram (ECG) parameters compared to baseline Incidence of suicidal ideation or behavior, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) at Days 2, 8, 29, 43, and 57 compared to baseline Impairment in cognitive performance, assessed by Cognitive Test Battery at Days 8 and 29 compared to baseline The frequency, emotional valence and functional impact of any reactivation events in the study, by dose group, as assessed by the ReActivation Questionnaire (ReAQ)
To evaluate the pharmacokinetics (PK) of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) and its metabolites (including bufotenine) in participants with TRD after nasal administration of BPL-003	Plasma levels of 5-MeO-DMT and its metabolites (including bufotenine) up to 60 minutes after nasal administration of BPL-003
To determine the effects on depression and disability of 0.3 mg, 8 mg, or 12 mg of BPL-003 given with psychological support to participants with TRD	Change from baseline in MADRS for 8 mg and 12 mg of BPL-003 compared to 0.3 mg of BPL-003 at Days 2 and 57 Percentage of responders (defined as 50% reduction in MADRS total score) at Days 2, 8, 29, and 57 compared to baseline, by dose group Percentage of participants in remission (defined as MADRS total score $\leq$ 10) at Days 2, 8, 29, and 57 by dose group

	Change in 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) score at Days 2, 8, 29, and 57 compared to baseline, by dose group Change in Quality of Life in Depression Scale (QLDS) score at Days 2, 8, 29, and 57 compared to baseline, by dose group Change in Sheehan Disability Scale (SDS) total score at Days 29, and 57 compared to baseline, by dose group Change in Clinical Global Impression-Severity (CGI-S) score at Days 2, 8, 29, and 57 compared to baseline, by dose group
CORE Exploratory	
To explore the changes in sexual functioning, anxiety, anhedonia, cognition, and overall quality of life	Difference in sexual functioning, assessed by the Arizona Sexual Experiences Scale at Days 29 and 57 compared to baseline, by dose group Difference in anxiety, assessed by the 7-item Generalized Anxiety Disorder Assessment (GAD-7) at Days 29 and 57 compared to baseline, by dose group Difference in self-reported anhedonia symptoms, assessed by Snaith-Hamilton Pleasure Scale at Days 29 and 57 compared to baseline, by dose group Improvement or no change in cognition, assessed by the Cognitive Test Battery at Days 8, 29, and 57 compared to baseline, by dose group Patient Global Impression of Change at Days 2, 8, 29, and 57, by dose group Improvement in self-reported quality of life, assessed by EuroQoL- 5 Dimension-5 Level (EQ-5D-5L) at Day 29 and 57 compared to baseline, by dose group

To determine the correlation between mystical experience and treatment response and qualitatively characterize the BPL-003 psychedelic experience	30-item Mystical Experience Questionnaire (MEQ-30) sub-domain and total scores on Day 1 Correlation between MEQ-30 total score and changes in MADRS total score Proportion of participants reporting a complete mystical experience per the criteria of the MEQ-30 on Day 1 Ego Dissolution Inventory scores on Day 1 Psychological Insights Scale scores on Days 2, 15, and 29
To determine the abuse potential of BPL-003	Number of events and percentage of participants with TEAEs that may be indicative of abuse potential, by dose group
To determine the impact on healthcare utilization as a result of treatment	Difference in healthcare utilization, assessed by the Treatment Inventory of Costs in Patients (TiC-P) at the end of the study, by dose group
To determine participant expectations of treatment outcomes and the adequacy of the masking procedures	Pre-treatment participant expectancy, assessed by the Stanford Expectations of Treatment Scale (SETS) before the start of psychological support preparation, and its relationship to outcomes Adequacy of the blind, assessed by feedback from the participant, clinician, and rater using the Bang Blinding Index (BBI) to determine impression of treatment allocation on Day 2
Open Label Extension (OLE) Primary	
To determine the safety of a second dose of BPL-003 given with psychological support to participants with TRD	Number of events and percentage of participants with TEAEs Percentage of participants with clinically significant abnormal laboratory tests compared to OLE and CORE baseline Percentage of participants with clinically significant abnormal vital sign measurements (heart rate, blood pressure, and body

	temperature) compared to OLE and CORE baseline Percentage of participants with clinically significant ECG parameters compared to OLE and CORE baseline Incidence of suicidal ideation or behavior, as assessed by the C-SSRS compared to OLE and CORE baseline The frequency, emotional valence and functional impact of any reactivation events in the study, by dose group, as assessed by the ReActivation Questionnaire (ReAQ)
OLE Secondary	
To determine the efficacy of a second dose of BPL-003 given with psychological support to participants with TRD	Change in MADRS compared to OLE and CORE baseline Percentage of responders (defined as 50% reduction in MADRS total score) compared to OLE and CORE baseline Percentage of participants in remission (defined as MADRS total score ≤ 10) compared to OLE and CORE baseline
To evaluate the PK of 5-MeO-DMT and its metabolites (including bufotenine) in participants with TRD after nasal administration of BPL-003	Plasma levels of 5-MeO-DMT and its metabolites (including bufotenine) up to 60 minutes after nasal administration of BPL-003
To determine the effects of a second dose of BPL-003 on depression and disability, given with psychological support to participants with TRD	Change in QIDS-SR-16 score compared to OLE and CORE baseline Change in QLDS score compared to OLE and CORE baseline Change in SDS total score compared to OLE and CORE baseline Change in CGI-S score compared to OLE and CORE baseline
OLE Exploratory	

To explore the changes in sexual functioning, anxiety, anhedonia, cognition and overall quality of life after a second dose of BPL-003	Difference in sexual functioning, assessed by the Arizona Sexual Experiences Scale Difference in anxiety, assessed by the GAD-7 Difference in self-reported anhedonia symptoms, assessed by Snaith-Hamilton Pleasure Scale Patient Global Impression of Change at Days 2, 8, 29, 57, and 85, by dose group Improvement in self-reported quality of life, assessed by EuroQoL- 5 Dimension
To determine the correlation between mystical experience and treatment response and qualitatively characterize the psychedelic experience after a second dose of BPL-003	MEQ-30 sub-domain and total scores Correlation between MEQ-30 total score and changes in MADRS total score Proportion of participants reporting a complete mystical experience per the criteria of the MEQ-30 Ego Dissolution Inventory scores Psychological Insights Scale scores
To determine the abuse potential of a second dose of BPL-003	Number of events and percentage of participants with TEAEs that may be indicative of abuse potential
To determine the impact on healthcare utilization as a result of longer-term treatment	Difference in healthcare utilization, assessed by the TiC-P

Study Design:	Globally this Phase 2b study consists of a CORE and an optional Open label extension (OLE). The OLE is active in European and Australian sites and will now be offered to some US-based sites. The CORE is a randomized, quadruple masked (participant, therapists, investigator, and MADRS rater), multi-center study designed to investigate the efficacy and safety of BPL-003 combined with psychological support in patients with TRD not currently taking antidepressants. The OLE is designed to investigate the safety and efficacy during and after a second dose of BPL-003 combined with psychological support in patients with TRD not currently taking antidepressants. **CORE Study**

	A maximum of approximately 203 eligible participants will be randomized to 1 of 3 treatment arms initially with a 1:1:1 ratio which is modified to a ratio of 3:1:3 on protocol version 3.0 approval: 0.3 mg, 8 mg, or 12 mg of BPL-003, given intranasally as a single dose (administered as 1 nasal spray) on the Dosing Visit (Day 1). **Screening:** An informed consent form must be signed by participants before any study-related assessments are performed. Eligibility will be determined during the Screening Period (2 to 8 weeks [Days -56 to -15], before Dosing Visit, Day 1). Participants will also complete washout of any current antidepressants under supervision of a designated member of the study team (See Section 6.8, 6.9 and 7.2.2 of the protocol). The duration of the Washout Period will depend on the medication dose and label and will be guided by the investigator but is required to be complete at least 2 weeks prior to the Dosing Visit (Day 1). Participants will have at least weekly follow-up calls during the Washout Period. Disease diagnosis will be confirmed centrally by the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI) utilizing the SAFER Clinical Interview (SCI) and the Antidepressant Treatment Response Questionnaire (ATRQ). Other eligibility data will be reviewed and confirmed by the medical monitor and the Clinical Assessment Technologies (CAT) team who will issue approval of participant eligibility. **Psychedelic Preparation Visits:** Three Psychedelic Preparation Visits (PPVs) (Days -14, -7, and -3) are scheduled to be performed over approximately 2 weeks prior to the Dosing Visit (Day 1). Each PPV will last approximately 60 to 90 minutes. Additional PPVs may be performed, if required, but should be discussed with the medical monitor. PPVs on Days -14 and -3 will be performed in-clinic and the PPV at Day -7 may be performed remotely. During the PPVs, a therapeutic alliance will be established with the therapists and participants will receive advice on what to expect and how to respond to the psychedelic experience during the dosing session. **Dosing Visit (Day 1):** BPL-003 will be administered on the Dosing Visit (Day 1). Pre-dose assessments will be performed to ensure the participant is still eligible to continue in the study. The dosing session will be supported by a lead and an assistant therapist, who will provide psychological support as described further below. The physician and therapists should discuss any safety concerns participants may have before dosing.

	Participants will be dosed once they are relaxed and the study team has addressed any practical issues. Therapists will remain with the participant while they are in an altered state of consciousness, until the effects of the dosing have resolved. Site staff will be in the dosing room to conduct assessments and a physician will either be in attendance or close by for the duration of the dosing session. The physician should have a de-brief with therapists and participants, separately, at the end of the psychological support, to ensure any issues and potential adverse events are captured. After dosing, psychometric scales will be administered to provide quantitative measures of the participant's psychedelic experience. All participants will have their "readiness for discharge" assessed every 30 minutes starting 90 minutes after dosing. The earliest a participant can be discharged will be 4 hours after receiving the dose, at which point the investigator or psychiatrist will assess the participant's psychological wellbeing and will instruct participants that they may leave the site if is safe to do so. When released from the study site, participants should be accompanied by a responsible adult. Participants must not drive a car or work with machines post-dose on the Dosing Visit (Day 1). In cases where a participant has a challenging experience, an unexpectedly prolonged altered state of consciousness, or a significant worsening of depression the study sites should be prepared to keep them in overnight for monitoring. **Psychological Support During the Dosing Visit (Day 1):** Therapists will provide psychological support to participants during the Dosing Visit (Day 1) pre-dose, during dosing, and post-dose: • **Pre-dose:** Therapists will have a psychedelic preparation discussion with the participant, including a review of what will happen during dosing, review of intentions, short meditation, and check-in on how the participant is feeling. • **During dosing:** Therapists will provide emotional and physical support during dosing. Therapists will be supportive and non-directive, and not attempt to influence the participant's psychedelic experience. • **Post-dose:** Therapists will have a psychological support discussion, including a review and instructions of after-care, check in on how participants are feeling, reminder of integration process, reminder of scheduled Psychedelic Integration Visits (PIVs), and closing of the session.

	Psychedelic Integration Visits: Three PIVs (Days 2, 8, and 15) will be performed over approximately 2 weeks after the Dosing Visit (Day 1). Each PIV will last approximately 60 – 90 minutes. Additional PIVs may be performed, if required but should be discussed with the medical monitor. PIVs on Days 2 and 8 will be performed in-clinic and the PIV at Day 15 may be performed remotely. During PIVs, participants will discuss their experience on a one-to-one basis with the therapists. **Follow-up**: After the last PIV, participants will have Follow-Up Visits every 2 weeks for 6 weeks (Days 29, 43, and 57). Visits on Days 29 and 57 will be held in-clinic. The Day 43 Visit can be performed remotely via a video call. Withdrawn participants should come back to the clinic to complete the assessments as outlined at the final Follow-Up Visit (Day 57). **Optional OLE** Eligible participants will be randomized to 1 of 2 treatment arms in a 1:1 ratio: Monophasic dosing: 12 mg of BPL-003 given intranasally as a single dose (administered as 1 nasal spray) Biphasic dosing: 12 mg of BPL-003 given intranasally as a single dose (administered as 2 nasal sprays administered approximately 10 minutes apart [4 mg followed by 8 mg]) **Screening:** Participants that complete the last CORE study Follow-Up Visit (Visit [V] 11, Day 57) and have consented to the OLE will be assessed for their eligibility to proceed into the OLE. Day 57 of the CORE study will also be the first OLE Visit (V12, OLE Day -7). **Psychedelic Preparation Visits:** Two PPVs (OLE Days -7 and -3) will be performed over approximately 1 week prior to the Dosing Visit (OLE Day 1). Each PPV will last approximately 60 to 90 minutes. Additional PPVs may be performed, if required but should be discussed with the medical monitor. PPV on OLE Day -3 will be performed in-clinic and the PIV at OLE Day-7 may be performed remotely. During the PPVs, a therapeutic alliance will be re-established with the therapists and participants will be reminded what to expect and how to respond to the psychedelic experience during the dosing session. **Dosing Visit (Day 1), Psychological Support, and Psychedelic Integration Visits:**

	Requirements for the Dosing Visit (OLE Day 1), psychological support, and the 3 PIVs conducted over a 2-week period will be identical to that of the CORE study. **Follow-Up:** After the last PIV, participants will have Follow-Up Visits every 2 weeks for 6 weeks (OLE Days 29, 43, and 57). Visits on OLE Days 29 and 57 will be held in-clinic. The OLE Day 43 Visit can be performed remotely via a video call. Withdrawn participants should come back to the clinic to complete the assessments as outlined at the final Follow-Up Visit (OLE Day 57). **Psychological Support During the Dosing Visit (Day 1) CORE and OLE:** Enrolled participants will complete the PPVs, will receive psychological support during the Dosing Visit, and will complete PIVs with a lead therapist. The lead therapist will be assisted by an assistant therapist during the last PPV, on the Dosing Visit and the first PIV in both the CORE and OLE. More details of the psychological support is provided in the psychological support manual. Both lead and assistant therapists will be trained in accordance with the psychological support manual. The lead therapist will be licensed to practice independently, with acceptable professional credentials such as clinical or counseling psychologist (PhD or PsyD), psychiatrist or other physician (MD or DO), Master of Social Work (MSW), masters Licensed Clinical Professional Counselor (LCPC), or licensed Psychiatric Nurse Practitioner (Psychiatric NP). The assistant therapist will have a minimum of a bachelor's degree and at least 1 year of clinical experience in a licensed mental health care setting. For safeguarding, adherence, and quality assurance purposes, the dosing sessions will be video recorded. All PPVs and PIVs will be audio recorded only. A portion of these recordings will be reviewed for adherence and quality assurance purposes and if any issues arise that may be improved from a review of these sessions. **Duration of Participation CORE and OLE** Study participation during the CORE study will last a maximum of 16 weeks. This includes a Screening Period (maximum of 6 weeks), PPVs performed over approximately 2 weeks, a Dosing Visit at Day 1, PIVs performed over approximately 2 weeks, and a Follow-Up Period (performed over approximately 6 weeks) consisting of in-clinic visits and video calls.

	OLE participation will last approximately 9 weeks. This includes a Screening Visit (V11, Day 57), PPVs performed over 1 week, a Dosing Visit at Day 1, PIVs performed over approximately 2 weeks, and a Follow-up Period (performed over approximately 6 weeks) consisting of in-clinic visits and video calls.
Duration of Treatment:	CORE: BPL-003 will be given intranasally as a single dose (administered as 1 nasal spray) on the Dosing Visit (Day 1). Optional OLE: BPL-003 will be given intranasally as a single dose, either administered as 1 nasal spray (monophasic dosing) or as 2 nasal sprays (biphasic dosing) approximately 10 minutes apart on the Dosing Visit (Day 1).
Planned Sample Size and Treatment Group(s):	CORE: The planned sample size is approximately 173 participants (64 in the 0.3 mg and 12 mg arms and 45 in the 8 mg arm. This assumes an initial randomization ratio of 1:1:1, which is modified to 3:1:3 (0.3 mg: 8 mg: 12 mg), effective on protocol version 3.0 approval. Assuming a 15% drop out rate, this equates to a total of approximately 203 participants randomized into the study. Participants will be stratified by country or region (dependent on projected enrollment into the study). OLE: Approximately 138 participants (69/arm), assuming an 80% roll over rate from the participants that complete the CORE. Participants will be stratified by CORE treatment.
Target Population:	The participant population will include males and females who are 18 to 75 years of age, diagnosed with TRD.
CORE Study Eligibility:	**Inclusion Criteria** 1. Willing and able to give informed consent, with written informed consent available before any study assessments. 2. Male and female participants, age 18 to 75 years at the time of informed consent. 3. At least moderate major depressive disorder (MDD), (single or recurrent episode as informed by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] criteria; if single episode, duration of ≥3 months and ≤ 2 years) based on medical records, clinical assessment, and

	documented completion of the version 7.0.2 Mini International Neuropsychiatric Interview (MINI). • For clarification, if recurrent MDD, there is no limit on episode duration 4. Diagnosed with TRD defined as failure to respond to an adequate dose and duration of at least 2 pharmacological treatments, in the current episode, based on the MGH ATRQ assessment. Augmentation with an add-on treatment counts as a second treatment. Participants must not have failed more than 5 prior pharmacological treatments in the current episode (psychotherapy is not counted towards treatment failure). • For clarification, pharmacological treatments initially effective but subsequently ineffective (tachyphylaxis) will be considered treatment failures if they fulfil the ATRQ criteria for dose and duration of failure. 5. Hamilton Depression Rating Scale (HDRS) (17 item) score ≥19 at Screening (Visit 1) and baseline (Day -3). 6. CGI-S ≥4 at Screening and baseline (Day -3). 7. If currently taking antidepressant medications, willing and able to discontinue current antidepressants including selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and any augmentation medication such as antipsychotics or lithium. Withdrawal will follow local treatment guidelines and should aim to avoid withdrawal symptoms by gradually reducing the antidepressant treatment dose (see Section 7.2.2). 8. Able (in the investigator's opinion) and willing to undertake and comply with all study requirements, including ability to complete all protocol required assessment tools and to comply with all study visits in language used by study site. 9. Willing to abstain from alcohol for 48 hours before Day 1. 10. Willing to abstain from recreational drugs from Screening until the end of the study. Intermittent use of cannabinoids prior to Screening is not exclusionary as long as the participant does not meet the criteria for substance use disorder, as assessed using the DSM-5.

	11. Willing to allow their own general practitioner, and consultant if appropriate, to be informed of study participation. **Exclusion Criteria** 1. Use of cannabinoids is not allowed for the duration of the study. Participants should not be administered the study drug if they have a positive urine drug screen for cannabinoids pre-dose on Day 1 (retesting is allowed if there is a suspected false positive test). 2. Current or past history of schizophrenia, post-traumatic stress disorder, psychotic disorder including psychotic depression, bipolar disorder, delusional disorder, schizoaffective disorder, or any other severe psychiatric disorder as assessed by medical history and a structured clinical interview (MINI). 3. Current personality disorders: Cluster A (paranoid, schizoid, schizotypal), Cluster B (antisocial, borderline, histrionic, narcissistic), or Cluster C (avoidant, dependent, -obsessive compulsive) assessed via McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD), MINI, and clinical judgement. 4. First-degree family history of schizophrenia, bipolar disorder, delusional disorder, or schizoaffective disorder. 5. Current (within the last year) alcohol or substance use disorder (other than caffeine or nicotine) according to DSM-5 and assessed by the MINI at Screening in the opinion of the investigator will be a safety concern for enrollment in the study or that could interfere with the therapeutic process or with other aspects of study participation. Any participant who is not able to agree or adhere to a plan to reduce and manage use will be excluded. 6. A participant who at any time has been unresponsive to ketamine or esketamine, unresponsive to an adequate course of treatment with electroconvulsive therapy (ECT) defined as at least 7 treatments with unilateral/bilateral ECT, or has received vagal nerve stimulation or has received deep brain stimulation.

	7. Currently receiving prohibited medications or therapy (See Section 6.9 of the protocol and Appendix 14.2 of the protocol). 8. Suicidal ideation with some intent to act within 12 months prior to the start of Screening, per the investigator's clinical judgement or based on the 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 any suicidal behavior within the 12 months prior to the start of Screening. Participants reporting suicidal ideation with intent to act or suicidal behavior as assessed on Day 1 should be excluded. 9. Suicide attempt and/or self-injurious behavior within the last 12 months prior to Screening. 10. Depression is secondary to other severe medical conditions according to the investigator's opinion. 11. Other personal circumstances and behavior judged to be incompatible with establishment of rapport or safe exposure to the study medication. 12. Any other clinically significant psychiatric condition that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study. **General Medical Exclusion Criteria:** 13. Participants with a history of any medical condition that could make receiving a sympathomimetic drug harmful because of transient and marked increases in blood pressure and heart rate. This includes, but is not limited to, atherosclerotic cardiovascular disease, obstructive coronary artery disease, myocardial infarction, hospitalization for unstable angina, stroke, hospitalization for transient ischemic attacks, known aortic or cerebral aneurysm or revascularization procedure within 12 months prior to Screening, significant valvular heart disease, hospitalization for heart failure, hospitalization for atrial or ventricular arrhythmias.

	14. Participant with other mild, stable chronic medical problems should be excluded if in the opinion of the investigator would significantly increase the risks related to the administration of the study medication or be likely to produce significant symptoms during the study that could interfere with study participation or be confused with side effects of the study medication. 15. History of uncontrolled hypertension despite adequate therapy or any past history of a hospital admission for hypertension. Participants with controlled hypertension, who have been successfully treated with antihypertensive medicines are excluded if repeated clinic seated or semi-recumbent systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 80 mmHg. Participants without a diagnosis of hypertension are excluded if repeated clinic seated or semi-recumbent systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Antihypertensive medication regimen adjustments during the Screening to assess blood pressure control is allowable, but participants must be on a stable anti-hypertensive regimen for at least 2 weeks before randomization. Blood pressure eligibility should be assessed during Screening and predose on Day 1 16. Uncontrolled medical conditions hypo/hyperthyroidism with abnormal thyroid stimulating hormone values, uncontrolled or insulin dependent diabetes with HbA1c >8, renal failure with Creatinine Clearance <45 mL/min as judged by the investigator to significantly increase the risk of harm from exposure to the study medication by any mechanism would exclude a participant. 17. Seizure disorder or any seizure in the 2 years prior to Screening. 18. Any other clinically significant, neurological, 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 the participant if he/she takes part in the study.

	19. Has clinically significant results on ECG or a QT interval corrected using Fridericia's formula (QTcF) ≥450 msec for males or ≥470 msec for females during the Screening Period. 20. History of intolerance to 5-MeO-DMT or related compounds. 21. Any nasal obstruction, blockage, or symptoms of congestion at the time of dosing that in the investigator's opinion may interfere with the administration of the study medication. 22. Female participants who are pregnant, lactating, or of childbearing potential and not willing to use adequate forms of contraception during the study (See Section 6.9.1 of the study protocol). 23. Male participants who are sexually active and not willing to use adequate forms of contraception during the study (See Section 6.9.1 of the study protocol). 24. Participants who have participated in an interventional clinical research study within the last 8 weeks prior to Screening, regardless of not receiving a study medication. 25. Participants who, in the opinion of the investigator, are not suitable to participate in the study for any other reason not mentioned in the eligibility criteria. 26. Participants that have a conflict of interest, such as links to the Sponsor, Investigator or site. 27. Participants that are housed in an institution by court or official order. 28. Participants with a personal or family history of malignant hyperthermia.
OLE Study Eligibility	**Inclusion Criteria** 1. Participants who complete the CORE study. 2. Willing and able to give informed consent for the OLE. 3. Willing to abstain from alcohol for 48 hours before OLE Day 1. 4. Willing to abstain from recreational drugs throughout the duration of the study.

	Exclusion Criteria 1. Currently taking antidepressant medication. 2. Currently taking any other prohibited medication. 3. Participants who, in the opinion of the investigator, are not suitable to participate in the OLE. 4. Participants who met the Subject Dosing Stopping Criteria in the CORE. 5. Participants with controlled hypertension, who have been successfully treated with anti-hypertensive medicines, excluded if repeated clinic seated or semi-recumbent systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 80 mmHg. Participants without a diagnosis of hypertension excluded if repeated clinic seated or semi-recumbent systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Blood pressure eligibility should be assessed during Screening and predose on Day 1. 6. Participants where the CORE dose was not well tolerated.
Study Medication(s):	BPL-003 is a benzoate salt formulation of 5-MeO-DMT. All eligible enrolled participants will receive BPL-003, with the 0.3 mg (potentially subperceptual) dose serving as the comparator. BPL-003 will be administered intranasally by a trained member of the research team using an Aptar Pharma Unidose dry powder delivery system. Each dose will be pre-loaded into the delivery device by the manufacturer. CORE: 0.3 mg, 8 mg, and 12 mg of BPL-003, given intranasally as a single dose (administered as 1 nasal spray) on the Dosing Visit (Day 1). Selection of the 3 dose levels was based upon the safety, tolerability, PK, and subjective psychedelic experience data from the Phase 1 single ascending dose study (BPL-003-103): • 0.3 mg of BPL-003 (Potentially subperceptual dose) • 8 mg of BPL-003 (Intermediate dose)

	• 12 mg of BPL-003 (Highest well-tolerated dose with no serious adverse events) OLE: Eligible participants will be randomized to 1 of 2 treatment arms in a 1:1 ratio: Monophasic dosing: 12 mg of BPL-003 given intranasally as a single dose (administered as 1 nasal spray) Biphasic dosing: 12 mg of BPL-003 given intranasally as a single dose (administered as 2 nasal sprays administered approximately 10 minutes apart [4 mg followed by 8 mg])
Statistical Procedures:	For this primary analysis, a sample size of 64 participants for the primary comparison dose groups will provide 80% power at alpha = 0.05 level to detect a 6-point difference in average MADRS total score between 12 mg and 0.3 mg of BPL-003, assuming the common standard deviation (SD) is 12.0. Allowing for up to 15% drop out, a total of 203 participants (75 for the 0.3 mg and 12 mg arms and 53 for the 8 mg arm) will be randomized to 1 of 3 treatment arms initially with a 1:1:1 ratio which is modified to a 3:1:3 ratio (0.3 mg: 8 mg: 12 mg) upon approval of protocol version 3.0. The primary efficacy analysis will be performed on the change in MADRS from CORE baseline to Day 29 and will be assessed using a Mixed Model for Repeated Measures, with treatment, time, and the interaction of treatment with time as fixed effects, participant as random effect, and CORE baseline MADRS as a covariate. The least squares means differences between active treatment with comparator dose group will be presented along with a 95% confidence interval. The treatment comparisons for the primary efficacy analysis is 12 mg compared to 0.3 mg of BPL-003 at Day 29. The same analysis will be repeated for key secondary endpoints between 12 mg compared to 0.3 mg of BPL-003 at Day 8, 8 mg compared to 0.3 mg of BPL-003 at Day 29, and 8 mg compared to 0.3 mg of BPL-003 at Day 8. To control family-wise type 1 error, a fixed closed test procedure will be used for hypothesis testing. First, the 12 mg dose group will be compared with the 0.3 mg dose group at Day 29. Only if this comparison is statistically significant at the 2-sided 5% level will the key secondaries be tested in a hierarchical manner (12 mg dose group at Day 8, then 8 mg dose group at Day 29, then 8 mg dose group at Day 8).
