1. GENERAL INFORMATION

Clinical Study Protocol:

A Phase I/IIa, Randomized, Double-Blind, Placebo-Controlled Study with an Open -Label Relative Bioavailability Cohort to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of CYB003 in Healthy Participants with and without Major Depressive Disorder (MDD)

Sponsor: Cybin IRL Limited
One Spencer Dock
North Wall Quay
Dublin 1 D01 X9R7

Sponsor Contacts: Angela Sorie
Sr. Director, Clinical Programs
E-mail: angela@cybin.com
Tel: 1-866-292-4601, x749

Amir Inamdar, MBBS, DNB (Psych), MFPM
Chief Medical Officer
E-mail: amir@cybin.com
Tel: +44 7796 198 857

CRO Contact:
Ronni Spanola
Director, Phase 1 Services
Clinilabs Drug Development Corporation
4 Industrial Way West, 2nd Floor
Eatontown, NJ 07724 USA
E-mail: rspanola@clinilabs.com
Tel: 646-215-6427

Confidentiality Statement
The confidential information in this document is provided to you as a Principal Investigator or consultant for review by you, your staff and the applicable Institutional Review Board / Independent Ethics Committee . Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Revision History:

Protocol Section	Description of Change
Summary of Change from Version 1.0 to Version 2.0	
Section 3. Protocol Synopsis (page 7) and Section 8.2 (page 36)	*The following sentence was added to address FDA requirement:* A licensed physician will be on call and able to reach the clinical site within 15 minutes on study drug dosing Days 1 and 22 in the event of a physiological or psychiatric emergency. The physician should be available at least until 4 hours after all vital signs and mental status/neurological effects return to baseline.
Section 3. Protocol Synopsis (page 7) and new Section 8.2.6. (page 41)	*To address FDA requirements with respect to the professional credentials, training and experience of psychotherapy session facilitators, the following text was added to the Protocol Synopsis (new language in bold):* During these sessions, participants will be paired with two facilitators who will have completed specialized training in EMBARK for MDD; one or both facilitators will be a licensed psychotherapist. **Specific professional qualifications and requirements of the lead facilitator and second facilitator are described in Section 8.2.6.** *In addition, a new Section 8.2.6 was created which reads:* **8.2.6 Psychotherapy Session Facilitators and On Call Physician** In consideration of this study evaluating an investigational psychedelic medicine and to address FDA requirements with respect to the professional credentials, training and experience of facilitators, the following requirements will be adhered to in this study for psychotherapy session facilitators. The lead facilitator must be a licensed healthcare provider with professional training and clinical experience in psychotherapy and must be licensed to practice independently. Acceptable professional credentials are limited to the following: 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 second facilitator must have a bachelor's degree and at least one year of clinical experience in a licensed mental health care setting. Additionally, a licensed physician must be on call and able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency during Day 1 and Day 22 dosing sessions. The physician should be available at least until 4 hours after all vital signs and mental status/neurological effects return to baseline.
Section 3. Protocol Synopsis (page 10) and Section 8.3.2 (page 44)	*Exclusion criterion 11 had inconsistent language between the two sections, with the synopsis incorrectly referring to a family history of schizophrenia or schizoaffective disorder in first or second degree relatives. In Section 8.3.2, only first degree relatives were to be excluded. This exclusion criterion was made consistent in both sections and now reads:* 11. A family history of schizophrenia or schizoaffective disorder (first degree relatives), or bipolar disorder type 1 (first degree relatives).
Section 6.3, CYB003 Investigational Product, last sentence (page 26)	*This sentence previously read:* Bulk CYB003 API bottles will be stored at -20°C. *This sentence was changed and now reads:* Bulk CYB003 API bottles will be stored at 2-8°C.
Note that Protocol Version 2.0 was internally approved at Cybin but was not distributed to the site or IRB.	

<table>
<tr><th>Protocol Section</th><th>Description of Change</th></tr>
<tr><td colspan="2">Summary of Change from Version 2.0 to Version 3.0</td></tr>
<tr><td>Section 3. Protocol Synopsis, page 8</td><td>The following sentence was added to the synopsis:
The proposed Day 1 and Day 22 dose escalations and fed or fasted dosing conditions for study drug are presented in Table 8-1.</td></tr>
<tr><td>Section 8.2, Study Design (pages 36 and 37)</td><td>On page 37, Figure 8-1 was deleted and replaced with the following table:
Table 8-1: Proposed Dose Escalation Scheme
<table>
<tr><th>Cohort</th><th>Day 1 Dose (mg)</th><th>Day 1 Fed/Fasted</th><th>Day 22 Dose (mg)</th><th>Highest Day 22 Dose (mg)</th><th>Day 22 Fed/Fasted</th></tr>
<tr><td>1</td><td>1</td><td>Fasted</td><td>2</td><td>3</td><td>Fasted</td></tr>
<tr><td>2</td><td>4</td><td>Fasted</td><td>6</td><td>8</td><td>Fed*</td></tr>
<tr><td>3</td><td>9</td><td>Fasted</td><td>9</td><td>9</td><td>Fasted</td></tr>
<tr><td>4</td><td>12</td><td>Fasted</td><td>12</td><td>12</td><td>Fasted</td></tr>
<tr><td>5</td><td>14</td><td>Fasted</td><td>16</td><td>18</td><td>Fasted</td></tr>
<tr><td>6</td><td>20</td><td>Fasted</td><td>22</td><td>24</td><td>Fasted</td></tr>
</table>
* To be confirmed, based on PK profile for preceding dose levels

On page 36, reference is made to the above table (and reference to Figure 8-1 was deleted):
Contingent on this review, it is proposed to test another dose level in the second period of these cohorts, as presented in the dose escalation Table 8-1.</td></tr>
<tr><td colspan="2">Summary of Change from Version 3.0 to Version 4.0</td></tr>
<tr><td>Title page 1, Section 3 Protocol Synopsis page 7, Section 15, page 73</td><td>Since the protocol is being amended to include multiple sites and investigators, reference to the single Clinilabs Principal Investigator was removed and the Investigator statement page was modified to allow multiple investigators (sites) to be listed and to sign.</td></tr>
<tr><td>Table 4-1 Schedule of Assessments</td><td>Footnote 17 was added to specify that C-SSRS SLV can be administered remotely on D10, D17, D31 and D38 visits (MADRS and C-SSRS SLV are the only scheduled procedures in Table 4-1 on these visit days and both can be conducted remotely).</td></tr>
<tr><td>Table 4-1 Schedule of Assessments</td><td>Footnote 18 (formerly Footnote 17) was modified to include 6 hour ECG assessment and Footnote 18 was deleted per Protocol Note to File #1.
[18] 12-lead safety ECGs will be printed in triplicates from the Holter device with 5 minutes between each recording. ECGs will be obtained after participants have rested in the supine position for at least 10 minutes at the following time points on Day 1 and Day 22: 3 time points prior to dosing (-45, -30 and-15 minutes) and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours, immediately before the PK sample. When ECG recordings coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in said order.</td></tr>
<tr><td>Table 4-1 Schedule of Assessments</td><td>Holter footnote 19 was modified to allow a ± 10 minutes time window as stated below:
[19] 12-lead Holter data will be collected for 6 hours (± 10 minutes) on Day -1 to establish a baseline; and from 1 hour predose until 12 hours (± 10 minutes) postdose on Day 1 and Day 22.</td></tr>
</table>

Protocol Section	Description of Change
Table 4-1 Schedule of Assessments	TSH test was added at Screening (Day -28 to -2) and Day 42 per Protocol Note to File #3.
Table 4-1 Schedule of Assessments	Vital signs D1 footnote 8 was incorrect, it was corrected to be footnote 7.
Table 4-2 Preparatory and Integration Psychotherapy Sessions, and Sections 9.2, 9.3 and 9.4	Footnote 3 was added to allow for remote/telemedicine visits as an option on certain session days: [3] All psychotherapy visits (preparatory & integration) are preferred in person but for the D-9, D10, D31 and D38 sessions, psychotherapy session facilitators have the option to conduct these sessions as remote/telemedicine visits. Text was also added to Section 9.2, 9.3 and 9.4 indicating this option.
Section 6.4, CYB003 non-clinical data	Updates were made to the dog toxicology study results based on feedback received by FDA for this study.
Section 8.2, Study Design	Dose escalation language was modified per Protocol Note to File #4 to allow for more flexible dose escalation within a cohort relative to recruitment of participants.
Inclusion criterion 4, Synopsis and Section 8.3.1	Upper age range was extended from 55 to 65 years of age.
Inclusion criterion 9, Synopsis and Section 8.3.1	Inclusion criterion 9 was removed.
Exclusion criterion 9, Synopsis and Section 8.3.2	Exclusion criterion 9 was modified to allow TSH to be repeated once at Screening to confirm thyroid function is normal before randomizing a participant.
Exclusion criterion 22, Synopsis and Section 8.3.2	Current exclusion criteria states that the participant must test negative for cannabinoids on Day -1 and Day 20. The check in day for the second dose is Day 21 so this should read that they must test negative on Day -1 and Day 21.
Exclusion criterion 27, Synopsis and Section 8.3.1 and Section 12, Concomitant Medications	Antianxiety medications (except for buspirone) are allowed during the study except no dose can be taken at least 12 hours before a study drug dose. Preexposure prophylaxis (PrEP) medication for prevention of HIV infection, such as TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) or DESCOVY® (emtricitabine and tenofovir alafenamide), is allowed.

<table>
<tr><th>Protocol Section</th><th>Description of Change</th></tr>
<tr><td>Section 9.5, End of Treatment (Day 42)</td><td>Current wording: “For participants who discontinue prematurely, this visit should be performed as an early treatment visit and all assessments should be performed to the extent feasible.” Early treatment visit was changed to early termination visit.</td></tr>
<tr><td>Section 11.1.4.6 Potential Abuse-Related Adverse Events and Section 13.9 Safety Analyses</td><td>New Section 11.1.4.6 was added per FDA Guidance 2017 regarding abuse-related AEs and listing potential abuse-related AE categories and preferred terms. Guidance was added as a reference and statistical analysis text was added.</td></tr>
<tr><td colspan="2">Summary of Change from Version 4.0 to Version 5.0</td></tr>
<tr><td>Title page and protocol synopsis title</td><td>Title of study was amended to allow healthy participants <u>with</u> and <u>without</u> major depressive disorder (MDD) (i.e., addition of normal healthy volunteers at CYB003 doses expected to have sub-therapeutic psychedelic effects). In addition, an open-label cohort was added to evaluate the relative bioavailability of the CYB003 powder in solution compared to CYB003 powder-filled capsules and to assess the effect of food on CYB003 absorption.</td></tr>
<tr><td>Protocol Synopsis</td><td>Protocol synopsis was updated to include healthy participants with and without MDD.
Cohorts 1-6 were revised and an open-label relative bioavailability cohort was added for 8 NHV participants to be evaluated for a crossover fed:fasted evaluation of the oral powder in capsule study medication and also to compare the oral powder in solution study medication with a powder-filled capsule for relative bioavailability. Eight NHV participants will receive doses of the oral powder in solution orange drink and of the powder-filled capsule on Day 1 and Day 8, in a random crossover manner. A third dose of CYB003 will be administered on Day 15 to evaluate effect of food. Dose will be determined based on previous cohorts available data. Dosing scheme is illustrated below and will be broken out separately from Cohorts 1-6 in a separate table.
<table>
<tr><th>Sequence</th><th>Dose 1</th><th></th><th>Dose 2</th><th></th><th>Dose 3</th></tr>
<tr><td>1</td><td>4 HV participants, CYB003 powder in solution, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fed</td></tr>
<tr><td>2</td><td>4 HV participants, CYB003 powder-filled capsules, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder in solution, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fed</td></tr>
</table>
Study objective language was updated in the synopsis and body of the protocol to describe which objectives are relevant to both participant populations and only the MDD participants.
An exploratory study objective was added to assess the relative bioavailability of the oral powder in solution with the powder-filled capsule and to evaluate the effect of food on absorption.</td></tr>
<tr><td>Figure 4-1, Figure 4-2 and Figure 4-3 Study Schematics</td><td>Double-Blind Cohorts 1-6: Figure 4-1 was modified to be specific to healthy participants with MDD (MDD participants) and Figure 4-2 was added to be specific to healthy participants without MDD (normal healthy volunteers or NHV participants).
Open-Label Cohort: Figure 4-3 was added for the relative bioavailability / food effect cohort of NHV participants.</td></tr>
</table>

Protocol Section	Description of Change
Table 4-1, Table 4-3, and Table 4-4 Schedules of Procedures	Double-Blind Cohorts 1-6: Table 4-1 was modified to be specific to MDD participants and Table 4-3 was created to specify study procedures for NHV participants. PK sampling for MDD participants eliminated the 0.5 and 2 hour PK time points for CYB003 plasma concentration determination to minimize the blood draws during the medicine session. These PK samples were kept for the NHV participants. This change was incorporated in other relevant sections in the protocol. Open-Label Cohort: Table 4-4 was added for the relative bioavailability / food effect cohort.
Psychotherapy Sessions for MDD Participants	Table 4-2 title was modified to specify that this table pertains to MDD participants Footnote 1 was revised with the last sentence modified to read: Additional preparatory psychotherapy sessions and integration sessions may be performed at the discretion of the facilitator in coordination with the Investigator and research staff. Footnote 3 was revised to allow for more flexibility for remote/telemedicine visits as an option on certain session days at the Investigator's discretion: [3] All psychotherapy visits (preparatory & integration) are preferred in person, but psychotherapy session facilitators have the option to conduct any two of the three preparatory sessions and all of the integration sessions as remote/telemedicine visits. This language was also revised where applicable in other sections throughout the protocol.
Preparation, Medicine, and Debrief Sessions for NHV participants	For NHV participants, it was specified that they would have at least one predose preparation session, a medicine session during dosing day, and at least one debrief session following each study medication dose. The predose preparation sessions and debrief sessions can be done remotely. Additional preparatory sessions or debrief sessions may be conducted by study facilitators at the Investigator's discretion.
Number of Participants and planned cohorts	The number of participants was increased to up to 64 participants, including up to 48 MDD participants and 16 NHV participants. Individual cohorts 1-6 and the relative bioavailability / food effect cohort were specified.
Inclusion Criteria	Inclusion criteria were modified to break out which inclusion criteria applied to MDD participants, NHV participants, or both groups of participants; in addition, smokers are now allowed to participate in the study
Exclusion Criteria	Exclusion criteria were modified to break out which exclusion criteria applied to MDD participants, NHV participants, or both groups of participants. Allowable concomitant medications for both groups of participants were specified.
Study Medication Dosing and Clinical Assessments	Study procedures throughout the amended protocol were revised and clarified as to which procedures will be performed for MDD participants or NHV participants or both groups. Dosing language for the cohorts was updated, including language for the relative bioavailability cohort throughout the protocol.

<table>
<tr><th>Protocol Section</th><th>Description of Change</th></tr>
<tr><td>Table 8-1 Dose Escalation Scheme Table Revised</td><td>
Table 8-1: Proposed Dose Escalation Scheme for Cohorts 1-6
<table>
<tr><th>Cohort</th><th>Day 1 Dose (mg)</th><th>Day 1 Fed/Fasted</th><th>Day 8 or Day 22 Dose (mg)</th><th>Highest Day 8 or Day 22 Dose (mg)</th><th>Day 8 or Day 22 Fed/Fasted</th></tr>
<tr><td>1</td><td>1</td><td>Fasted</td><td>1</td><td>1</td><td>Fasted</td></tr>
<tr><td>2</td><td>3</td><td>Fasted</td><td>6</td><td>8</td><td>Fasted</td></tr>
<tr><td>3</td><td>9</td><td>Fasted</td><td>9</td><td>9</td><td>Fasted</td></tr>
<tr><td>4</td><td>12</td><td>Fasted</td><td>12</td><td>12</td><td>Fasted</td></tr>
<tr><td>5</td><td>14</td><td>Fasted</td><td>14</td><td>14</td><td>Fasted</td></tr>
<tr><td>6</td><td>16</td><td>Fasted</td><td>16</td><td>16</td><td>Fasted</td></tr>
</table>
Dose levels >12 mg are pending FDA review.
Note: Study participants who have received Day 1 dose may receive the same dose level on Day 8 or Day 22 dose if agreed upon by the Investigator and Sponsor to allow for flexibility and more time with respect to recruitment of a sufficient number of participants at the Day 1 dose level.
</td></tr>
<tr><td>Table 8-2 Estimated Number and Type of Participants by Cohort and Proposed Dose added</td><td>
Table 8-2: Estimated Number and Type of Participants by Cohort and Proposed Dose
<table>
<tr><th>Cohort</th><th>Cohort size</th><th>Additional enrolled after soft lock</th><th>Potential CYB003 doses (mg)</th></tr>
<tr><td>1</td><td>4 MDD</td><td>0</td><td>1</td></tr>
<tr><td>2</td><td>4 NHVs</td><td>0</td><td>3 and 6</td></tr>
<tr><td>3</td><td>4 NHVs or 8 MDD</td><td>0</td><td>9</td></tr>
<tr><td>4</td><td>8 MDD</td><td>4</td><td>12</td></tr>
<tr><td>Relative BA/Food Effect</td><td>8 NHV</td><td>0</td><td>≤12</td></tr>
<tr><td>5</td><td>8 MDD</td><td>4</td><td>14*</td></tr>
<tr><td>6</td><td>8 MDD</td><td>4</td><td>16*</td></tr>
</table>
* Pending FDA review
</td></tr>
<tr><td>Table 8-3 Proposed Dosing Scheme for Relative Bioavailability / Food Effect Cohort added</td><td>
Table 8-3: Proposed Dosing Scheme for Relative Bioavailability/Food Effect Cohort
<table>
<tr><th>Sequence</th><th>Dose 1</th><th></th><th>Dose 2</th><th></th><th>Dose 3</th></tr>
<tr><td>1</td><td>4 HV participants, CYB003 powder in solution, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fed</td></tr>
<tr><td>2</td><td>4 HV participants, CYB003 powder-filled capsules, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder in solution, fasted</td><td>⇨</td><td>4 HV participants, CYB003 powder-filled capsules, fed</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th></tr>
<tr><td colspan="2">Summary of Change from Version 5.0 to Version 6.0</td></tr>
<tr><td>Inclusion criterion 8 in Section 3. Protocol Synopsis and Section 8.3.1.</td><td>Wording clarified:Participants of non-childbearing potential who are or were capable of producing eggs (ova) must be postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy or bilateral oophorectomy;</td></tr>
<tr><td>Exclusion criterion 4 added in Section 3. Protocol Synopsis and Section 8.3.2.</td><td>Exclusion criterion 4 added and applies to MDD and NHV participants:
Clinically relevant abnormal results for heart rate (resting supine heart rate >100 bpm) or blood pressure (resting supine systolic blood pressure (BP) above 145 mmHg) at screening.</td></tr>
<tr><td>Section 3. Protocol Synopsis</td><td>Synopsis modified to read (new first sentence and modified second sentence):
Remote MADRS assessments will be completed at 4-, 8- and 12-weeks post-Day 42 visit. Optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO. The maximum expected duration of participation for an MDD participant is approximately 12 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 8 weeks (but excluding the additional 12 weeks for remote MADRS assessments and optional ePRO follow up).</td></tr>
<tr><td>Section 3. Study Title, Protocol Synopsis, Study Schematics, multiple places throughout the protocol.</td><td>The 3-dose Relative Bioavailability/Food Effect Cohort was modified to only evaluate 2 doses in the fasted state (powder in solution versus powder filled capsules). The third dose food effect cohort was removed from the study, and all references to food effect comparison were deleted, including:
Study title
Protocol synopsis text and the following table were revised to specify only Doses 1 and 2:
<table>
<tr><th>Sequence</th><th>Dose 1</th><th></th><th>Dose 2</th></tr>
<tr><td>1</td><td>4 NHV participants, CYB003 powder in solution, fasted</td><td>⇨</td><td>4 NHV participants, CYB003 powder-filled capsules, fasted</td></tr>
<tr><td>2</td><td>4 NHV participants, CYB003 powder-filled capsules, fasted</td><td>⇨</td><td>4 NHV participants, CYB003 powder in solution, fasted</td></tr>
</table>
Figure 4-3 was revised to delete third dose arm and adjust the visits.
Table 4-4 was revised to delete third dose arm and adjust the visits.
Trial objectives and endpoints were revised to delete food effect assessment.
Table 8-1 and Table 8-2 were revised to remove reference to fed state and food effect cohort.
Table 8-3 was revised to match the above protocol synopsis table.
Meal content for the fed cohort was deleted. Multiple other references were modified or deleted.
For the open-label NHV Participants Relative Bioavailability Cohort, previously the 1 week interval between doses could be extended to 1 to 4 weeks. This was modified to 1 to 2 weeks to be consistent with the double-blind NHV Participant cohorts.</td></tr>
</table>

Protocol Section	Description of Change
Table 4-1 modifications	Table 4-1, Footnotes 8, 15 and 18 – Time window sentence added. All collection timepoints are ±10 min. Table 4-1, Footnote 10 – delete PCR (also in the abbreviations, not needed) Table 4-1 – remote MADRS assessments added at 4-, 8- and 12-weeks post-Day 42 visit. Table modified to incorporate follow-up column to far right of the table and remote MADRS and optional QIDS SR-16 at these post-study visits. Footnote 16 modified to read: [16] Participants will complete a remote MADRS follow-up assessment post-study at 4-, 8- and 12-weeks post-Day 42 visit (allowable time window for completion is ± 3 days). Participants will be asked to complete an optional QIDS SR-16 follow-up assessment post-study done via ePRO at 4-, 8- and 12-weeks post-Day 42 visit.
Table 4-3 modifications	Table 4-3, Footnotes 9, 14 and 15 – Time window sentence added. All collection timepoints are ±10 min. Table 4-3, Footnote 11 – delete PCR (also in the abbreviations, not needed)
Table 4-4 modifications	Table 4-4, Footnotes 9, 14 and 15 – Time window sentence added. All collection timepoints are ±10 min. Table 4-4, Footnote 11 – delete PCR (also in the abbreviations, not needed)
Section 6.8 Starting Dose Justification	Modified to read: The maximum dose of CYB003 in this study will depend on the PK/PD, efficacy and safety data of cohorts 1-5 (**doses higher than 12 mg are subject to FDA review**)...
Section 3. Protocol Synopsis and Section 8.2 Study Design	Cohort 3 added to the following sentence: In Cohorts 1, 2, **3,** 5 and 6, there may be a dose escalation within the cohort, such that participants will receive one dose level of CYB003 for the first dose. Section 3 and Section 8.2 with respect to the timing of the soft lock and Cohorts 5 and 6 currently reads: • Pending data review from Cohorts 1 to 4, 8 MDD participants (6 active and 2 placebo) will be enrolled in Cohort 5. Doses > 12 mg will only be administered in Cohort 5, subject to FDA approval. • Cohort 6 will enroll 8 MDD participants (6 active and 2 placebo). • After Cohort 6, a soft lock of the data will be performed. • 4 additional MDD participants (3 active and 1 placebo) will be enrolled in Cohorts 5 and 6 after the soft lock (8 additional MDD participants in total). Revised to read: • Up to 12 MDD participants (9 active and 3 placebo) will be enrolled in Cohort 4. • Up to 12 MDD participants (9 active and 3 placebo) will be enrolled in Cohort 5. • After Cohort 5 is completed, a soft lock of the data will be performed. • Doses > 12 mg will only be administered in Cohort 6, subject to FDA approval. • Cohort 6 will enroll up to 12 MDD participants (9 active and 3 placebo).

<table>
<tr><th>Protocol Section</th><th>Description of Change</th></tr>
<tr><td>Table 8-1 modification</td><td>Table 8-1 Cohort 3 proposed second dose changed from 9 to 12. Reference to fed state deleted.
<table>
<tr><th>Cohort</th><th>Day 1 Dose (mg)</th><th>Day 1 Fasted</th><th>Day 8 or Day 22 Dose (mg)</th><th>Highest Day 8 or Day 22 Dose (mg)</th><th>Day 8 or Day 22 Fasted</th></tr>
<tr><td>1</td><td>1</td><td>Fasted</td><td>1</td><td>1</td><td>Fasted</td></tr>
<tr><td>2</td><td>3</td><td>Fasted</td><td>6</td><td>8</td><td>Fasted</td></tr>
<tr><td>3</td><td>9</td><td>Fasted</td><td>12</td><td>12</td><td>Fasted</td></tr>
<tr><td>4</td><td>12</td><td>Fasted</td><td>12</td><td>12</td><td>Fasted</td></tr>
<tr><td>5</td><td>12</td><td>Fasted</td><td>12</td><td>12</td><td>Fasted</td></tr>
<tr><td>6</td><td>9 or up to 16</td><td>Fasted</td><td>Up to 16</td><td>Up to 16</td><td>Fasted</td></tr>
</table>
Dose levels >12 mg are pending FDA review.
Note: Study participants who have received Day 1 dose may receive the same dose level on Day 8 or Day 22 dose if agreed upon by the Investigator and Sponsor to allow for flexibility and more time with respect to recruitment of a sufficient number of participants at the Day 1 dose level.</td></tr>
<tr><td>Table 8-2 modifications</td><td>Table 8-2 Cohort 3 potential doses changed from 9 to 9 and 12. Soft lock column removed as no longer relevant for Cohorts 5 and 6. +4 MDD participants will be added in Cohort 4 during FDA review of prior data. Cohort 5 and 6 size is up to 12 MDD. Reference to Food Effect was deleted.
<table>
<tr><th>Cohort</th><th>Cohort size</th><th>Potential CYB003 doses (mg)</th></tr>
<tr><td>1</td><td>4 MDD</td><td>1</td></tr>
<tr><td>2</td><td>4 NHVs</td><td>3 and 6</td></tr>
<tr><td>3</td><td>4 NHVs or 8 MDD</td><td>9 and 12</td></tr>
<tr><td>4</td><td>Up to 12 MDD * * *</td><td>12</td></tr>
<tr><td>Relative BA</td><td>8 NHV</td><td>≤12</td></tr>
<tr><td>5</td><td>Up to 12 MDD * * *</td><td>12 **</td></tr>
<tr><td>6</td><td>Up to 12 MDD * * *</td><td>Up to 16 *</td></tr>
</table>
* Pending FDA review and SRC recommendation; ** Soft lock and data review will occur after Cohort 5 is completed. * * * a minimum of 8 completers is intended</td></tr>
<tr><td>Section 8.2 Study Design</td><td>Section 8.2 sentence modified to read:
The maximum expected duration of participation for an MDD participant is approximately 12 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 8 weeks (but excluding the additional 12 weeks for remote MADRS assessments and optional ePRO follow up).</td></tr>
</table>

Protocol Section	Description of Change
Section 3. Protocol Synopsis and Section 8.3.3.2. Individual Stopping Criteria	Two additional individual stopping criteria added as numbered items 5 and 6: 5. Any participant who experiences tachycardia defined as resting supine heart rate >125 bpm, persisting for at least 10 minutes. 6. Any participant who develops hypertension defined as an increase in resting supine systolic blood pressure (BP) >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
Section 8.3.3.3. Trial Stopping Rules	Section 8.3.3.3. The following paragraph is replaced by a new paragraph (referencing the dog toxicology study instead of the rat toxicology study): Dose escalation will be stopped if PK data indicates the predefined maximum exposure levels (i.e., C_{max} of 343 ng/mL or AUC_{0-24} of 3630 hr*ng/mL) based on toxicokinetic data from the 14-day toxicology DRF study in rats have been achieved or exceeded should the dose be increased as planned. The exposure limits will be applied on mean values within a cohort. Replacement paragraph: Dose escalation will be stopped if PK data indicates the predefined maximum exposure levels (i.e., C_{max} of 63.0 ng/mL or AUC_{0-24} of 123 hr*ng/mL, combined male and female data) based on toxicokinetic data from the 28-day toxicology study in dogs have been achieved or is predicted to be achieved or exceeded should the dose be increased as planned. The exposure limits will be applied on mean values within a cohort.
9.3.5. Follow-Up Remote Assessments	A new Section 9.3.5 has been added (table of contents also updated to reflect the additional section): 9.3.5. Follow-Up Remote Assessments Remote MADRS assessments will be completed at 4-, 8- and 12-weeks post-Day 42 visit. The allowable time window for these assessments is ± 3 days. Optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO.
Section 10.1.11. QIDS-SR-16	Section 10.1.11 Last sentence modified to read: For MDD participants, QIDS SR-16 assessments will be completed prior to each study medication dose (Day -1, Day 21 and Day 42) and optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO.
Section 11.7. 12-Lead Holter Monitoring	Protocol Section 11.7 12-Lead Holter Monitor excerpt is modified to read: Twelve-lead Holter monitoring will be performed for 6 hours (± 10 minutes) on Day -1 beginning in the morning at approximately 08:00 hours and on Day 1 and Day 22 (MDD participants), Day 1 and Day 8 (NHV participants, double-blind study part), and Day 1, Day 8 and Day 15 (NHV participants, open-label study part) for approximately 12.5 hours beginning approximately **1 hour** predose to 12 hours (± 10 minutes) postdose.
Section 13.9. Safety Analyses	Protocol Section 13.9 excerpt is modified to read (incorrectly referenced Section 11.1.4.6): Potential abuse-related TEAEs as listed in Section 11.1.4**.7** will be summarized by category (i.e., euphoria-related terms; terms indicative of impaired attention, cognition, and mood; dissociative/psychotic terms; and related terms not captured elsewhere) and individual MedDRA Preferred Term.

2. TABLE OF CONTENTS

1. GENERAL INFORMATION 1
2. TABLE OF CONTENTS 12
3. PROTOCOL SYNOPSIS 15
4. STUDY SCHEMATICS AND SCHEDULES OF PROCEDURES 28
5. LIST OF ABBREVIATIONS 41
6. BACKGROUND INFORMATION 44
6.1. MAJOR DEPRESSIVE DISORDER 44
6.2. BACKGROUND INFORMATION ON PSILOCYBIN AND PSILOCIN 44
6.3. CYB003 INVESTIGATIONAL PRODUCT 45
6.4. CYB003 NON-CLINICAL DATA 47
6.5. CYB003 CLINICAL DATA 47
6.6. STUDY RATIONALE 48
6.7. STUDY DESIGN CONSIDERATIONS 48
6.8. STARTING DOSE JUSTIFICATION 49
6.9. STUDY POPULATION 54
6.10. ETHICAL CONDUCT OF THE STUDY 55
7. TRIAL OBJECTIVES 55
7.1. PRIMARY OBJECTIVE 55
7.2. SECONDARY OBJECTIVES 55
7.3. EXPLORATORY OBJECTIVES 55
8. TRIAL DESIGN 56
8.1. STUDY ENDPOINTS 56
8.2. STUDY DESIGN 56
8.2.1. Study Duration 64
8.2.2. Study Drug Dosing 65
8.2.3. Test Article Accountability 66
8.2.4. Randomization 66
8.2.5. Emergency Unblinding 67
8.2.6. Psychotherapy Session Facilitators and On Call Physician 67
8.3. SELECTION AND WITHDRAWAL OF PARTICIPANTS 68
8.3.1. Inclusion Criteria 68
8.3.2. Exclusion Criteria 69
8.3.3. Dose Stopping and Adjustment Criteria 73
8.3.4. Withdrawal Criteria 75
8.3.5. Handling of Withdrawals 76
9. STUDY MEDICATION DOSING AND CLINICAL ASSESSMENTS 76
9.1. PARTICIPANT SCREENING 76
9.2. PSYCHOLOGICAL SUPPORT SESSIONS 76
9.3. DOUBLE-BLIND TREATMENT PERIOD (COHORTS 1-6) 77
9.3.1. First Dosing Session 77
9.3.2. Second Dosing Session 78
9.3.3. End of Treatment Visit (Day 42) 79

9.3.4. End of Study Visit (Day 28 or Day 56) 79
9.3.5. Follow-Up Remote Assessments 79
9.4. OPEN-LABEL TREATMENT PERIOD (RELATIVE BA COHORT) 79
9.4.1. First Dosing Session 79
9.4.2. Second Dosing Session 80
9.4.3. End of Study Visit (Day 28) 80
10. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS 81
10.1. EFFICACY (PHARMACODYNAMICS) ASSESSMENTS 81
10.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS) 81
10.1.2. Mini International Neuropsychiatric Interview (MINI 7.0.2) 81
10.1.3. Remote Diagnostic Interview 82
10.1.4. Psychedelic-Assisted Psychotherapy (EMBARK) 82
10.1.5. Mystical Experience Questionnaire (MEQ30) 83
10.1.6. 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) 83
10.1.7. Hallucinogen Rating Scale (HRS) 84
10.1.8. Persisting Effects Questionnaire (PEQ) 84
10.1.9. 36-Item Short Form Survey (SF-36) 84
10.1.10. Any Drug Effect Visual Analogue Scale 85
10.1.11. Quick Inventory of Depressive Symptomatology (QIDS SR-16) 85
10.2. PHARMACOKINETICS 85
10.2.1. Blood Sample Collection and Processing 85
10.2.2. Plasma PK Sample Shipment 86
10.2.3. Bioanalysis 86
11. ASSESSMENT OF SAFETY 87
11.1. ADVERSE EVENTS 87
11.1.1. Reporting Adverse Events 87
11.1.2. Definitions 87
11.1.3. Serious Adverse Events (SAEs) 89
11.1.4. Recording of Adverse Events 89
11.1.4.1. Time Period for Collection of Adverse Events 89
11.1.4.2. Follow-up of Unresolved Adverse Events 89
11.1.4.3. Variables 89
11.1.4.4. Causality Collection 90
11.1.4.5. Adverse Events Based on Signs and Symptoms 90
11.1.4.6. Adverse Events Based on Examinations and Tests 90
11.1.4.7. Potential Abuse-Related Adverse Events 91
11.1.5. Adverse Event Follow-up 91
11.1.6. Pregnancy 92
11.2. COLUMBIA-SUICIDE SEVERITY RATING SCALE 92
11.3. CLINICAL LABORATORY ASSESSMENTS 92
11.4. VITAL SIGN ASSESSMENTS 92
11.5. PHYSICAL EXAMINATIONS 93
11.6. RESTING 12-LEAD ECG 93
11.7. 12-LEAD HOLTER MONITORING 93
12. CONCOMITANT MEDICATIONS 93
13. STATISTICAL METHODS 94
13.1. GENERAL CONSIDERATIONS 94

13.2. Sample Size Determination 95
13.3. Analysis Populations 95
13.4. Efficacy (Pharmacodynamics) 95
13.5. Pharmacokinetics 96
13.6. Demographic and Baseline Characteristics 97
13.7. Exposure to Study Drug 97
13.8. Prior/Concomitant Medications 97
13.9. Safety Analyses 97
14. ETHICS 98
14.1. Participant Information and Consent 98
14.2. Institutional Review Board 99
14.3. Study Monitoring 99
14.4. Study Records Retention 99
14.5. Data Quality Assurance 99
14.6. Confidentiality 100
14.7. Publications 100
15. PRINCIPAL INVESTIGATOR'S STATEMENT AND SPONSOR APPROVAL SIGNATURE 101
16. REFERENCES 102
17. APPENDIX 1 – CLINICAL LABORATORY TESTS 106

3. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Cybin	
Name of Investigational Product: CYB003	
Title of Study: A Phase I/IIa, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Relative Bioavailability Cohort to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of CYB003 in Healthy Participants with and without Major Depressive Disorder (MDD)	
Study Center(s): Multicenter	
Principal Investigator: Multiple Investigators	
Studied Period: Estimated date of first participant enrolled: August 2022 Estimated date of last participant completed: November 2023	**Phase of development:** Phase I/IIa
Objectives:	**Endpoints:**
Primary	
To determine the safety and tolerability of ascending oral doses of CYB003 in healthy participants with and without MDD	Clinical safety data from AE reporting, 12 lead ECG, Holter monitoring, clinical safety laboratory evaluations, physical examinations and suicidality as assessed by the C-SSRS
Secondary	
1. To determine the PK of ascending oral doses of CYB003	Plasma CYB003 concentrations and PK parameters including but not limited to: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$
2. To characterize the psychedelic effects of CYB003 administration	Mystical Experience Questionnaire (MEQ30), the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), the Hallucinogen Rating Scale (HRS) and visual analogue scale (VAS) ratings of 'Any drug effect' and a 5-item Persisting Effects Questionnaire (PEQ) assessing the meaningfulness, spirituality and psychological insights and challenges of the experience and overall drug effect
3. To evaluate the efficacy of CYB003 in treating symptoms of MDD	Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) scores
Exploratory	
1. To assess the relative bioavailability of CYB003 oral powder in solution compared to powder-filled capsules	PK parameters, AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and t_{max} for CYB003 powder-filled capsules versus powder in solution in the fasted state

2. To evaluate the effect of CYB003 on ECG parameters, including concentration-QTc (C-QTc) analysis	• Change-from-baseline heart rate, PR, QTcF and QRS intervals (ΔHR, ΔPR, ΔQTcF and ΔQRS) • Placebo-corrected ΔHR, ΔPR, ΔQTcF and ΔQRS • Categorical outliers for HR, PR, QRS and QTc • Frequency of treatment emergent T- and U-wave abnormalities

This is a Phase I/IIa, randomized, double-blind, placebo-controlled study in healthy participants with and without MDD. The study also includes an open-label relative bioavailability (BA) cohort in healthy participants without MDD. For sake of clarity throughout the protocol, otherwise healthy participants with MDD will be referred to as **MDD participants**, and healthy participants without MDD will be referred to as normal healthy volunteer (NHV) participants, or simply, **NHV participants**.

This study initially evaluated the lowest dose of CYB003 or placebo (1 mg) in MDD participants. Cohort 1 MDD participants have been dosed at the starting dose of CYB003 1 mg (4 subjects dosed with 1 early dropout). The protocol has been amended following completion of Cohort 1 to enroll the following Cohorts 2-6 and a relative BA cohort:

- Cohort 2 will enroll 4 NHV participants (3 active and 1 placebo);
- A decision whether to enroll NHVs or MDD patients in Cohort 3 will be dependent on ratings on the VAS – any drug effect score. If the CYB003 doses administered in this cohort are associated with ratings on the VAS any drug effect" of <7 in 75% of NHV participants, then Cohort 3 will enroll 4 NHV participants (3 active and 1 placebo).
- If the CYB003 doses administered in this Cohort 2 are associated with ratings on the VAS – any drug effect of >7 in 75% of NHV participants, then Cohort 3 will enroll 8 MDD participants (6 active and 2 placebo).
- Cohort 4 is planned for up to 12 MDD participants (9 active and 3 placebo). After 12 participants have been dosed and evaluated (first dose) in Cohort 4, and if dose escalation has reached 12 mg of CYB003, data will be submitted to FDA for review.
- Up to 12 MDD participants (9 active and 3 placebo) will be enrolled in Cohort 5.
- After Cohort 5 is completed, a soft lock of the data will be performed.
- Cohort 6 will enroll up to 12 MDD participants (9 active and 3 placebo). Doses > 12 mg will only be administered in Cohort 6, subject to FDA approval.
- A single cohort of 8 NHV participants will be enrolled to assess the relative bioavailability of the oral powder in solution compared to powder-filled capsules in a cross-over design. This cohort can be initiated any time after Cohort 4 dosing commences.

The study will investigate the safety, tolerability, PK and PD of ascending oral doses of CYB003 in MDD participants and NHV participants, and the relative bioavailability of CYB003 powder in solution compared to powder-filled capsules.

A study schematic is included in Figure 4-1 for MDD Participants, Figure 4-2 for NHV Participants (Cohorts 2-6), and Figure 4-3 for NHV Participants (Relative BA Cohort). A schedule of assessments is included in Table 4-1 for MDD Participants, Table 4-3 for NHV Participants (Cohorts 2-6), and Table 4-4 for NHV Participants (Relative BA Cohort).

Up to 64 participants are planned to be enrolled into 7 cohorts, including up to 48 MDD participants and 16 NHV participants. All participants will have a Screening visit between 28 and 17 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good general health. Some of the Screening procedures may be performed remotely, while others will be required on-site. All screening assessments must be completed and participants confirmed eligible by the Investigator based on inclusion and exclusion criteria review before the psychological support sessions described below can commence.

Cohorts 1-6: For the first dose (Day 1), participants will receive either an active CYB003 dose or placebo (3:1 ratio). For the second dose (Day 22 for MDD participants or Day 8 for NHV participants), all participants will receive an active CYB003 dose. For NHV participants, the second dose may be given after a two-week interval (Day 15) instead of on Day 8, at the discretion of the Investigator.

The starting dose of CYB003 in Cohort 1 was 1 mg, based on initial human dose safety calculations per FDA guidance, modelling of predicted exposures, and taking into account safety data from non-clinical studies. The dose will be escalated in increments up to 3x from the previous dose following satisfactory review of available safety, tolerability, pharmacodynamic (PD) and PK data from the preceding cohort(s). The maximum dose of CYB003 in this study will be determined based on maximum C_{max} and AUC_{0-24} exposures of 343 ng/mL and 3630 hr*ng/mL, respectively, obtained from the rat 14-day dose range finding (DRF) study at 40 mg/kg in female rats, as well as emerging pharmacodynamic, safety and tolerability data.

The proposed first dose (Day 1) and second dose (Day 8 or Day 22) dose escalations and fed or fasted dosing conditions for study drug are presented in Table 8-1. Sentinel dosing will occur at each dose level. Each cohort will include 2 sentinel participants; 1 participant will receive CYB003 and 1 participant will receive matched placebo. The remaining participants in the cohort will commence treatment at least 24 hours after commencement of treatment in the sentinel participants after satisfactory review of the safety and tolerability data by the Investigator. A licensed physician will be on call and able to reach the clinical site within 15 minutes on study drug dosing Day 1 and Day 8 or 22 in the event of a physiological or psychiatric emergency. The physician should be available at least until 4 hours after all vital signs and mental status/neurological effects return to baseline.

Relative Bioavailability Cohort: A dose level that has been tested in a prior cohort will be selected for this open-label cohort and will be determined based on PK and safety data generated in previous cohorts. Eight NHV participants will receive two doses of active CYB003 study medication on separate study days. For Dose 1 (Day 1), 4 participants (Sequence 1) will receive CYB003 powder in solution and 4 participants (Sequence 2) will receive CYB003 powder-filled capsules. For Dose 2 (Day 8), participants will cross over to the alternate formulation (i.e., CYB003 powder-filled capsules or powder in solution). Dose 1 and Dose 2 will be administered in the fasting state. For this cohort, the preferred interval between doses is 1 week, however, this interval between doses may be stretched from 1 to 4 weeks at the Investigator's discretion.

Sequence	Dose 1		Dose 2
1	4 NHV participants, CYB003 powder in solution, fasted	⇨	4 NHV participants, CYB003 powder-filled capsules, fasted
2	4 NHV participants, CYB003 powder-filled capsules, fasted	⇨	4 NHV participants, CYB003 powder in solution, fasted

Psychological Support Sessions:

Supportive Psychotherapy for MDD participants: Supportive psychotherapy, EMBARK for MDD ("A Treatment Manual for EMBARK: A Six-Domain Framework of Psilocin-Assisted Therapy for Major Depressive Disorder"), will be provided during at least three sessions of preparatory psychotherapy (predose), medicine sessions, and at least three sessions of integration psychotherapy (postdose) following each dose administration. During these sessions, participants will be paired with two facilitators who will have completed specialized training in EMBARK for MDD; one or both facilitators will be a licensed psychotherapist. Specific professional qualifications and requirements of the lead facilitator and second facilitator are described in Section 8.2.6.

Participants will have preparatory psychotherapy sessions A1, A2 and A3 occurring within a flexible time window, with the first two preparatory sessions occurring any time after eligibility screening and the third preparatory session occurring on or about Day -1 (see Table 4-2 for time windows). Each preparatory session will last for 90 minutes. Flexibility is allowed for the scheduling of these sessions at the facilitator's discretion and coordination with the participant and Investigator provided that all three preparatory sessions are completed prior to any study medication dosing.

For the last of three preparatory psychotherapy predose sessions, the preferred default schedule is the final preparatory session on Day -1 in the afternoon or evening before dosing, first dosing on Day 1, and the first postdose integration session on the morning of Day 2, so the participant completes these study activities during one extended visit. Similarly, for the last of three integration psychotherapy sessions before the second dose administration, the preferred default schedule is the final session on Day 21 in the afternoon or evening before dosing, then dosing on Day 22, and the first postdose integration session on the morning of Day 23, so the participant completes these study activities during one extended visit.

After each dose, postdose integration psychotherapy sessions, Sessions B1, B2 and B3, will occur on approximately Day 2, 10 and 21 following the first dose and Sessions C1, C2 and C3 will occur on

approximately Day 23, 31 and 38 following the second dose. Each postdose integration session will last for 90 minutes. The scheduling of these integration sessions is meant to be flexible and may occur on different days rather than a fixed weekly schedule depending on an assessment of an individual study participant by the facilitator, provided there are at least three postdose integration sessions following each study medication dose. Additional preparatory psychotherapy sessions or integration psychotherapy sessions may be conducted by study facilitators at the Investigator's discretion.

Psychological Support for NHV participants: Healthy volunteers will receive at least one preparation session (prior to the first dose), a medicine session during dose administration, and at least one debrief session following each dose. The predose preparation sessions and debrief sessions can be done remotely. Additional preparatory sessions or debrief sessions may be conducted by study facilitators at the Investigator's discretion.

Double-Blind Treatment Period:

All participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter session. This baseline Holter recording must be reviewed prior to dosing on Day 1 to confirm that there are no abnormal findings that may preclude a participant's involvement in the clinical trial.

Dose 1: Randomization to double-blind study medication will occur on Day 1 after successful completion of the three preparatory psychotherapy sessions (MDD participants) or the predose preparation session (NHV participants) and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

All participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 or matched placebo in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing (Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 1, 6, 8, 12 and 24 hours postdose for MDD participants and predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose for NHV participants. Other safety and PD assessments will be performed as described in Table 4-1 for MDD Participants and Table 4-3 for NHV Participants.

For all participants, the CYB003 treatment session may last from 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

MDD participants will have at least three postdose integration psychotherapy sessions as described above under "Supportive Psychotherapy Sessions." NHV participants will have at least one debrief session following the study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits.

Dose 2: Participants will be re-admitted to the research site on Day 7 (NHV participants) or Day 21 (MDD participants) for the collection of safety assessments and mood and psychological health questionnaires to assess their response to the first dosing session. The same study procedures will be performed on Day 7 through Day 9 (NHV participants) or Day 21 through Day 23 (MDD participants) as were done on Days -1 through Day 2. All participants will receive an oral dose of CYB003 in the morning of Day 8 (NHV participants) or Day 22 (MDD participants). Two trained facilitators will be present to support the participant throughout the dosing session. There will be a +7 day window allowed for the Day 7 or Day 21 visit to allow for review of safety data, if needed.

Participants will reside at the research site until the morning of Day 9 (NHV participants) or Day 23 (MDD participants) (approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

MDD participants will have at least three postdose integration psychotherapy sessions as described above under "Supportive Psychotherapy Sessions." NHV participants will have at least one debrief session following the study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits.

Study medication will be administered in the fasted state, following an overnight fast of approximately 10 hours in cohorts 1-6.

Open-Label Relative Bioavailability Cohort:

NHV participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter session. This baseline Holter recording must be reviewed prior to dosing on Day 1 to confirm that there are no abnormal findings that may preclude a participant's involvement in the clinical trial.

Dose 1: Randomization to open-label study medication sequence 1 or 2 will occur on Day 1 after successful completion of the predose preparation session and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

Participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 powder in solution or powder-filled capsules in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing (Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose. Other safety and PD assessments will be performed as described in Table 4-4.

The CYB003 medicine session may last from 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

Dose 2: Participants will be re-admitted to the research site on Day 7 for the collection of safety assessments and mood and psychological health questionnaires. The same study procedures will be performed on Day 7 through Day 9 as were done on Days -1 through Day 2. Participants will crossover to the alternate study medication (CYB003 powder in solution or powder-filled capsule) in the morning of Day 8 in the fasted state.

Two trained facilitators will be present to support the participant throughout each dosing session. Participants will have at least one debrief session following each study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits. The preferred schedule is for participants to receive the two doses 1 week apart (i.e., Days 1 and 8). However, the time interval may be extended up to 4 weeks between doses at the Investigator's discretion. If the time interval between doses is extended to 2 to 4 weeks, participants will have approximately weekly telephonic safety assessments.

Cohorts 1-6 Follow-Up Assessments and Visits:

MDD participants will have approximately weekly telephonic assessments for the three weeks following study drug administration for MADRS assessments and for safety assessments. MDD participants will return to the research site for an outpatient visit on Day 42 for collection of safety assessments and completion of mood and psychological health questionnaires to assess their response to the second dosing session. MDD participants will return to the research site for a final in-person Follow-up visit on Day 56 (±3 days) for collection of end-of-study safety assessments and completion of mood and psychological health questionnaires. Remote MADRS assessments will be completed at 4-, 8- and 12-weeks post-Day 42 visit. Optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO. The maximum expected duration of participation for an MDD participant is approximately 12 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 8 weeks (but excluding the additional 12 weeks for remote MADRS assessments and optional ePRO follow up).

NHV participants will have approximately weekly telephonic assessments for two weeks following the second dose study drug administration for safety assessments. NHV participants will return to the research site for a final in-person Follow-up visit on Day 28 (±3 days) for collection of end-of-study safety assessments. The maximum expected duration of participation for a NHV participant is approximately 8 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 4 weeks. If the Investigator extends the time between the two doses from 1 to 2 weeks, the treatment phase and follow-up will be up to 6 weeks, for a total expected duration of participation of approximately 10 weeks.

Relative Bioavailability Cohort Follow-Up Assessments and Visits:

NHV participants will have approximately weekly telephonic assessments for two weeks following the second dose study drug administration for safety assessments. NHV participants will return to the research site one week later for a final in-person Follow-up visit on Day 28 (±3 days) for collection of end-of-study safety assessments. The maximum expected duration of participation for a NHV participant is approximately 8 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 4 weeks. If the Investigator extends the time between the two doses by up to 4 weeks after each dose, the treatment phase and follow-up will be up to 10 weeks, for a total expected duration of participation of approximately 14 weeks.

Study Population:

Inclusion Criteria

MDD and NHV Participants:

Participants meeting the following criteria will be included in the study:

1. Participant is assigned female or male at birth.
2. Participant is aged between 21 to 65 years, inclusive, at Screening.
3. Participant has a BMI of 18 to 30 kg/m^2, inclusive, at Screening.
4. Participant is ≥60 kg.
5. Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test at Screening and Day -1.
6. Participants capable of producing sperm must use a condom during the trial and for 3 months after their final dose of trial medication, if their partner is a person of childbearing potential. In addition, their partner of childbearing potential must use a highly effective method of contraception (i.e., failure rate less than 1% when used consistently and correctly) from first dosing until 3 months following final dosing.
7. Participants of childbearing potential must agree to use a highly effective method of contraception (i.e., failure rate less than 1% when used consistently and correctly) in combination with a partner who is capable of producing sperm must use a condom during the trial and for 3 months after their final dose of trial medication. Such participants must have a negative pregnancy test at Screening and Day -1.
8. Participants of non-childbearing potential who are or were capable of producing eggs (ova) must be postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy or bilateral oophorectomy. Postmenopausal is defined as spontaneous amenorrhea for at least 12 months, and a serum follicle stimulating hormone (FSH) level in the menopausal range, unless the participant is taking hormone replacement therapy or is using hormonal contraception.
9. Provision of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

MDD Participants:

Participants meeting the following criteria will be included in the study:

1. Participant has a diagnosis of MDD (as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V] of moderate to severe degree (scoring ≥21 on the Montgomery-Åsberg Depression Scale [MADRS], established through a full psychiatric work up that includes the Mini-International Neuropsychiatric Interview [MINI]), who are otherwise healthy.
2. Confirmation of MDD diagnosis, a depression severity of moderate to severe based on MADRS score, inadequate response to current antidepressant medication, and absence of treatment-resistant depression, based on a diagnostic interview conducted by a clinician.
3. Participant has been on a stable dose of antidepressant medication (no more than 50% change) in the last month prior to Screening and has had an inadequate response, as judged by the Investigator.

Exclusion Criteria

MDD Participants:

Participants with the following will be excluded from study participation:

1. A reduction in the MADRS score of 25% or more between Screening and randomization.

2. Current or previous diagnosis of treatment-resistant MDD, defined as failure to respond to 2 or more antidepressant treatments given at an adequate dose for an adequate duration.
3. Current or previously diagnosed schizophrenia spectrum or other psychotic disorders, including schizophrenia, schizoaffective disorder, schizotypal disorder, schizophreniform disorder or brief psychotic disorder; current or previous history of bipolar disorder, or current personality disorder (as determined by MINI at Screening).
4. Currently receiving a monoamine oxidase inhibitor, tricyclic antidepressant, mirtazapine, an antipsychotic or a mood stabilizer.
5. Exposure to psilocin, or any other psychedelics, such as ayahuasca, mescaline, LSD or peyote more than 10 times in the last 10 years, or any psychedelic use within 6 months prior to Screening.
6. Use of a prescription medicine (except participants may take a stable chronic dose of antidepressant medication(s) and/or sedatives/hypnotics, and may take hormonal contraceptives, if applicable), certain herbal supplements (to be reviewed by the Investigator), or over-the-counter (OTC) medicine, during the 28 days before dosing. Exceptions include the following medications:
   a. Antianxiety medication, other than buspirone, is allowed if taken chronically (as needed or daily), provided that the participant must refrain from taking a dose of the antianxiety medication for at least 12 hours prior to a dose of study medication.
   b. Preexposure prophylaxis (PrEP) medication for prevention of HIV infection, such as TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) or DESCOVY® (emtricitabine and tenofovir alafenamide), is allowed.
   c. Acetaminophen/paracetamol (less or equal 4 g/day) may be taken for up to 48 hours prior to dosing.
   d. Stable chronic therapy with hormone replacement medication is also allowed.

   The Investigator and study team may review medication on a case-by-case basis to determine if its use would compromise participant safety or interfere with study procedures or data interpretation.

NHV Participants:

Participants with the following will be excluded from study participation:

1. Current or previously diagnosed mental health disorder as defined by DSM-V criteria.
2. Exposure to psilocin, or any other psychedelics, such as ayahuasca, mescaline, LSD or peyote or any psychedelic use within 6 months prior to Screening.
3. Use of any prescription medicine (except participants may take hormonal contraceptives, if applicable), certain herbal supplements (to be reviewed by the Investigator), or over-the-counter (OTC) medicine, during the 28 days before dosing or need to take any prescription or OTC medicine or herbal supplement during the study. Acetaminophen/paracetamol (less or equal 4 g/day) may be taken for up to 48 hours prior to dosing.

   The Investigator and study team may review medication on a case-by-case basis to determine if its use would compromise participant safety or interfere with study procedures or data interpretation.

MDD and NHV Participants:

Participants with the following will be excluded from study participation:

1. Clinically significant risk of suicidality, as determined through a comprehensive psychiatric interview that incorporates the Columbia Suicide Severity Rating Scale (CSSRS); a score of 4 or higher on the suicidal ideation subscale of C-SSRS (lifetime) or any suicidal behaviour (lifetime), would be exclusionary.
2. Clinically relevant history of abnormal physical health interfering with the study as determined by medical history and physical examinations obtained during Screening as judged by the Investigator (including [but not limited to], neurological, endocrine, cardiovascular, respiratory, gastrointestinal (including dyspepsia or gastroesophageal reflux disease), hepatic, or renal disorder).
3. Diagnosis of hypertension or an arrhythmia.
4. Clinically relevant abnormal results for heart rate (resting supine heart rate >100 bpm) or blood pressure (resting supine systolic blood pressure (SBP) above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg) at screening. Screening supine SBP, DBP and heart rate for evaluation will be the average of 3 readings obtained after at least 5 minutes rest.

5. History of hypothyroidism and/or current abnormal thyroid function tests. In case of uncertain or questionable screening thyroid function test results, the TSH test may be repeated once during screening. The TSH test must be reviewed to ensure that it is within normal limits before randomizing a participant into the study.
6. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at Screening. In case of uncertain or questionable results, tests performed during Screening may be repeated once to confirm eligibility or judged to be clinically irrelevant for healthy participants.
7. A family history of schizophrenia or schizoaffective disorder (first degree relatives), or bipolar disorder type 1 (first degree relatives).
8. Other eligibility considerations (i.e., participant personal circumstances, behavior, and/or any current problem that might interfere with participation or that is incompatible with establishment of rapport or safe exposure to psilocin), as judged by the Investigator.
9. Participants with abnormal vital signs which are out of range and deemed clinically significant by the Investigator at Screening or Day 1, following triplicate readings.
10. QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec at Screening, following triplicate ECG readings.
11. Presence of clinically significant ECG abnormalities at the Screening visit, as defined by medical judgement.
12. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion (ADME) of the study drug.
13. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.
14. Participant is not fluent in English.
15. Participant has a presence or relevant history of any of the following medical conditions: organic brain disorders (e.g., epilepsy, seizure, intracranial hypertension, intracranial bleed and aneurysmal disease, brain tumor or other medical conditions associated with seizures or convulsions).
16. Aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) or total bilirubin levels ≥1.5 x the upper limit of normal (ULN) at Screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the participant may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
17. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV) or human immunodeficiency virus I and II (anti-HIV I/II) at Screening.
18. Positive urine test for drugs of abuse (see Appendix 1) or alcohol breath test at Screening or Day -1. A positive test for cannabinoids (e.g., marijuana) at Screening may not exclude a participant if after discussion with and evaluation by the Investigator, the participant agrees not to use any marijuana or other cannabinoid products during the study, and if allowed to participate, the participant must test negative for cannabinoids on Day -1 (all participants), Day 7 (NHV participants, double-blind study part), Day 14 (NHV participants, open-label study part), and Day 21 (MDD participants).
19. History of substance use disorder within the last year, as assessed by a structured clinical interview (Mini International Neuropsychiatric Interview [MINI], Version 7.0.2) or determined by self-report, or intake of >21 units of alcohol weekly, and the inability to refrain from alcohol use from 48 hours before Screening and each scheduled visit until discharge from the study site. One unit is equivalent to a 285 mL glass of full-strength beer or 1 (30 mL) measure of spirits or 1 glass (100 mL) of wine.
20. Participant who consumes excessive amounts of caffeine (e.g., coffee, tea, caffeinated sodas) or (methyl) xanthines (e.g., chocolate) based on the Investigator's determination and discretion.
21. The participant has participated in a clinical study and has received a medication or a new chemical entity within 3 months prior to dosing of current study medication.

22. Known sensitivity to psilocin and/or any excipients present in the formulation. Known fructose malabsorption or intolerance, since the orange drink vehicle for study drug contains fructose.
23. Participant is taking or has taken any drugs known to inhibit monoamine oxidase within 28 days prior to study drug administration.
24. Participant is taking or has taken OTC doses of 5-hydroxytryptophan or St John's Wort within 28 days prior to study drug administration.
25. Strenuous exercise within 48 hours prior to each visit, and while at the study site.
26. Donation of blood or plasma of >400 mL within 1 month prior to first dosing until 4 weeks after final dosing.
27. Participants capable of producing sperm who will not abstain from sperm donation between first dosing and 3 months after final dosing.
28. Participants of childbearing potential who are pregnant, breastfeeding or planning to conceive.
29. Known difficulty with obtaining intravenous access.

Planned Number of Participants:

Up to 64 study participants are planned to be enrolled in up to 7 cohorts, including an estimated 48 MDD participants and 16 NHV participants. The proportion of MDD participants and NHV participants may vary depending on safety review of individual cohorts and FDA feedback from the Cohorts 1-4 data review.

Test Product, Dose, and Mode of Administration:

Double-Blind Study Medication for Cohorts 1-6: The starting dose of CYB003 will be 1 mg in Cohort 1 participants. Participants in each cohort will receive a dose of CYB003 or matched placebo in the first dosing session (Day 1), and a dose of CYB003 in the second dosing session (Day 22 for MDD participants and Day 8 for NHV participants).

CYB003 will be provided to the Investigator and research pharmacist (or other appropriately trained personnel as designated by the Investigator) as a powder Active Pharmaceutical Ingredient (API). An unblinded pharmacist or other designee will prepare active CYB003 and placebo doses and will administer doses to the participants in a manner that preserves the integrity of the blind for the Investigator, the participants, and other research personnel.

API will be dissolved in 0.1M citric acid to give a 1 mg/mL stock solution. An appropriate volume of study drug (e.g., 1 mL for a 1 mg dose) will be mixed with Tang orange drink to mask taste and to make a 30 mL dose in a dose cup. Matched placebo will consist of similar volume of Tang orange drink without the CYB003 study drug. Participants will ingest the 30 mL dose from a dose cup and will then drink 210 mL Tang orange drink for a total volume of approximately 240 mL. All doses will be administered in the fasted state, following an overnight fast of at least 10 hours. Detailed instructions for preparing and administering individual study drug doses will be provided in a Pharmacy Manual.

Open-Label Study Medication for Relative Bioavailability Cohort: The dose will be determined based on data from previous cohorts. Study medication in this cohort will be open-label.

CYB003 will be provided to the Investigator and research pharmacist (or other appropriately trained personnel as designated by the Investigator) as a powder Active Pharmaceutical Ingredient (API) and powder-filled capsules. A pharmacist or other designee will prepare appropriate doses of CYB003 powder in solution in Tang orange drink as described above or the appropriate number of powder-filled capsules as per a randomization schedule.

For the CYB003 powder in solution dose, participants will ingest the 30 mL dose from a dose cup and will then drink 210 mL Tang orange drink for a total volume of approximately 240 mL. For the CYB003 powder-filled capsule dose, participants will ingest the capsule(s) with approximately 240 mL room temperature water. Dose 1 and Dose 2 will be administered in the fasted state, following an overnight fast of at least 10 hours. Detailed instructions for preparing and administering individual study drug doses will be provided in a Pharmacy Manual.

Reference Product, Dose, and Mode of Administration:

For double-blind Cohorts 1-6, the reference product for this study will be orally administered matched placebo orange drink solution.

For the open label cohort, CYB003 powder in solution in the fasted state will be the reference formulation and CYB003 powder-filled capsule in the fasted state will be the test formulation for the relative BA assessment.

Duration of Treatment:

Double-Blind Treatment: MDD participants' duration of treatment will be up to 6 weeks, inclusive of study drug dosing and supportive psychotherapy sessions (i.e., Days 1 through 42). NHV participants' duration of treatment will be up to 4 weeks, inclusive of study drug dosing and follow-up safety assessments (i.e., Days 1 through 28). The duration of treatment may be extended for NHV participants by 1 week following each dose at the Investigator's discretion or up to 6 weeks total duration.

Open-Label Treatment: In the relative BA cohort, NHV participants' duration of treatment will be up to 4 weeks, inclusive of study drug dosing and follow-up safety assessments (i.e., Days 1 through 28). If the time between doses is extended at the Investigator's discretion up to 4 weeks between doses (i.e., Days 1 through 56), the duration of treatment will be up to 10 weeks.

Duration of Study Participation:

Double-Blind Treatment: 12 week screening and treatment phases followed by 12-week remote MADRS assessments and optional ePRO assessments for MDD participants and 8 to 10 weeks for NHV participants.

Open-Label Treatment: 8 weeks screening and treatment phases for NHV participants, except if the time interval between doses is extended to 2 weeks, then up to 10 weeks.

Dose Stopping and Adjustment Criteria:

Cohort Stopping Criteria

If any of the following safety concerns are observed in a cohort, dosing of all participants at the given dose level or higher may be suspended/halted and all available data will be evaluated by the Safety Review Committee (SRC). Dose continuation (remaining participants within a cohort) or escalation will not proceed, without SRC review, for any of, but not limited to, the following reasons:

1. One or more Hy's Law cases in participants who have been administered CYB003; Hy's Law is defined as AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN, in the absence of a significant increase in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that could explain the increase in bilirubin.
2. The occurrence of one serious adverse event (SAE) considered related to CYB003.
3. Two severe drug-related AEs in the same cohort, independent of within, or not within, the same system-organ class (SOC), considered related to CYB003.
4. Other findings that indicate dose escalation should be halted, e.g., if there is an unacceptable tolerability profile based on the nature, frequency and intensity of observed AEs and/or clinical safety monitoring in the opinion of the Investigator.
5. Two or more participants in a cohort find anxiety, fear, or distress caused by CYB003 to be intolerable during the dosing session, requiring rescue medication.
6. Two or more participants in a cohort develop clinically significant anxiety, fear, or distress following the dosing session that persists beyond the day of dosing, as assessed by the Investigator.
7. Psychedelic effects scales indicate either a complete mystical experience has been achieved in at least 75% of participants in two consecutive cohorts (MEQ30 scores > 60), or that scores on the oceanic boundlessness subscale of the 5D-ASC > 60 (percent of total maximum score) have been achieved in at least 75% of participants in two consecutive cohorts, or scores on the Intensity subscale of the HRS > 2.79 have been achieved in at least 75% of participants in two consecutive cohorts or scores on the VAS "any drug effect" of 7 or higher have been achieved in at least 75% of participants in two consecutive cohorts.
8. Clinically significant abnormalities in the laboratory parameters, vital signs or ECGs in 2 or more participants within the same cohort indicating dose-related intolerance, considered related to CYB003.

9. Two or more participants that receive CYB003 have QTc prolongation defined as an absolute QTcF value of >500 msec, or a change from baseline of >60 msec, that persists for at least 5 minutes following triplicate ECGs.
10. Two or more participants that receive CYB003 have tachycardia defined as resting supine heart rate >125 bpm, persisting for at least 10 minutes.
11. Two or more participants who receive CYB003 have symptomatic bradycardia defined as resting supine heart rate <45 bpm, or asymptomatic bradycardia defined as resting supine heart rate <30 bpm while awake persisting for at least 10 minutes.
12. Two or more participants who receive CYB003 develop hypertension defined as an increase in resting supine systolic blood pressure (BP) >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
13. Two or more participants who receive CYB003 develop more than one episode of symptomatic orthostatic hypotension, defined as a decrease of >20 mmHg for systolic BP, or asymptomatic systolic BP decrease of >30 mmHg which causes the systolic BP to fall below 100 mmHg, or >20 mmHg which causes the systolic BP to fall below 90 mmHg; or for single episodes associated with prolonged hypotension or a clinically significant event such as syncope, or other serious or severe cardiovascular signs or symptoms.
14. Two or more participants who are receiving CYB003 report treatment-emergent suicidality (an increase in Suicidal Ideation score to 4 or 5, or any Suicidal Behavior on the Since Last Visit version of C-SSRS) that is considered related to the study drug.

Individual Stopping Criteria

Individual stopping criteria will include:

1. Any participant who experiences severe nausea or vomiting that can't be controlled by medical and/or nursing support.
2. Any participant who experiences a severe headache or migraine that can't be controlled by medical and/or nursing support.
3. Any participant who experiences intolerable anxiety, panic, or suicidal thoughts that can't be controlled by medical and/or nursing and/or psychological support.
4. Any participant who experiences enduring perceptual distortions beyond the day of dosing.
5. Any participant who experiences tachycardia defined as resting supine heart rate >125 bpm, persisting for at least 10 minutes.
6. Any participant who develops hypertension defined as an increase in resting supine systolic blood pressure (BP) >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
7. Investigator discretion based on clinical safety grounds.

For clarification, CYB003 is expected to cause commonly seen transient psychedelic drug effects, including auditory, visual, somatic, gustatory and olfactory hallucinations, synaesthesia, ideas of reference, mood elevation, time distortion, anxiety, agitation/ restlessness, confusion, connectedness, loosening of associations, mystical experiences and ego dissolution. CYB003 is also expected to produce some physical effects inc luding nausea, vomiting, headache and transient HR and BP increases. The Investigator and SRC may take these expected class effects into consideration in their safety monitoring and decision-making with respect to whether to continue or discontinue a participant from the study.

Trial Stopping Rules

Dose escalation will be stopped if PK data indicates the predefined maximum exposure levels (i.e., C_{max} of 63.0 ng/mL or AUC_{0-24} of 123 hr*ng/mL, combined male and female data) based on toxicokinetic data from the 28-day toxicology study in dogs have been achieved or is predicted to be achieved or exceeded should the dose be increased as planned. The exposure limits will be applied on mean values within a cohort.

The Sponsor will terminate the study if the occurrence of AEs or other findings suggests an unacceptable risk to the health of the participants. The study may also be terminated by regulatory authorities for safety or administrative reasons.

Safety, Pharmacokinetic and Pharmacodynamic (Efficacy) Variables

Safety:

The occurrence of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs), reported through the completion of study will be collected and evaluated. AEs will be categorized by severity (intensity), and relationship to study medication. Clinical laboratory parameters (hematology, chemistry, urinalysis), ECG parameters, Holter monitoring, vital signs (seated SBP, DBP and pulse rate), and physical examination data will be collected and evaluated relative to baseline values.

Pharmacokinetic:

Plasma concentrations of CYB003 will be measured and pharmacokinetic (PK) parameters will be calculated using a non-compartmental analysis method. The primary PK parameters will be plasma CYB003 $AUC_{0-\infty}$, AUC_{0-t} and C_{max}. Secondary PK parameters for plasma CYB003 will include T_{max}, V_z/F, CL/F, K_{el} and $T_{1/2}$.

Pharmacodynamic (Efficacy) Variables:

Mystical Experience Questionnaire (MEQ30), the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), the Hallucinogen Rating Scale (HRS), Visual Analogue Scale (VAS) ratings of 'Any drug effect', and the Persisting Effects Questionnaire (PEQ) will be used to characterize the psychedelic effects of CYB003 administration.

Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) scores will be used to evaluate the efficacy of CYB003 in treating symptoms of MDD (in MDD participants).

Statistical Methods and Planned Analysis:

Data collected in this study will be presented using summary tables and participant data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum and maximum. Categorical variables will be summarized by frequencies and percentages.

Full details with respect to statistical methods will be prepared in a Statistical Analysis Plan.

Sample Size Determination:

Up to 64 participants are planned to be enrolled in up to 7 cohorts, including up to 48 MDD participants and 16 NHV participants. Given the exploratory nature of this study, the sample size is not based on power calculations. The number of participants to be included is typical for this kind of study, and the results give sufficient safety and tolerability data, in addition to adequate description of the PK and PD parameters.

Safety Analyses:

The safety and tolerability of a CYB003 will be assessed by the evaluation of treatment-emergent adverse events, including serious and non-serious AEs, study discontinuation information, laboratory test results, vital signs and physical examination findings.

Treatment-emergent AEs (TEAEs) will be summarized by treatment, where treatment-emergent is defined as any event with a start date on or after the date and time of the first dose date and time of study drug within a treatment period. All TEAEs will be summarized by relationship to study drug and by intensity.

Pharmacokinetic Analyses:

Plasma CYB003 concentrations will be listed at each time point by participant, and summarized by treatment at each time point using descriptive statistics and graphical displays. Pharmacokinetic parameters will be calculated using noncompartmental analysis methods, including $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, T_{max}, V_z/F, CL/F, K_{el}, and $T_{1/2}$, and will be listed by participant and summarized by treatment.

Relative Bioavailability Comparison: The geometric mean ratios and associated 90% confidence intervals between the powder in solution (Reference) and powder-filled capsule (Test) formulations administered in the fasted state will be provided for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} and will be used to assess the relative bioavailability of the two dosage forms.

Pharmacokinetic parameters will be summarized by dose, MDD or NHV participant group and overall, as appropriate.

Pharmacodynamic (Efficacy) Analyses:

Efficacy analyses will mainly focus on MDD participants, however, questionnaires will also be reviewed, summarized and listed for NHV participants for evidence of pharmacodynamic activity.

These questionnaires and rating scales will evaluate the psychedelic effects of CYB003 administration:

- Mystical Experience Questionnaire (MEQ30)
- 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
- Hallucinogen Rating Scale (HRS)
- Visual Analogue Scale (VAS) ratings of 'Any drug effect'
- Persisting Effects Questionnaire (PEQ)

This standard efficacy assessment tool will be used to evaluate the clinical efficacy of CYB003 in treating the symptoms of MDD:

- Montgomery-Åsberg Depression Rating Scale (MADRS) score

Between-group effects will use the MADRS baseline score after the 3 preparatory psychotherapy sessions (post-randomization) for change from baseline scores, and within-group effects for the entire treatment will use MADRS screening scores to reflect the entire course of treatment, including all the preparatory psychotherapy sessions, as well as post-randomization study drug dosing and integration psychotherapy sessions.

Descriptive statistics will be calculated for quantitative efficacy data and frequency counts will be compiled for classification of categorical efficacy data. Summary statistics will be calculated for each endpoint by treatment, time, and group.

Summary statistics will be calculated for each PD endpoint by treatment, time and group. Total values and changes from baseline will be calculated.

Pooled analyses across cohorts (pools consisting of cohorts 1-6, 2-6, 3-6, 4-6, 5-6) of within-group and between group effects will be calculated for pharmacodynamic (efficacy) endpoints and analyses.

The primary ECG analysis will be based on concentration-QTc (C-QTc) modeling of the relationship between the plasma concentrations of CYB003 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma concentrations. The effect of CYB003 on the placebo-corrected ΔQTcF, ΔHR (heart rate), ΔPR, and ΔQRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. In addition, an analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology and U-wave presence. The ECG analysis will initially be performed on safety ECGs, but may at the completion of the study be performed on ECGs extracted from Holter recordings.

4. STUDY SCHEMATICS AND SCHEDULES OF PROCEDURES

Figure 4-1: MDD Participants – Study Schematic

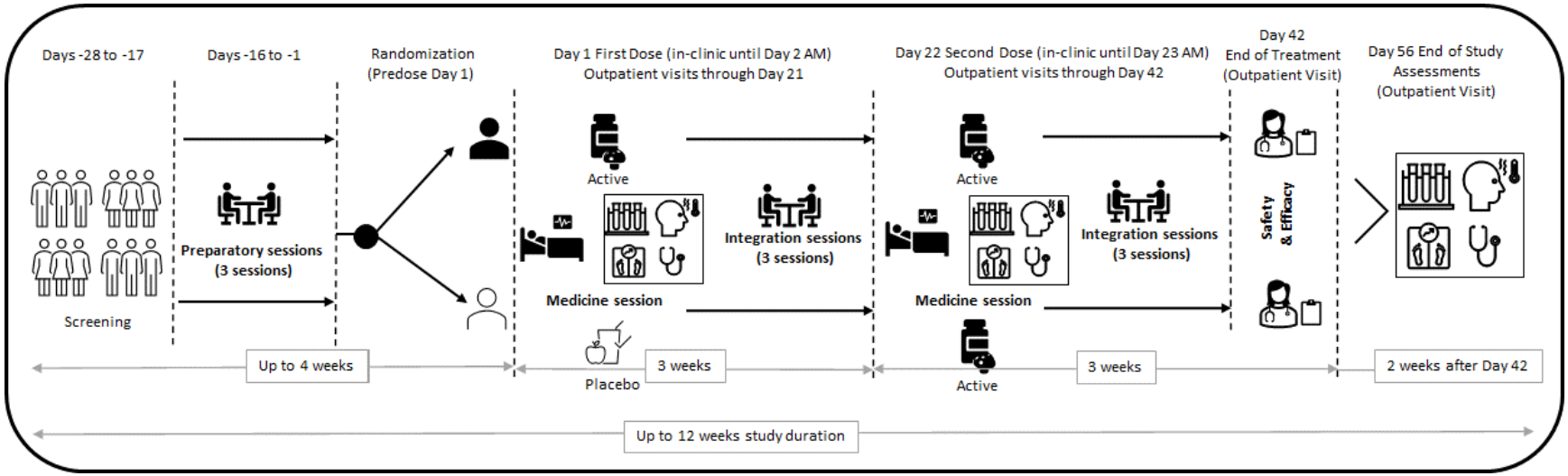


Figure 4-2: NHV Participants – Study Schematic

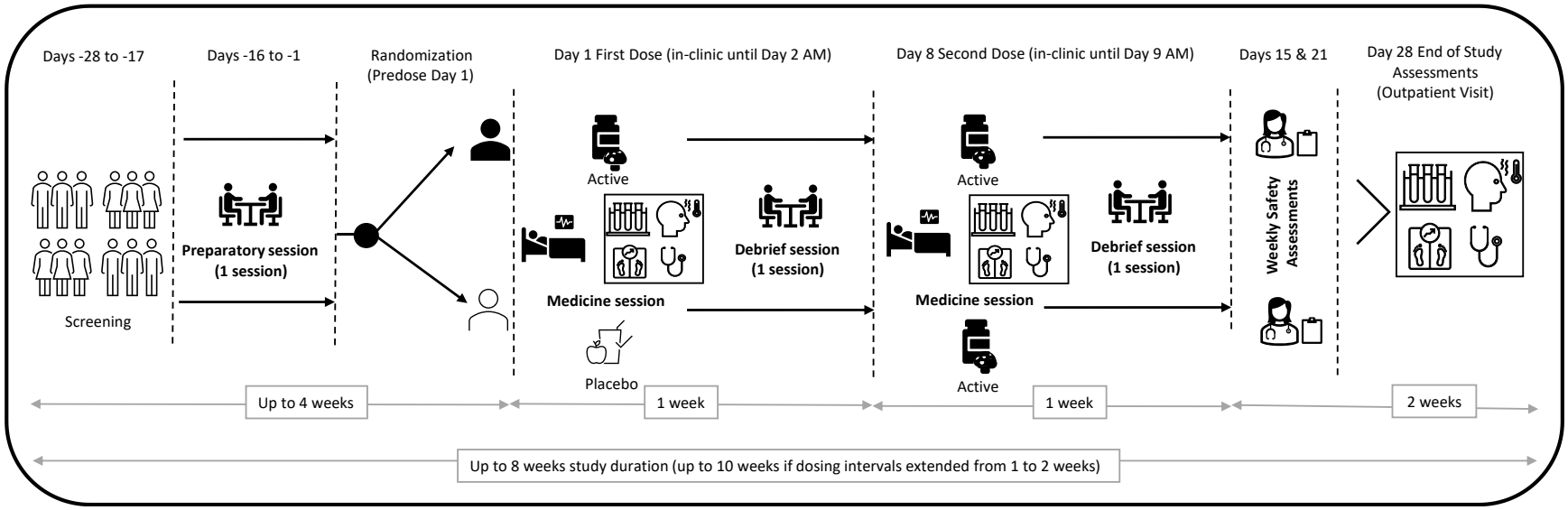


Figure 4-3: NHV Participants in Relative Bioavailability Cohort – Study Schematic

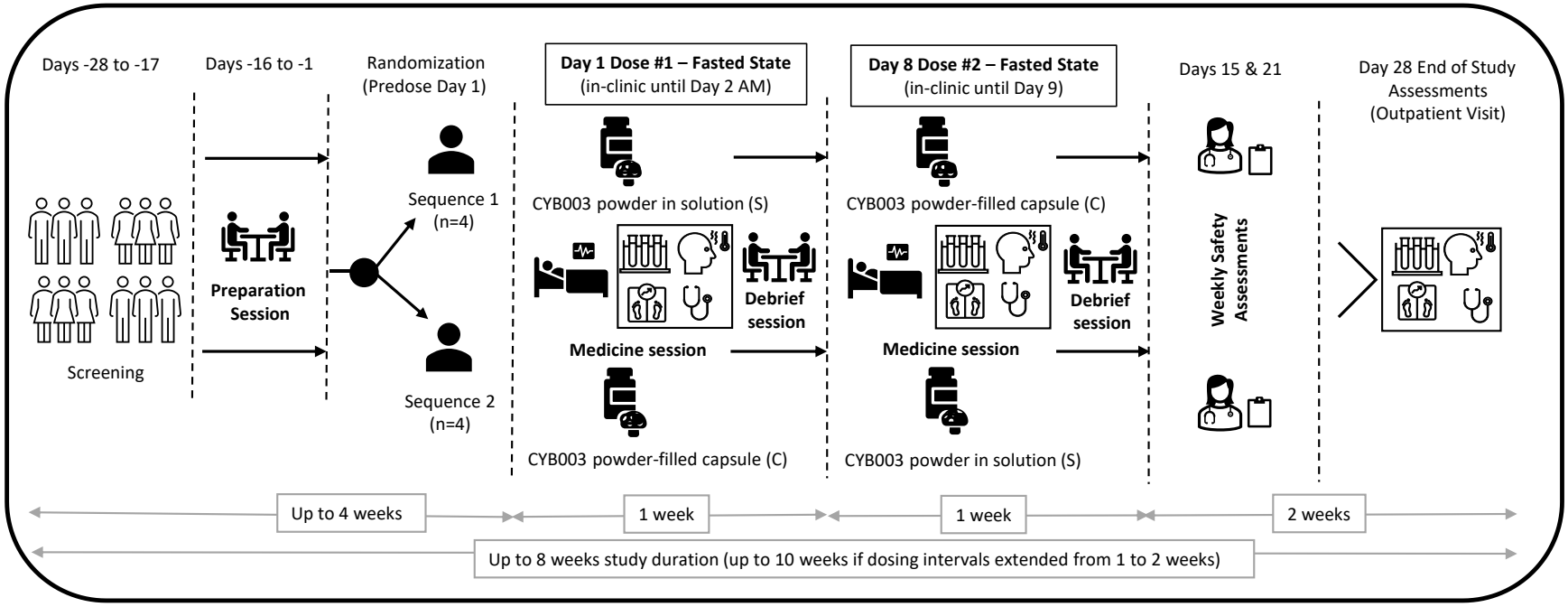


Table 4-1: MDD Participants – Schedule of Assessments

Study Days / Evaluations[3]	Screening Period[1]		First Dosing Period					Second Dosing Period + Weekly Safety Assessments					End of Study Follow-Up Assess-ments[2]	Post-Study Remote Assess-ments[16]
	D-28 to D-2	D-1	D1 (First Dose)	D2	D10 +/- 3	D17 +/-3	D21 +7	D22 (Second Dose)	D23	D31 +/- 3	D38 +/-3	D42	D56[2] +/-3	
Informed Consent	X													
Inclusion/ Exclusion Criteria	X	X												
Medical History / Demographics	X													
Physical Examination	X[4]	X		X[5]			X		X			X	X[6]	
Vital Signs[7]	X	X	X[8]	X			X	X[8]	X			X	X	
Clinical Safety Labs	X	X		X			X		X			X		
TSH	X											X		
Serology	X													
Urine Drugs of Abuse, Alcohol Breath Screen[9]	X	X					X							
COVID-19 Testing[10]	X	X					X							
Pregnancy Test[11]	X	X					X						X	
Diagnostic Interview[12]	X													
MINI[13]	X													
MADRS (in clinic)	X	X	X[14]				X	X[14]				X		
MADRS (remote)					X	X				X	X			X[16]
MEQ30			X[14]					X[14]						
5D-ASC			X[14]					X[14]						
HRS			X[14]					X[14]						
PEQ			X[14]					X[14]						
VAS Ratings of "Any Drug Effect"			X[15]					X[15]						
QIDS SR-16[16]		X					X					X		X[16]

Study Days Evaluations[3]	Screening Period[1]		First Dosing Period					Second Dosing Period + Weekly Safety Assessments					End of Study Follow-Up Assess-ments[2]	Post-Study Remote Assess-ments[16]
	D-28 to D-2	D-1	D1 (First Dose)	D2	D10 +/- 3	D17 +/-3	D21 +7	D22 (Second Dose)	D23	D31 +/- 3	D38 +/-3	D42	D56[2] +/-3	
SF-36	X	X		X			X		X			X		
C-SSRS-Lifetime	X													
C-SSRS-SLV		X		X	X[17]	X[17]	X		X	X[17]	X[17]	X	X	
ECG[18]	X	X	X	X			X	X	X					
12-lead Holter Monitoring[19]		X	X					X						
Admission to Inpatient Unit		X					X							
Randomization[20]			X											
Study Drug administration[21]			X					X						
Blood PK sampling[22]			X[23]	X[23]				X[23]	X[23]					
Treatment-emergent AE Monitoring			X ---------- X											
Prior and Concomitant medications	X	X	X ---------- X											
Discharge from Inpatient Unit				X					X					
Discharge from Study													X	

Abbreviations: 5D-ASC – 5-Dimensional Altered States of Consciousness Rating Scale; AE – adverse event; COVID-19 – Coronavirus disease caused by SARS-CoV-2 virus; C-SSRS – Columbia-Suicide Severity Rating Scale; C-SSRS-SLV – Columbia-Suicide Severity Rating Scale – Since Last Visit; ECG – electrocardiogram; HRS – Hallucinogen Rating Scale; MADRS – Montgomery-Åsberg Depression Rating Scale; MEQ30 – Mystical Experience Questionnaire, 30-item version; MINI – Mini-International Neuropsychiatric Interview; PEQ – Persist Effects Questionnaire; PK – pharmacokinetics; SF-36 – 36-item Short Form Survey; VAS – Visual Analogue Scale.

Note that Day 21 is the end of the first dose session evaluations and is also re-admission to the inpatient unit for the start of the second dose session. The timing of Day 21 and the start of the second dose session may be delayed up to 7 days for some cohorts to review available safety, PK and PD data.

[1] Screening Period will include Days -28 to -17 screening assessments and Preparatory Psychotherapy Sessions as described in Table 4-2.

[2] An End of Study final outpatient visit will take place 2 weeks (± 3 days) after the Day 42 visit or at early discontinuation (if applicable).

[3] For timepoints with multiple assessments, the ECG will be collected first, then vital signs, then the PK blood draw (the PK sample will be collected at the scheduled time postdose).

[4] Physical examinations at Screening will include body weight, BMI and height.

[5] Body weight and BMI only.

[6] Physical examinations at the EOS visit will also include body weight and BMI.

[7] Vital signs measurements include BP, pulse, respiratory rate and body temperature. BP and pulse will be measured in the supine position. Measurements will be obtained after participants have rested in the supine position for at least 5 minutes.

[8] On Day 1 and Day 22, BP, pulse, respiratory rate, and body temperature will be evaluated predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. On Day 2 and Day 23, BP, pulse, respiratory rate, and body temperature will be evaluated at 24 hours postdose. All collection timepoints are ±10 min.

[9] Urine dipsticks may be used on Day -1 and Day 21 for drugs of abuse testing. A breathalyser may be used on Day -1 and Day 21 for alcohol testing.

[10] A COVID-19 test will be performed at Screening and on Day -1 and Day 21. Participants who test positive for COVID-19 infection at Screening will be excluded from participating in the study.

[11] Women of childbearing potential only. A serum pregnancy test will be conducted at Screening; a serum or urine pregnancy test will be conducted on Day -1 and Day 21. A urine pregnancy test will be conducted at subsequent visits; if a urine pregnancy test is positive, a serum pregnancy test will be conducted.

[12] A diagnostic interview will be conducted by a clinician done in coordination with research site staff during the Screening assessments prior to the preparatory sessions, to confirm the MDD diagnosis and that the participant does not have treatment-resistant depression.

[13] The MINI may be performed remotely, if required.

[14] The MADRS, MEQ30, 5D-ASC, HRS and PEQ will be administered at the end of the study drug administration session (4 to 10 hours postdose).

[15] VAS ratings of 'Any drug effect' will be conducted predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. All collection timepoints are ±10 min.

[16] Participants will complete a remote MADRS follow-up assessment post-study at 4-, 8- and 12-weeks post-Day 42 timepoints (allowable time window for completion is ± 3 days). Participants will be asked to complete an optional QIDS SR-16 follow-up assessment post-study done via ePRO at 4-, 8- and 12-weeks post-Day 42 timepoints.

[17] C-SSRS-SLV may be administered remotely on D10, D17, D31 and D38 visits.

[18] 12-lead safety ECGs will be printed in triplicates from the Holter device with 5 minutes between each recording. ECGs will be obtained after participants have rested in the supine position for at least 10 minutes at the following time points on Day 1 and Day 22: 3 time points prior to dosing (-45, -30 and -15 minutes) and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose and on Day 2 and Day 23 at 24 hours postdose, immediately before the PK sample. All collection timepoints are ±10 min. When ECG recordings coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in said order.

[19] 12-lead Holter data will be collected for 6 hours (± 10 minutes) on Day -1 to establish a baseline; and from 1 hour predose until 12 hours (± 10 minutes) postdose on Day 1 and Day 22.

[20] Participants will be randomized on Day -1 or the morning of Day 1 after completion of all 3 preparatory sessions and re-confirmation by the Investigator that all inclusion criteria are met and none of the exclusion criteria are met.

[21] Study drug will be administered in the fasting state (following an overnight fast of at least 10 hours and except for the ingestion of the orange drink study drug solution).

[22] Pharmacokinetic blood samples will be conducted within the following allowable time windows for timepoints: Predose (from 0 to 30 minutes predose), 1 h timepoint (±2 min), 6 h timepoint (±5 min), 8 and 12 h timepoints (±10 min), and 24 h timepoint (±15 min).

[23] On Day 1 and Day 22, plasma samples for PK analysis will be collected predose and at 1, 6, 8, and 12 hours postdose. On Day 2 and Day 23, plasma samples for PK analysis will be collected at 24 hours postdose.

Table 4-2: MDD Participants – Preparatory and Integration Psychotherapy Sessions

Study Days / Evaluations	Baseline Preparatory Psychotherapy Sessions			Post-First Dose Integration Psychotherapy Sessions			Post-Second Dose Integration Psychotherapy Sessions		
	After Eligibility Confirmation	After Eligibility Confirmation	D-1 -7	D2 +7	D10 +/- 4	D21 -7	D23 +7	D31 +/- 4	D38 +/-4
Psychotherapy – Preparation (predose)[1]	X	X[3]	X						
Psychotherapy Integration - (postdose)[2]				X	X[3]	X	X	X[3]	X[3]

[1] Three baseline preparatory psychotherapy sessions lasting 90 minutes each will be performed, with the first two preparatory psychotherapy sessions occurring after eligibility confirmation and the third session occurring on Day -1 (-7 day window). The preparatory sessions have a flexible time window as indicated in the table, provided that all the screening assessments are performed and the participant is determined to be eligible by the Investigator. Additional preparatory psychotherapy sessions and integration sessions may be performed at the discretion of the facilitator in coordination with the Investigator and research staff.

[2] Three postdose integration psychotherapy sessions lasting 90 minutes will be performed following the first dose, and again following the second dose. The time windows for these postdose sessions are flexible as indicated in the table. D1 and D22 dose columns are listed in this table as reference anchors relative to the psychotherapy sessions.

[3] All psychotherapy visits (preparatory & integration) are preferred in person but psychotherapy session facilitators have the option to conduct any two of the three preparatory sessions and all of the integration sessions as remote/telemedicine visits.

Table 4-3: NHV Participants– Schedule of Assessments

Study Days / Evaluations[4]	Screening Period[1]	First Dosing Period				Second Dosing Period + Weekly Safety Assessments				End of Study Follow-Up Assess-ments[2]
	D-28 to D-2	D-1	D1 (First Dose)	D2	D7	D8 (Second Dose)[2]	D9	D15	D21	D28[3] +/-3
Informed Consent	X									
Inclusion/ Exclusion Criteria	X	X								
Medical History / Demographics	X									
Physical Examination	X[5]	X		X[6]	X		X		X	X[7]
Vital Signs[8]	X	X	X[9]	X	X	X[9]	X		X	X
Clinical Safety Labs	X	X		X	X		X		X	
TSH	X								X	
Serology	X									
Urine Drugs of Abuse, Alcohol Breath Screen[10]	X	X			X					
COVID-19 Testing[11]	X	X			X					
Pregnancy Test[12]	X	X			X					X
MEQ30			X[13]			X[13]				
5D-ASC			X[13]			X[13]				
HRS			X[13]			X[13]				
PEQ			X[13]			X[13]				
VAS Ratings of "Any Drug Effect"			X[14]			X[14]				
C-SSRS-Lifetime	X									
C-SSRS-SLV		X		X	X		X	X	X	X
ECG[15]	X	X	X	X	X	X	X			
12-lead Holter Monitoring[16]		X	X			X				
Admission to Inpatient Unit		X			X					

Study Days Evaluations[4]	Screening Period[1] D-28 to D-2	First Dosing Period D-1	 D1 (First Dose)	 D2	 D7	Second Dosing Period + Weekly Safety Assessments D8 (Second Dose)[2]	 D9	 D15	 D21	End of Study Follow-Up Assess-ments[2] D28[3] +/-3
Predose Preparation Session		X								
Randomization[17]			X							
Study Drug administration[18]			X			X				
Blood PK sampling[19]			X[20]	X[20]		X[20]	X[20]			
Medicine Session			X			X				
Postdose Debrief Session				X			X			
Treatment-emergent AE Monitoring		X ----------								----------X
Prior and Concomitant medications	X	X ----------								----------X
Discharge from Inpatient Unit				X			X			
Telephone Safety Assessments								X	X	
Outpatient Safety Assessment Visit										X
Discharge from Study										X

Abbreviations: 5D-ASC – 5-Dimensional Altered States of Consciousness Rating Scale; AE – adverse event; COVID-19 – Coronavirus disease caused by SARS-CoV-2 virus; C-SSRS – Columbia-Suicide Severity Rating Scale; C-SSRS-SLV – Columbia-Suicide Severity Rating Scale – Since Last Visit; ECG – electrocardiogram; HRS – Hallucinogen Rating Scale; MEQ30 – Mystical Experience Questionnaire, 30-item version; PEQ – Persist Effects Questionnaire; PK – pharmacokinetics; VAS – Visual Analogue Scale.

[1] Screening Period will include Days -28 to -2 screening assessments and predose Preparation Session on Day -1 prior to Day 1 dosing.

[2] The second dose may be administered 2 weeks instead of 1 week after the first dose on Day 15 at the Investigator's discretion, and all visit days for the second dosing period would shift by 1 week; e.g., D14 admission, D15 second dose, D16, D21±3 days, D28 visits during second dosing period, and follow-up assessments on D35±3 days. If the interval between doses is extended, participants should receive a telephonic safety assessment at approximately weekly intervals. Weekly telephonic safety assessments have an allowable visit window of ±3 days.

[3] An End of Study final outpatient visit will take place on Day 28 ± 3 days visit or at early discontinuation (if applicable).

[4] For timepoints with multiple assessments, the ECG will be collected first, then vital signs, then the PK blood draw (the PK sample will be collected at the scheduled time postdose).

[5] Physical examinations at Screening will include body weight, BMI and height.

[6] Body weight and BMI only.

[7] Physical examinations at the EOS visit will also include body weight and BMI.

[8] Vital signs measurements include BP, pulse, respiratory rate and body temperature. BP and pulse will be measured in the supine position. Measurements will be obtained after participants have rested in the supine position for at least 5 minutes.

[9] On Day 1 and Day 8, BP, pulse, respiratory rate, and body temperature will be evaluated predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. On Day 2 and Day 9, BP, pulse, respiratory rate, and body temperature will be evaluated at 24 hours postdose. All collection timepoints are ±10 min.

[10] Urine dipsticks may be used on Day -1 and Day 7 for drugs of abuse testing. A breathalyser may be used on Day -1 and Day 7 for alcohol testing.

[11] A COVID-19 test will be performed at Screening, Day -1 and Day 7. Participants who test positive for COVID-19 infection at Screening will be excluded from participating in the study.

[12] Women of childbearing potential only. A serum pregnancy test will be conducted at Screening; a serum or urine pregnancy test will be conducted on Day -1 and Day 7. A urine pregnancy test will be conducted at subsequent visits; if a urine pregnancy test is positive, a serum pregnancy test will be conducted.

[13] The MEQ30, 5D-ASC, HRS and PEQ will be administered at the end of the study drug administration session (4 to 10 hours postdose).

[14] VAS ratings of 'Any drug effect' will be conducted predose and at 0.5, 1, 2, 4, 6, 8 and 12 hours postdose. All collection timepoints are ±10 min.

[15] 12-lead safety ECGs will be printed in triplicates from the Holter device with 5 minutes between each recording. ECGs will be obtained after participants have rested in the supine position for at least 10 minutes at the following time points on Day 1 and Day 8: 3 time points prior to dosing (-45, -30 and-15 minutes) and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose and on Day 2 and Day 9 at 24 hours postdose, immediately before the PK sample. All collection timepoints are ±10 min. When ECG recordings coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in said order.

[16] 12-lead Holter data will be collected for 6 hours (± 10 minutes) on Day -1 to establish a baseline; and from 1 hour predose until 12 hours (± 10 minutes) postdose on Day 1 and Day 8.

[17] Participants will be randomized on Day -1 or the morning of Day 1 after completion of the predose preparation session and re-confirmation by the Investigator that all inclusion criteria are met and none of the exclusion criteria are met.

[18] Study drug will be administered in the fasting state (following an overnight fast of at least 10 hours and except for the ingestion of the orange drink study drug solution).

[19] Pharmacokinetic blood samples will be conducted within the following allowable time windows for timepoints: Predose (from 0 to 30 minutes predose), 0.5 and 1 h timepoints (±2 min), 2 to 6 h timepoints (±5 min), 8 and 12 h timepoints (±10 min), and 24 h timepoint (±15 min).

[20] On Day 1 and Day 8, plasma samples for PK analysis will be collected predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. On Day 2 and Day 9, plasma samples for PK analysis will be collected at 24 hours postdose.

Table 4-4: NHV Participants (Relative Bioavailability Cohort) – Schedule of Assessments

	Screening Period[1]	First Dosing Period				Second Dosing Period + Weekly Safety Assessments				End of Study Follow-Up Assess-ments[2]
Study Days **Evaluations[4]**	**D-28 to D-2**	**D-1**	**D1 (First Dose)**	**D2**	**D7**	**D8 (Second Dose)[2]**	**D9**	**D15**	**D21**	**D28[3] +/-3**
Informed Consent	X									
Inclusion/ Exclusion Criteria	X	X								
Medical History / Demographics	X									
Physical Examination	X[5]	X		X[6]	X		X		X	X[7]
Vital Signs[8]	X	X	X[9]	X	X	X[9]	X		X	X
Clinical Safety Labs	X	X		X	X		X		X	
TSH	X								X	
Serology	X									
Urine Drugs of Abuse, Alcohol Breath Screen[10]	X	X			X					
COVID-19 Testing[11]	X	X			X					
Pregnancy Test[12]	X	X			X					X
MEQ30			X[13]			X[13]				
5D-ASC			X[13]			X[13]				
HRS			X[13]			X[13]				
PEQ			X[13]			X[13]				
VAS Ratings of "Any Drug Effect"			X[14]			X[14]				
C-SSRS-Lifetime	X									
C-SSRS-SLV		X		X	X		X	X	X	X
ECG[15]	X	X	X	X	X	X	X			
12-lead Holter Monitoring[16]		X	X			X				
Admission to Inpatient Unit		X			X					

Study Days Evaluations[4]	Screening Period[1]	First Dosing Period				Second Dosing Period + Weekly Safety Assessments				End of Study Follow-Up Assess-ments[2]
	D-28 to D-2	D-1	D1 (First Dose)	D2	D7	D8 (Second Dose)[2]	D9	D15	D21	D28[3] +/-3
Predose Preparation Session		X								
Randomization[17]			X							
Study Drug administration[18]			X			X				
Blood PK sampling[19]			X[20]	X[20]		X[20]	X[20]			
Medicine Session			X			X				
Postdose Debrief Session				X			X			
Treatment-emergent AE Monitoring		X ----------								X
Prior and Concomitant medications	X	X ----------								X
Discharge from Inpatient Unit				X			X			
Telephone Safety Assessments								X	X	
Outpatient Safety Assessment Visit										X
Discharge from Study										X

Abbreviations: 5D-ASC – 5-Dimensional Altered States of Consciousness Rating Scale; AE – adverse event; COVID-19 – Coronavirus disease caused by SARS-CoV-2 virus; C-SSRS – Columbia-Suicide Severity Rating Scale; C-SSRS-SLV – Columbia-Suicide Severity Rating Scale – Since Last Visit; ECG – electrocardiogram; HRS – Hallucinogen Rating Scale; MEQ30 – Mystical Experience Questionnaire, 30-item version; PEQ – Persist Effects Questionnaire; PK – pharmacokinetics; VAS – Visual Analogue Scale.

[1] Screening Period will include Days -28 to -2 screening assessments and predose Preparation Session on Day -1 prior to Day 1 dosing.

[2] The preferred dosing interval for each dose is 1 week between the first and second doses, however, this interval may be increased up to 2 weeks between doses at the Investigator's discretion. All visit days for the second dosing day would shift. If the interval between doses is extended, participants should receive a telephonic safety assessment at approximately weekly intervals. Weekly telephonic safety assessments have an allowable visit window of ±3 days.

[3] An End of Study final outpatient visit will take place on Day 28 ± 3 days visit or at early discontinuation (if applicable).

[4] For timepoints with multiple assessments, the ECG will be collected first, then vital signs, then the PK blood draw (the PK sample will be collected at the scheduled time postdose).
[5] Physical examinations at Screening will include body weight, BMI and height.
[6] Body weight and BMI only.
[7] Physical examinations at the EOS visit will also include body weight and BMI.
[8] Vital signs measurements include BP, pulse, respiratory rate and body temperature. BP and pulse will be measured in the supine position. Measurements will be obtained after participants have rested in the supine position for at least 5 minutes.
[9] On Day 1 and Day 8, BP, pulse, respiratory rate, and body temperature will be evaluated predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. On Day 2 and Day 9, BP, pulse, respiratory rate, and body temperature will be evaluated at 24 hours postdose. All collection timepoints are ±10 min.
[10] Urine dipsticks may be used on Day -1 and Day 7 for drugs of abuse testing. A breathalyser may be used on Day -1 and Day 7 for alcohol testing.
[11] A COVID-19 test will be performed at Screening, Day -1 and Day 7. Participants who test positive for COVID-19 infection at Screening will be excluded from participating in the study.
[12] Women of childbearing potential only. A serum pregnancy test will be conducted at Screening; a serum or urine pregnancy test will be conducted on Day -1 and Day 7. A urine pregnancy test will be conducted at subsequent visits; if a urine pregnancy test is positive, a serum pregnancy test will be conducted.
[13] The MEQ30, 5D-ASC, HRS and PEQ will be administered at the end of the study drug administration session (4 to 10 hours postdose).
[14] VAS ratings of 'Any drug effect' will be conducted predose and at 0.5, 1, 2, 4, 6, 8 and 12 hours postdose. All collection timepoints are ±10 min.
[15] 12-lead safety ECGs will be printed in triplicates from the Holter device with 5 minutes between each recording. ECGs will be obtained after participants have rested in the supine position for at least 10 minutes at the following time points on Day 1 and Day 8: 3 time points prior to dosing (-45, -30 and -15 minutes) and at 0.5, 1, 2, 4, 6, 8, 12 hours postdose and on Day 2 and Day 9 at 24 hours postdose, immediately before the PK sample. All collection timepoints are ±10 min. When ECG recordings coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in said order.
[16] 12-lead Holter data will be collected for 6 hours (± 10 minutes) on Day -1 to establish a baseline; and from 1 hour predose until 12 hours (± 10 minutes) postdose on Day 1 and Day 8.
[17] Participants will be randomized on Day -1 or the morning of Day 1 after completion of the predose preparation session and re-confirmation by the Investigator that all inclusion criteria are met and none of the exclusion criteria are met.
[18] Study Drug Dose #1 and Dose #2 will be administered in the fasting state (following an overnight fast of at least 10 hours and except for the ingestion of the orange drink study drug solution).
[19] Pharmacokinetic blood samples will be conducted within the following allowable time windows for timepoints: Predose (from 0 to 30 minutes predose), 0.5 and 1 h timepoints (±2 min), 2 to 6 h timepoints (±5 min), 8 and 12 h timepoints (±10 min), and 24 h timepoint (±15 min).
[20] On Day 1 and Day 8, plasma samples for PK analysis will be collected predose and at 0.5, 1, 2, 4, 6, 8, and 12 hours postdose. On Day 2 and Day 9, plasma samples for PK analysis will be collected at 24 hours postdose.

5. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the last quantifiable time point
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
BA	Bioavailability
BLOQ	Below limit of quantitation
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
C_{max}	maximum plasma concentration
CFR	Code of Federal Regulations
CK	creatine kinase
CNS	central nervous system
COVID-19	coronavirus disease caused by SARS-CoV-2 virus
C-SSRS	Columbia-Suicide Severity Rating Scale
$C\text{-}SSRS_{SLV}$	C-SSRS since last visit
CYB003	Investigational product being evaluated in this study, an oral, deuterated psilocin
CRF	case report form
CYP	cytochrome P450
DBP	diastolic blood pressure
DRF	dose range finding
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	ethics committee
ECG	electrocardiogram
EMBARK	a six-domain framework for psychedelic-assisted psychotherapy; the six domains are: Existential-Spiritual, Mindfulness, Body Aware, Affective-Cognitive, Relational, and Keeping Momentum
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
h or hr	hour(s)
HRS	Hallucinogen Rating Scale

HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC	informed consent
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal rate-constant
kg	kilogram(s)
L	liter
LC-MS/MS	liquid chromatography tandem mass spectrometry
Ln	natural logarithm
MADRS	Montgomery-Åsberg Depression Rating Scale
MCH	mean corpuscular or cell hemoglobin
MCHC	mean corpuscular or cell hemoglobin concentration
MCV	mean corpuscular or cell volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MEQ30	Revised Mystical Experience Questionnaire
mg	milligram(s)
min	minute or minutes
MINI	Mini International Neuropsychiatric Interview, Version 7.0.2
mL	milliliter(s)
NCE	new chemical entity
ng	nanogram(s)
NHV	normal healthy volunteer
NIMH	National Institute of Mental Health
OTC	over-the-counter
PAP	psychedelic-assisted psychotherapy
PEQ	Persisting Effects Questionnaire
PK	pharmacokinetic(s)
PD	pharmacodynamic(s)
PrEP	preexposure prophylaxis
PT	prothrombin time
QD	once daily
QIDS SR-16	Quick Inventory of Depressive Symptomatology, Self Report 16 item scale
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	reference formulation
RBC	red blood cell
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SF-36	36-item Short Form Survey
SOC	System Organ Class
SRC	Safety Review Committee
T	test formulation

TK	toxicokinetic(s)
T_{max}	time to maximum plasma concentration
TOX	toxicology
$T_{1/2}$	half-life
USA	United States of America
VAS	visual analogue scale
WBC	white blood cell
5D-ASC	5-Dimensional Altered States of Consciousness Rating Scale

6. BACKGROUND INFORMATION

CYB003 is a synthetic, deuterated isotopomer of psilocin, being developed by Cybin for the treatment of MDD. Psilocin is the active metabolite of psilocybin responsible for the psychedelic effects of the parent compound.

6.1. Major Depressive Disorder

Major Depressive Disorder (MDD) is the leading cause of disability worldwide (Cosgrove 2020), and results in a significant economic and societal cost (Vigo 2016). In the United States, MDD is a significant public health issue, with an estimated 21.0 million adults having at least one major depressive episode in 2020, which represents 8.4% of all US adults (NIMH, January 2022 publication). The prevalence of major depressive episode was higher among adult females (10.5%) compared to males (6.2%), and was highest among individuals aged 18-25 years (17.0%) (NIMH, January 2022).

While multiple medications and psychological interventions are available to treat MDD, up to 30% of patients do not respond to first line treatment with up to 30% not benefiting despite multiple treatments (treatment resistant) (Rizvi 2014; Rush 2006). Further, available antidepressant medications require daily dosing, have a slow onset of action and take several weeks to show any beneficial effect (Cipriani 2018), require long term treatment and are associated with dose-limiting side effects such as gastrointestinal (GI) disturbances, sedation, and sexual dysfunction (FDA 2019). There is therefore a significant unmet need for treatments that start working swiftly, are well tolerated and are not required to be taken long term.

Treatments for MDD have traditionally focused on the monoamine transmitters, preventing the reuptake of serotonin and/or norepinephrine and thereby increasing their availability at the synaptic cleft. While this has been met with some success, these treatments are symptomatic and do not address the underlying biopsychosocial causes. The resurrection of research into serotonergic psychedelic medicines offers the opportunity to explore an alternative approach where the use of psychedelics opens a therapeutic window to facilitate insight and, with psychotherapeutic support, carry out the necessary emotional work to improve depressive symptomatology (Nutt 2020).

6.2. Background Information on Psilocybin and Psilocin

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a natural product produced by numerous species of Psilocybe mushrooms. It is a tryptamine derivative, and in humans the phosphate group is rapidly enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin (5-hydroxytryptamine [5-HT]) receptors, the most important of which in this setting is the 5-HT2A receptor (Carhart-Harris 2014; Nichols, 2004). Psilocin is detectable in plasma within 15 minutes of administration of psilocybin (Brown 2017;

Hasler 1997), with a half-life of approximately 3 ± 1 hours (Brown 2017). Onset of noticeable psychoactive effects occurs within 1 hour, peaks at about 2 to 3 hours after dosing, and diminishes typically around 6 hours post-dose (Griffiths 2018). Based on this time course, in the clinical trial setting, it is medically prudent to observe participants for at least approximately 8 hours after dosing (Griffiths 2018).

Psilocybin was first isolated from Psilocybe mushrooms in 1957, followed by de novo synthesis in 1958 (Passie 2002). It was marketed worldwide in the 1960s as Indocybin™ for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substance, placed in Schedule I in 1970, and effectively removed from clinical use and scientific study. Several lines of evidence suggested that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically beneficial behavior change in a variety of psychiatric conditions. Psilocybin has been previously studied in clinical trials in various diseases including anxiety (Nutt 2019), depression (Carhart-Harris 2021), obsessive compulsive disorder (OCD) (Moreno 2006), cancer related depression and anxiety (Griffiths 2016; Ross 2016), different types of headaches (Schindler 2021; Sewell 2006), and substance use (e.g., alcohol [Nielson 2018], smoking [Noorani 2018]) disorder.

Notably, psilocybin was recently granted the "breakthrough therapy" designation by the US Food and Drug Administration (FDA) for MDD (Staines 2019), and treatment-resistant depression (TRD) (Compass Pathways 2018). This designation represents a significant milestone for psychedelic research as this is a recognition that this class of treatments could be developed to produce a substantial improvement in outcomes over currently available treatments for these disorders (FDA 2018).

The PK, pharmacology and human metabolism of psilocybin are well known and well characterized. The clinical safety of psilocybin has also been extensively studied, both as a single agent and as adjunctive treatment in adult populations.

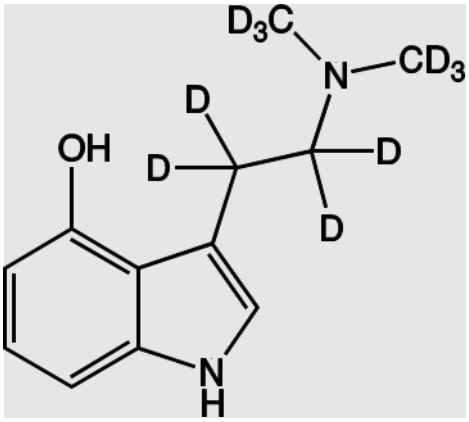
Studies using oral psilocybin have shown its therapeutic utility and have explored its mechanism of action (Carhart-Harris 2016; Carhart-Harris 2021; Davis 2021; Kraehenmann 2017; Nutt 2020; Vollenweider 2010). However, these studies also highlighted that the conventional oral psilocybin formulation has its limitations; PK variability, prolonged duration of treatment effect, and therefore, difficulty in optimizing treatment.

6.3. CYB003 Investigational Product

Cybin is developing a synthetic, deuterated isotopomer of psilocin where deuterium (^{2}H) is substituted for 10 hydrogen (^{1}H) atoms along the carbon chain and the 2 methyl groups of the molecule (Figure 6-1), presented below including CYB003 free base and CYB003 benzenesulfonate salt.

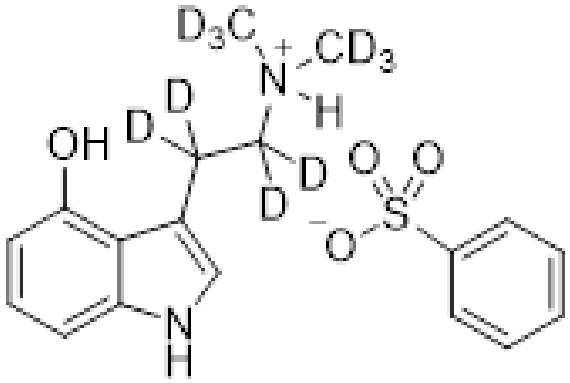
Figure 6-1: Structure of CYB003 Free Base (a) and CYB003 Benzenesulfonate Salt (b)

a)



Chemical Names: 3-[2-[bis(trideuteriomethyl)amino]-1,1,2,2-tetradeuterioethyl]-1H-indol-4-ol, or 3-[2-[di(methyl-d3)amino]ethyl-1,1,2,2-d4]-1H-indol-4-ol

b)



2-(4-hydroxy-1*H*-indol-3-yl)-*N*,*N*-bis(methyl-d_3)
ethan-1,1,2,2-d_4-1-aminium benzenesulfonate

Deuteration of psilocin, as has been demonstrated in the studies conducted by Cybin, enables consistent drug concentrations to be achieved (i.e., reduces variability in the plasma), for target receptor occupancy to be reached quickly and reliably, and shortens the duration of the psychedelic experience which in turn is expected to make it easier to provide this treatment on a larger scale.

The investigational product CYB003 will be provided to the clinical research site as the active pharmaceutical ingredient (Psilocin d10 free base API) and as powder-filled capsules containing the psilocin d10 benzenesulfonate salt. CYB003 drug substance will be dissolved in 0.1 M citric acid then further diluted in a drinkable orange flavored solution for oral administration.

The bulk API investigational product will be manufactured by Patheon Pharm Services, part of Thermo Fisher Scientific, Greenville, South Carolina. CYB003 API will be provided as bulk powder and will be packaged into amber glass containers and will be labeled with protocol number, lot number, and "Caution: New Drug–Limited by Federal (or United States) Law to Investigational Use". Bulk CYB003 API bottles will be stored at 2-8°C.

CYB003 powder-filled capsules will contain the psilocin d10 benzenesulfonate salt and will be manufactured by Patheon Pharmaceuticals Inc., Cincinnati, Ohio. CYB003 powder-filled capsules will be packaged into amber glass bottles and labeled with protocol number, lot number, and "Caution: New Drug–Limited by Federal (or United States) Law to Investigational Use". CYB003 powder-filled capsule bottles will be stored at 2-8°C.

6.4. CYB003 Non-Clinical Data

The first phase of the non-clinical development program for CYB003 was to demonstrate that CYB003 was comparable to psilocin based on pharmacology (primary and secondary pharmacodynamic and safety pharmacology studies), PK (concomitant administration of CYB003 and psilocin in comparison to psilocybin following IV and oral administration) and *in vitro* toxicology (preliminary genotoxicity assays and in vitro toxicity).

The studies conducted with CYB003 and psilocin demonstrated that CYB003 and psilocin were comparable in terms of pharmacology, PK and *in vitro* toxicity. The maximum tolerated dose (MTD) studies conducted with CYB003 in rats and dogs with dosing on Days 1 and 8, a standard ICH battery of genotoxicity studies, combined with the single-dose CNS, respiratory and cardiovascular (in vitro hERG and in vivo dog study) safety pharmacology studies, and clinical experience with psilocybin (active metabolite psilocin) as described in the literature, support the proposed initial dose in this clinical study.

The second phase of the non-clinical development program for CYB003 was conducted to establish the safety of CYB003 (safety pharmacology and toxicology) and the PK and TK profiles of CYB003. The pivotal studies were conducted in compliance with GLP standards and applicable regulations. No effects of CYB003 were reported at any of the doses tested in the dog 4-week GLP toxicology study (highest dose 5 mg/kg). In the rat 4-week GLP toxicology study, thyroid pigmentation was observed in all/ most animals across all dose levels.

Further details for these pharmacology, PK, in vitro toxicology, and GLP safety pharmacology and toxicology and TK studies are presented in the CYB003 Investigator's Brochure.

6.5. CYB003 Clinical Data

No clinical studies have been conducted with CYB003 to date.

6.6. Study Rationale

Psilocybin has already shown potential for the treatment of MDD. However, studies also highlighted that the conventional oral psilocybin formulation has its limitations; PK variability, prolonged duration of treatment effect, and therefore, difficulty in optimizing treatment.

In a rat single-dose pharmacokinetic (PK) study (CYB003+psilocin given concomitantly vs psilocybin) following oral administration, CYB003 exhibited shorter time to onset of activity (based on time taken to reach maximum plasma concentration [T_{max}]), less inter-individual variability, and a shorter duration of exposure, compared with psilocin as measured following psilocybin administration. These properties allow for the possibility of more rapid onset and a shorter duration of psychedelic experience, thus potentially shortening the overall required observation period for clinical use. The reduced intersubject variability may also result in more consistent dosing and level of effect in patients. CYB003 may also have an improved safety profile compared to psilocybin. It is speculated that the rapid absorption of CYB003 from the GI tract may reduce the symptoms of nausea observed with the oral administration of psilocybin by reduced interactions with gut serotonin (5-HT) receptors.

Taken together, Cybin believes that the unique PK properties of CYB003 provide a meaningful advantage over psilocybin for the treatment of an array of psychiatric disorders, including MDD.

6.7. Study Design Considerations

The current study design evaluates CYB003 compared to placebo in the first dose session in a double-blind manner. The study further evaluates the incremental benefit of a second dose of CYB003 with all participants receiving active CYB003 for the second dose. In MDD participants that receive placebo at baseline, the study provides an opportunity to make within-subject comparisons an evaluate the incremental benefit of CYB003 in the second period, over placebo and EMBARK supportive psychotherapy only in the first period.

An important aspect of this study design is the incorporation of psychedelic-assisted psychotherapy (PAP) sessions, initially in preparing participants for the potential psychedelic experience of taking CYB003 prior to study medication dosing, and subsequently supporting participants to integrate their experiences following each study dosing session.

The safety, tolerability, PK and clinical effects of CYB003 will be evaluated closely using standard safety assessments and well-established efficacy questionnaires and rating scales, with the primary endpoint for clinical efficacy being based on the MADRS, which is an accepted standard assessment tool in the treatment of MDD.

As CYB003 has not been administered previously to humans in clinical trials, a dose escalation design is being implemented, along with sentinel dosing for each cohort to maximize participant safety. It is anticipated that the initial dose or dose levels of CYB003 may be sub-psychedelic

doses, and dose escalation will proceed with full review of all relevant safety, PK and clinical effect data prior to proceeding to higher dose levels.

In one cohort of 8 healthy participants without MDD, the CYB003 powder in solution dosage form will be compared to the powder-filled capsule dosage form with each administered as a single oral dose in the fasted state in an open-label, randomized, crossover design. This allows for a comparison of the relative bioavailability of both dosage forms.

6.8. Starting Dose Justification

CYB003 is a synthetic, deuterated isotopomer of psilocin where deuterium is substituted for 10 hydrogen atoms along the carbon chain and the two methyl groups of the molecule. Studies comparing in vitro and in vivo pharmacology of CYB003 with psilocin have shown that CYB003 pharmacology is comparable to psilocin (CYB003 Investigators' Brochure). Therefore, pharmacology data reported in the literature for psilocin/ psilocybin can be applied to CYB003.

A PK model was constructed by utilizing existing population PK models of psilocybin and modifying them, based on available CYB003 non-clinical PK data. This model was then used to simulate clinical exposures at multiple CYB003 dosing levels, assuming linear pharmacokinetics, covering subtherapeutic, therapeutic, and supratherapeutic concentrations.

In clinical reports from the literature, high quality data were available for psilocin after psilocybin administration (Hasler, 1997; Holze, 2022; Brown, 2017). A population PK model was developed based on Brown et al (2017), which was able to predict exposures reported in Hasler et al (2017) but under predicted exposures reported by Holze et al (2022). This could potentially be due to food intake prior to dosing. Therefore, a worst-case scenario (Scenario 3), that accounts for increased and faster absorption is being utilized for calculation of safety margins (Table 6-1).

Table 6-1: Simulation scenarios utilized for exposure predictions

Scenario Description	Change compared to Brown et al.	Rationale
Scenario 1 - Identical	No change compared to Brown *et al.*	CYB003 absorption and bioavailability behaves identical to psilocin after psilocybin administration in Brown *et al.*
Scenario 2 – Faster absorption	Increased absorption rate constant (from 0.367/h to 1/h), same bioavailability	CYB003 behaves identical to psilocin after psilocybin but with a faster absorption rate due to orange juice administration

Scenario Description	Change compared to Brown et al.	Rationale
Scenario 3 – Faster absorption and Increased F	Increased absorption rate constant (from 0.367/h to 1/h) and AUC increase matches highest pre-clinical dog data (+60% increase in F relative to psilocybin from Brown *et al.*)	**Safety scenario** where the highest Cmax concentrations are reached with a faster absorption compared to literature and higher bioavailability
Scenario 4 – Decreased F	Reduced bioavailability based on pre-clinical rat data and Hasler *et al.* 1997 fasted administration (-50%)	Fasted administration might reduce the bioavailability, with comparable absorption kinetics

To evaluate potential psychedelic effects at various doses of CYB003, data were summarized from published literature for psilocybin (Table 6-2). These effects included VAS (any drug effect), MEQ30, 5D-ASC, HRS.

Table 6-2: Pharmacokinetic / Pharmacodynamic data reported for psilocin

Cmax (ng/mL)	Description	Reference
1.83	No change list of complaints + 5D-ASC	Studerus 2011
5.08	VAS – Any drug effect: 20	Holze 2022
10.2	VAS – Any drug effect: 40	Holze 2022
13	5D-ASC total: 19%	Holze 2022
14.53	MEQ30 total: 66% +	Griffiths 2018 and Holze 2022
15.34	VAS – Any drug effect: 60	Griffiths 2018 and Holze 2022
20.47	VAS – Any drug effect: 80	Holze 2022
25	5D-ASC total score: 29%	Holze 2022
343	Rat Cmax at 40 mg/kg	CYB003 DRF study
51.7	Dog Cmax at 0.5 mg/kg	CYB003 4-week GLP toxicology study

No adverse effects of CYB003 were reported at any of the doses tested in the dog 4-week GLP toxicology study (highest dose of 5 mg/kg) with the exception of cardiovascular and CNS-related clinical signs observed in the dog cardiovascular safety pharmacology study and the dog toxicology study, respectively. Per suggestion by the FDA based on increases in heart rate and the severity and duration of CNS-related clinical signs, the NOAEL in dogs was set at 0.5 mg/kg where the combined male and female C_{max} and AUC_{0-24} values were 63.0 ng/mL and 123 h*ng/mL, respectively. In the rat 4-week GLP toxicology study, thyroid pigmentation was observed in all/most animals across all dose levels. Therefore, safety margins against exposures in the rats have instead been calculated against the Day 8 exposures at 40 mg/kg in female rats in the 8-day DRF rat study (Table 6-3).

Table 6-3: Safety margins to predicted exposures

Dose level	Predicted C_{max}[1]	Predicted AUC[1, 2]	Margins to rat C_{max} at 40 mg/kg[3]	Margins to Dog C_{max} at 0.5 mg/kg[3]
1 mg	2.19/2.1±0.69 (1.21-3.42)	7.21/7.01±1.78 (4.66-10.33)	156.6	23.6
2 mg	4.38/4.18±1.41 (2.4-6.87)	14.56/14.17±3.68 (9.52-21.17)	78.3	11.8
3 mg	6.59/6.33±2.07 (3.62-10.32)	21.69/21.02±5.24 (14.1-31.06)	52.0	7.8
4 mg	8.79/8.51±2.86 (4.5-13.91)	28.92/27.82±7.36 (18.99-42.23)	39.0	5.9
5 mg	10.74/10.41±3.31 (6.03-16.34)	35.27/34.62±8.35 (23.35-50.37)	31.9	4.8
6 mg	12.94/12.58±4.19 (6.98-20.02)	42.96/41.98±10.4 (27.65-61.52)	26.5	4.0
7 mg	15.22/14.45±5.05 (8.24-24.25)	50.12/49.31±12.09 (32.75-72.58)	22.5	3.4
8 mg	17.27/16.89±5.53 (9.02-26.99)	57.48/56.34±13.88 (36.37-81.3)	19.9	3.0
9 mg	19.83/19.37±6.18 (10.78-31.08)	65.41/63.51±16.44 (42.72-96.81)	17.3	2.6
10 mg	21.51/20.7±7.13 (11.18-34.54)	71.96/70.31±17.73 (46.71-102.98)	15.9	2.4
12 mg	26.25/25.56±8.37 (14.11-41.69)	86.55/83.42±21.79 (56.4-126.77)	13.1	2.0
14 mg	30.45/29.8±9.25 (17.25-46.83)	100.37/97.79±23.89 (65.16-143.6)	11.3	1.7
16 mg	34.86/33.71±10.98 (18.78-55.33)	115.67/113.19±28.5 (74.81-168.53)	9.8	1.5
18 mg	38.82/37.75±12.01 (20.81-59.45)	130.09/126.87±31.1 (85.22-186.91)	8.8	1.3
20 mg	43.09/41.67±13.41 (23.73-67.82)	143.47/141.4±34.27 (95.26-205.54)	8.0	1.2
25 mg	53.74/51.6±17.08 (28.33-85.06)	178.49/175.09±43.77 (118.3-262.05)	6.4	1.0

[1] Predicted mean/median ± standard deviation (5%-95% distribution of the population) are reported.

[2] AUC_{0-24} is reported instead of AUC_{inf} because 24h concentrations are low.

[3] Safety margin calculated by dividing lowest mean C_{max} at Day 1 from non-clinical study by the predicted mean C_{max} for each dosing level.
CYB003 concentrations are presented as psilocin concentrations for comparison with other figures. Can be converted to CYB003 concentrations by multiplication of 1.049

A starting dose of 1 mg has been chosen for administration in the first period of Cohort 1.

At this dose, the mean predicted C_{max} is 2.19 ng/mL which is 157-fold lower than the mean C_{max} at 40 mg/kg in the rat and 24-fold lower than the mean C_{max} at 0.5 mg/kg in the dog (Table 6-3).

Given that the lowest exposure at which any drug effect (for psilocin) could be detected using a visual analogue scale is approximately 5.08 ng/mL, no pharmacodynamic effects of CYB003 are expected at a dose of 1 mg (Table 6-2). A dose of 1 mg is therefore considered a sub-psychedelic dose.

No effects of CYB003, tested at concentrations of 1 µM to 2.5 mM, were seen on the hERG tail current amplitude in human embryonic kidney (HEK)-293 cells stably expressing the hERG ion channel and the IC_{50} in this assay was 50.8 µM (10.87 µg/mL), which supports the selection of 1 mg as a safe starting dose.

No major behavioral or physiological findings were reported in the rat Irwin study at CYB003 doses of 75, 100 and 200 mg/kg PO. In the rat respiratory study, CYB003 was tested at 75, 100 and 200 mg/kg PO. Both tidal volume and minute volume were reduced at all doses of CYB003 but returned to pre-dose levels by the end of the 6-hour test.

In the dog cardiovascular (CV) telemetry study, CYB003 was tested at doses of 0.5, 2 and 5 mg/kg. CYB003 produced dose-dependent, transient, increases in blood pressure (systolic, diastolic and mean) and heart rate accompanied by decreases in PR interval. While no PK data were collected in this study, similar doses were tested in the dog 4-week GLP toxicology study, which can provide exposure data for comparison. The lowest Cmax at 0.5 mg/kg in the dog 4-week GLP toxicology study was 51.7 ng/mL (female, Day 29) which is 23-fold higher than the predicted mean exposure at the 1 mg starting dose. This is supported in addition by the comprehensive and frequent monitoring of vital signs included in the study to monitor participant safety.

Further, literature data from studying the head twitch response in mice following administration of psilocin indicates that doses ranging from 0.5 mg/kg to 1 mg/kg produce peak effects in mice (Halberstadt, 2011; Zhuk, 2015). Utilizing an allometric scaling approach, as described in the FDA Guidance for Industry on estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (2005), a human equivalent dose for a 60 kg person can be calculated as 2.4 mg.

Therefore, based on the above, a starting dose of 1 mg is considered a sub-psychedelic and safe dose to administer in this study in otherwise healthy participants with MDD, in a study being conducted in a fully equipped phase 1 unit.

The dose will be escalated up in increments up to 3x the prior dose in subsequent cohorts following satisfactory review of all available safety, tolerability, PK and PD data from the previous cohort. Similarly, decreases in doses from a previous dose level may also occur as appropriate.

The maximum dose of CYB003 in this study will be up to 16 mg (doses higher than 12 mg are subject to FDA review) and will not exceed the predefined maximum exposure levels (i.e., C_{max} of 63.0 ng/mL or AUC_{0-24} of 123 hr*ng/mL, combined male and female data based on

toxicokinetic data from the 28-day toxicology study in dogs), but will also take into account pharmacodynamic/ psychedelic effects observed/ reported in participants, such that when these effects appear to plateau, or intolerable side effects are seen, dose escalation will be stopped. A summary of the risk mitigation measures is provided in Table 6-4 below.

Table 6-4: Risk Mitigation Measures

Potential Risk	Summary of Data/Rationale for Potential Risks	Mitigation strategy
Anxiety	• Short lasting anxiety / panic has been reported with the use of psychedelics in general, especially during challenging experiences.	• Preparatory EMBARK psychotherapy • In-session EMBARK psychotherapeutic support • If necessary, a benzodiazepine such as diazepam 5 to 10 mg orally or lorazepam 1 mg intramuscularly or orally may be administered.
Increased blood pressure	• Transient increases in blood pressure during the acute drug effect phase have been reported in clinical studies with psilocybin. These increases resolve within hours, and the magnitude of increase is typically less than 10/5 mmHg. • In the dog CV study with CYB003, transient increases in blood pressure were reported	• Participants with diagnosed hypertension will be excluded. • Vital signs will be monitored extensively during the medicine session and at follow up. • If necessary, antihypertensive medication will be administered. • Stopping criteria based on changes in blood pressure
Thermoregulation	• Initial increase followed by a decrease in blood temperature was noted in the dog CV study and reductions in core body temperature were reported in the rat Irwin study.	• Body temperature of participants will be monitored during the dose session.

Potential Risk	Summary of Data/Rationale for Potential Risks	Mitigation strategy
Suicidality	• Suicidality is a core feature of MDD	• Patients with a high risk of suicidality - a score of 4 or higher on the Suicidal Ideation subscale of C-SSRS (lifetime) or any Suicidal Behavior (lifetime) are excluded from the study • Stopping criteria based on changes in suicidality - an increase in Suicidal Ideation score to 4 or 5, or any Suicidal Behavior • Participant wellbeing checks post-dose– at least weekly telephone calls • At least one licensed psychotherapist on site during medicine sessions • Procedure for warm referral handoff of participants needing to be discontinued established at the study site • Dissemination of patient emergency cards • EMBARK psychotherapy model and training is designed to minimize these harms

6.9. Study Population

Up to 64 healthy participants with or without MDD will be enrolled in the study in 7 cohorts, including up to 48 MDD participants and up to 16 NHV participants. Eligible participants will only participate in one cohort.

MDD participants will have an established and confirmed diagnosis of MDD that is moderate to severe based on their baseline MADRS score and MINI neuropsychiatric interview. Eligible participants must be on a stable dose of antidepressant medication (no more than 50% change) for 1 month prior to Screening and have had an inadequate response, as judged by the Investigator. Participants must be under the care of a healthcare professional for their MDD. Participants will also undergo a clinician diagnostic interview for confirmation of their MDD diagnosis.

6.10. Ethical Conduct of the Study

The study will be conducted in compliance with applicable FDA and ICH rules, regulations, and guidelines and applicable laws and regulations of the local and country where the study is conducted. The study will be conducted with the approval of a duly constituted institutional review board (IRB) or ethics committee (EC) in accordance with the requirement of 21 CFR 56 — Institutional Review Boards. The nature and risks of the study will be fully explained to each participant and written consent obtained in accordance with the requirements of 21 CFR 50 — Protection of Human Participants. Participants will be informed of their rights, including the right to withdraw from the study at any time.

7. TRIAL OBJECTIVES

7.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability of ascending oral doses of CYB003 in healthy participants with and without major depressive disorder (MDD).

7.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the PK of ascending oral doses of CYB003.
- To characterize the psychedelic effects of CYB003 administration.
- To evaluate the efficacy of CYB003 in treating symptoms of MDD.

7.3. Exploratory Objectives

- To assess the relative bioavailability of CYB003 oral powder in solution compared to powder-filled capsules.
- To evaluate the effect of CYB003 on ECG parameters, including concentration-QTc (C-QTc) analysis.

8. TRIAL DESIGN

8.1. Study Endpoints

The primary endpoints of the study are:

- Clinical safety data from AE reporting, 12-lead ECG, Holter monitoring, clinical safety laboratory evaluations, physical examinations and suicide risk as assessed by the C-SSRS

The secondary endpoints of the study are:

- Plasma CYB003 concentrations and PK parameters including but not limited to: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$
- Mystical Experience Questionnaire (MEQ30), the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), the Hallucinogen Rating Scale (HRS) and visual analogue scale (VAS) ratings of 'Any drug effect' and a 5-item Persisting Effects Questionnaire (PEQ) assessing the meaningfulness, spirituality and psychological insights and challenges of the experience and overall drug effect
- Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) scores in healthy participants with MDD

The exploratory endpoints of the study are:

- PK parameters, AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and t_{max} for CYB003 powder in solution compared to powder-filled capsules in the fasted state.
- Change-from-baseline heart rate, PR, QTcF and QRS intervals (ΔHR, ΔPR, ΔQTcF and ΔQRS)
- Placebo-corrected ΔHR, ΔPR, ΔQTcF and ΔQRS
- Categorical outliers for HR, PR, QRS and QTc
- Frequency of treatment emergent T- and U-wave abnormalities

8.2. Study Design

This is a Phase I/IIa, randomized, double-blind, placebo-controlled study in healthy participants with and without MDD. The study also includes an open-label relative bioavailability (BA) cohort in healthy participants without MDD. For sake of clarity throughout the protocol, otherwise healthy participants with MDD will be referred to as **MDD participants**, and healthy participants without MDD will be referred to as normal healthy volunteer (NHV) participants, or simply, **NHV participants**.

This study initially evaluated the lowest dose of CYB003 or placebo (1 mg) in MDD participants. Cohort 1 MDD participants have been dosed at the starting dose of CYB003 1 mg

(4 subjects dosed with 1 early dropout). The protocol has been amended following completion of Cohort 1 to enroll the following Cohorts 2-6 and a relative BA cohort:

- Cohort 2 will enroll 4 NHV participants (3 active and 1 placebo);
- A decision whether to enroll NHVs or MDD patients in Cohort 3 will be dependent on ratings on the VAS – any drug effect score. If the CYB003 doses administered in this cohort are associated with ratings on the VAS any drug effect" of <7 in 75% of NHV participants, then Cohort 3 will enroll 4 NHV participants (3 active and 1 placebo).
- If the CYB003 doses administered in this Cohort 2 are associated with ratings on the VAS – any drug effect of >7 in 75% of NHV participants, then Cohort 3 will enrol 8 MDD participants (6 active and 2 placebo).
- Cohort 4 is planned for up to 12 MDD participants (9 active and 3 placebo). After 12 participants have been dosed and evaluated (first dose) in Cohort 4, and if dose escalation has reached 12 mg of CYB003, data will be submitted to FDA for review.
- Up to 12 MDD participants (9 active and 3 placebo) will be enrolled in Cohort 5.
- After Cohort 5 is completed, a soft lock of the data will be performed.
- Cohort 6 will enroll up to 12 MDD participants (9 active and 3 placebo). Doses > 12 mg will only be administered in Cohort 6, subject to FDA approval.
- A single cohort of 8 NHV participants will be enrolled to assess the relative bioavailability of the oral powder in solution compared to powder-filled capsules in a cross-over design. This cohort can be initiated any time after Cohort 4 dosing commences.

The study will investigate the safety, tolerability, PK and PD of ascending oral doses of CYB003 in MDD participants and NHV participants, the relative bioavailability of CYB003 powder in solution compared to powder-filled capsules.

A study schematic is included in Figure 4-1 for MDD Participants, Figure 4-2 for NHV Participants (Cohorts 2-6), and Figure 4-3 for NHV Participants (Relative BA Cohort). A schedule of assessments is included in Table 4-1 for MDD Participants, Table 4-3 for NHV Participants (Cohorts 2-6), and Table 4-4 for NHV Participants (Relative BA Cohort).

Up to 64 participants are planned to be enrolled into 7 cohorts, including up to 48 MDD participants and 16 NHV participants.

All participants will have a Screening visit between 28 and 17 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good general health. Some of the Screening procedures may be performed remotely, while others will be required on-site. All screening assessments must be completed and participants confirmed eligible by the Investigator based on inclusion and exclusion criteria review before the psychological support sessions described below can commence.

Cohorts 1-6: For the first dose (Day 1), participants will receive either an active CYB003 dose or placebo (3:1 ratio). For the second dose (Day 22 for MDD participants or Day 8 for NHV participants), all participants will receive an active CYB003 dose. For NHV participants, the second dose may be given after a two-week interval (Day 15) instead of on Day 8, at the discretion of the Investigator.

The starting dose of CYB003 in Cohort 1 was 1 mg, based on initial human dose safety calculations per FDA guidance, modelling of predicted exposures, and taking into account safety data from non-clinical studies. The dose will be escalated in increments up to 3x from the previous dose following satisfactory review of available safety, tolerability, pharmacodynamic (PD) and PK data from the preceding cohort(s).

In Cohorts 1, 2, 3, 5 and 6, there may be a dose escalation within the cohort, such that participants will receive one dose level of CYB003 for the first dose. A review of available safety, PK and PD data by the SRC will take place on Day 7 or Day 21. For these cohorts, the scheduled Day 7 or Day 21 visit may be delayed up to 7 days to allow for this review. Contingent on this review, it is proposed to test the same or another dose level in the second period of these cohorts, as presented in the dose escalation Table 8-1. Proposed doses may be adjusted based on emerging PK, and safety data. The estimated number and type of participants (MDD or NHV) are summarized by cohort and proposed dose in Table 8-2.

The maximum dose of CYB003 in this study will be determined based on maximum C_{max} and AUC_{0-24} exposures of 343 ng/mL and 3630 hr*ng/mL, respectively, obtained from the rat 14-day dose range finding (DRF) study at 40 mg/kg in female rats, as well as emerging pharmacodynamic, safety and tolerability data.

The proposed first dose (Day 1) and second dose (Day 8 or Day 22) dose escalations and fed or fasted dosing conditions for study drug are presented in Table 8-1.

Table 8-1: Proposed Dose Escalation Scheme for Double-Blind Cohorts 1-6

Cohort	Day 1 Dose (mg)	Day 1 Fasted	Day 8 or Day 22 Dose (mg)	Highest Day 8 or Day 22 Dose (mg)	Day 8 or Day 22 Fasted
1	1	Fasted	1	1	Fasted
2	3	Fasted	6	8	Fasted
3	9	Fasted	12	12	Fasted
4	12	Fasted	12	12	Fasted
5	12	Fasted	12	12	Fasted
6	9 or up to 16	Fasted	Up to 16	Up to 16	Fasted

Dose levels >12 mg are pending FDA review.

Note: Study participants who have received Day 1 dose may receive the same dose level on Day 8 or Day 22 dose if agreed upon by the Investigator and Sponsor to allow for flexibility and more time with respect to recruitment of a sufficient number of participants at the Day 1 dose level.

Table 8-2: Estimated Number and Type of Participants by Cohort and Proposed Dose

Cohort	Cohort size	Potential CYB003 doses (mg)
1	4 MDD	1
2	4 NHVs	3 and 6
3	4 NHVs or 8 MDD	9 and 12
4	Up to 12 MDD * * *	12
Relative BA	8 NHV	≤12
5	Up to 12 MDD * * *	12 **
6	Up to 12 MDD * * *	Up to 16*

* Pending FDA review and SRC recommendation; ** Soft lock and data review will occur after Cohort 5 is completed. * * * a minimum of 8 completers is intended.

Sentinel dosing will occur at each dose level. Each cohort will include 2 sentinel participants; 1 participant will receive CYB003 and 1 participant will receive matched placebo. The remaining participants in the cohort will commence treatment at least 24 hours after commencement of treatment in the sentinel participants after satisfactory review of the safety and tolerability data by the Investigator. A licensed physician will be on call and able to reach the clinical site within 15 minutes on study drug dosing Day 1, Day 8 and Day 22 in the event of a physiological or psychiatric emergency. The physician should be available at least until 4 hours after all vital signs and mental status/neurological effects return to baseline.

Relative Bioavailability Cohort: This open-label cohort can commence after at least 4 participants have received the first dose in Cohort 4, and the dose in this cohort will be determined based on data generated in previous cohorts. Eight NHV participants will receive two doses of active CYB003 study medication on separate study days (Table 8-3). For Dose 1

(Day 1), 4 participants (Sequence 1) will receive CYB003 powder in solution and 4 participants (Sequence 2) will receive CYB003 powder-filled capsules. For Dose 2 (Day 8), participants will cross over to the alternate formulation (i.e., CYB003 powder-filled capsules or powder in solution). Dose 1 and Dose 2 will be administered in the fasting state. For this cohort, the preferred interval between doses is 1 week, however, this interval between doses may be stretched from 1 to 2 weeks at the Investigator's discretion.

Table 8-3: Proposed Dosing Scheme for Relative Bioavailability Cohort

Sequence	Dose 1		Dose 2
1	4 HV participants, CYB003 powder in solution, fasted	⇨	4 HV participants, CYB003 powder-filled capsules, fasted
2	4 HV participants, CYB003 powder-filled capsules, fasted	⇨	4 HV participants, CYB003 powder in solution, fasted

Psychological Support Sessions:

For MDD Participants: Supportive psychotherapy, EMBARK for MDD ("A Treatment Manual for EMBARK: A Six-Domain Framework of Psilocin-Assisted Therapy for Major Depressive Disorder"), will be provided during at least three sessions of preparatory psychotherapy (predose), medicine sessions, and at least three sessions of integration psychotherapy (postdose) following each dose administration. During these sessions, participants will be paired with a dyad of two facilitators who will have completed specialized training in EMBARK for MDD; one or both facilitators will be a licensed psychotherapist.

Participants will have a preparatory psychotherapy session A1, A2 and A3 occurring within a flexible time window, with the first two preparatory sessions occurring any time after eligibility screening and the third preparatory session occurring on or about Day -1 (see Table 4-2 for time windows). Each preparatory session will last for 90 minutes. Flexibility is allowed for the scheduling of these sessions at the facilitator's discretion and coordination with the participant and Investigator provided that all three preparatory sessions are completed prior to any study medication dosing.

For the last of three preparatory psychotherapy predose sessions, the preferred default schedule is the final preparatory session on Day -1 in the afternoon or evening before dosing, first dosing on Day 1, and the first postdose integration session on the morning of Day 2, so the participant completes these study activities during one extended visit. Similarly, for the last of three integration psychotherapy sessions before the second dose administration, the preferred default schedule is the final session on Day 21 in the afternoon or evening before dosing, then dosing on Day 22, and the first postdose integration session on the morning of Day 23, so the participant completes these study activities during one extended visit.

After each dose, postdose integration psychotherapy sessions, Sessions B1, B2 and B3, will occur on approximately Day 2, 10 and 21 following the first dose and Sessions C1, C2 and C3

will occur on approximately Day 23, 31 and 38 following the second dose. Each postdose integration session will last for 90 minutes. These integration sessions are meant to be flexible and may occur on different days rather than a fixed weekly schedule depending on an assessment of an individual study participant by the facilitator, provided there are at least three postdose integration sessions following each study medication dose. Additional preparatory psychotherapy sessions or integration psychotherapy sessions may be conducted by study facilitators at the Investigator's discretion.

For NHV participants: Healthy volunteers will receive at least one predose preparation session, a medicine session on Day 1 (first dose) and Day 8 (second dose), and at least one debrief session following each dose. The predose preparation sessions and debrief sessions can be done remotely. Additional preparation sessions or debrief sessions may be conducted by study facilitators at the Investigator's discretion.

Double-Blind Treatment Period:

All participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter session. This baseline Holter recording must be reviewed prior to dosing on Day 1 to confirm that there are no abnormal findings that may preclude a participant's involvement in the clinical trial.

Dose 1: Randomization to double-blind study medication will occur on Day 1 after successful completion of the three preparatory psychotherapy sessions (MDD participants) or the predose preparation session (NHV participants) and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

All participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 or matched placebo in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing (Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 1, 6, 8, 12 and 24 hours postdose for MDD participants and predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose for NHV participants. Other safety and PD assessments will be performed as described in Table 4-1 for MDD Participants and Table 4-3 for NHV Participants.

For all participants, the CYB003 treatment session may last from 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

MDD participants will have at least three postdose integration psychotherapy sessions as described above under "Supportive Psychotherapy Sessions." NHV participants will have at least one debrief session following the study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits.

Dose 2: Participants will be re-admitted to the research site on Day 7 (NHV participants) or Day 21 (MDD participants) for the collection of safety assessments and mood and psychological health questionnaires to assess their response to the first dosing session. The same study procedures will be performed on Day 7 through Day 9 (NHV participants) or Day 21 through Day 23 (MDD participants) as were done on Days -1 through Day 2. All participants will receive an oral dose of CYB003 in the morning of Day 8 (NHV participants) or Day 22 (MDD participants). Two trained facilitators will be present to support the participant throughout the dosing session. There will be a +7 day window allowed for the Day 7 or Day 21 visit to allow for review of safety data, if needed.

Participants will reside at the research site until the morning of Day 9 (NHV participants) or Day 23 (MDD participants) (approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

MDD participants will have at least three postdose integration psychotherapy sessions as described above under "Supportive Psychotherapy Sessions." NHV participants will have at least one debrief session following the study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits.

Study medication will be administered in the fasted state, following an overnight fast of approximately 10 hours in cohorts 1-6.

Open-Label Treatment Period:

NHV participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter session. This baseline Holter recording must be reviewed prior to dosing on Day 1 to confirm that there are no abnormal findings that may preclude a participant's involvement in the clinical trial.

Dose 1: Randomization to open-label study medication sequence 1 or 2 will occur on Day 1 after successful completion of the predose preparation session and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

Participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 powder in solution or powder-filled capsules in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing

(Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose. Other safety and PD assessments will be performed as described in Table 4-4.

The CYB003 medicine session may last from 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

Dose 2: Participants will be re-admitted to the research site on Day 7 for the collection of safety assessments and mood and psychological health questionnaires. The same study procedures will be performed on Day 7 through Day 9 as were done on Days -1 through Day 2. Participants will crossover to the alternate study medication (CYB003 powder in solution or powder-filled capsule) in the morning of Day 8 in the fasted state.

Two trained facilitators will be present to support the participant throughout each dosing session. Participants will have at least one debrief session following each study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits. The preferred schedule is for participants to receive the two doses 1 week apart (i.e., Days 1 and 8). However, the time interval may be extended up to 2 weeks between doses at the Investigator's discretion. If the time interval between doses is extended to 2 weeks, participants will have approximately weekly telephonic safety assessments.

Cohorts 1-6 Follow-Up Assessments and Visits:

MDD participants will have approximately weekly telephonic assessments for the three weeks following study drug administration for MADRS assessments and for safety assessments. MDD participants will return to the research site for an outpatient visit on Day 42 for collection of safety assessments and completion of mood and psychological health questionnaires to assess their response to the second dosing session. MDD participants will return to the research site for a final in-person Follow-up visit on Day 56 (±3 days) for collection of end-of-study safety assessments and completion of mood and psychological health questionnaires. Remote MADRS assessments will be completed at 4-, 8- and 12-weeks post-Day 42 visit (allowable time window for completion is ± 3 days). Optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO. The maximum expected duration of participation for an MDD participant is approximately 12 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 8 weeks (but excluding the additional 12 weeks for remote MADRS assessments and optional ePRO follow up).

NHV participants will have approximately weekly telephonic assessments for two weeks following the second dose study drug administration for safety assessments. NHV participants will return to the research site for a final in-person Follow-up visit on Day 28 (±3 days) for collection of end-of-study safety assessments. The maximum expected duration of participation for a NHV participant is approximately 8 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 4 weeks. If the Investigator extends the time between the two doses from 1 to 2 weeks, the treatment phase and follow-up will be up to 6 weeks, for a total expected duration of participation of approximately 10 weeks.

Relative Bioavailability Cohort Follow-Up Assessments and Visits:

NHV participants will have approximately weekly telephonic assessments for two weeks following the third dose study drug administration for safety assessments. NHV participants will return to the research site one week later for a final in-person Follow-up visit on Day 28 (±3 days) for collection of end-of-study safety assessments. The maximum expected duration of participation for a NHV participant is approximately 8 weeks, including a screening and preparatory period of up to 4 weeks and a treatment phase and follow-up of up to 4 weeks. If the Investigator extends the time between the two doses by up to 2 weeks after each dose, the treatment phase and follow-up will be up to 16 weeks, for a total expected duration of participation of approximately 10 weeks.

8.2.1. Study Duration

The duration of the double-blind portion of the study for individual MDD participants is up to 12 weeks including a screening visit and preparatory psychotherapy sessions of up to 4 weeks, a first dose with integration psychotherapy sessions of 3 weeks, a second dose with integration psychotherapy sessions of 3 weeks, and a follow-up period of 2 weeks.

The duration of the double-blind portion of the study for individual NHV participants is up to 8 weeks including a screening visit and a predose preparation session of up to 4 weeks, a first dose with medicine and debrief sessions of 1 week, a second dose with medicine and debrief sessions of 1 week, and a follow-up period of 2 weeks. If the Investigator decides to extend the time between doses to 2 weeks for each dose, this will extend the duration of the study for these NHV participants to 10 weeks.

The duration of the open-label relative BA portion of the study for individual NHV participants is up to 8 weeks including a screening visit and a predose preparation session of up to 4 weeks, two doses with medicine and debrief sessions of 1 week each, and a follow-up period of 2 weeks. If the Investigator decides to extend the time between doses to 2 weeks for each dose, this will extend the duration of the study for these NHV participants to 10 weeks.

8.2.2. Study Drug Dosing

The starting dose of CYB003 will be 1 mg in Cohort 1 participants. Subsequent dose escalations in additional cohorts will be decided upon after review of all relevant safety, PK and clinical data and agreed upon by the Investigator, Sponsor and SRC. The doses for subsequent cohorts will be documented in writing and communicated to the investigational pharmacist for implementation. Participants in each cohort will receive a dose of CYB003 or matched placebo in the first dosing session (Day 1), and an active dose of CYB003 in the second dosing session (Day 8 or Day 22).

CYB003 will be provided to the Investigator and research pharmacist (or other appropriately trained personnel as designated by the Investigator) as active pharmaceutical ingredient (Psilocin d10 free base API) for the powder in solution dosage form and as powder-filled capsules (containing the psilocin d10 benzenesulfonate salt). For the double-blind portion of the study, an unblinded pharmacist or other designee will prepare active CYB003 and placebo doses and will administer doses to the participants in a manner that preserves the integrity of the blind for the Investigator, the participants, and other research personnel. For the open-label portion of the study, a pharmacist or other designee will prepare and dispense the appropriate dose of powder in solution or powder-filled capsule(s) for participants.

API will be dissolved in 0.1M citric acid to give a 1 mg/mL stock solution. For the powder in solution dose, an appropriate volume of study drug (e.g., 1 mL for a 1 mg dose) will be mixed with Tang orange drink to mask taste and to make a 30 mL dose in a dose cup. Matching placebo will consist of similar volume of Tang orange drink without the CYB003 study drug. Participants will ingest the 30 mL dose from a dose cup and will then drink 210 mL Tang orange drink for a total volume of approximately 240 mL. For the CYB003 powder-filled capsule dose, participants will ingest the capsule(s) with approximately 240 mL room temperature water. Detailed instructions for preparing and administering individual study drug doses will be provided in a Pharmacy Manual. All study medication doses must be documented with date and time of administering and by all study personnel involved in dosing.

For Cohorts 1-6, study drug will be administered in the fasting state (following an overnight fast of at least 10 hours and except for the ingestion of the orange drink study drug solution).

For the relative BA/ cohort, 8 NHV participants will be enrolled and will receive two doses followed by a 7-day washout period between each dose. Participants will be randomly assigned to sequence 1 or 2 as presented in Table 8-3.

- For Dose 1, 4 participants will receive CYB003 powder in solution and 4 participants will receive CYB003 powder-filled capsules, in the fasted state (following an overnight fast of at least 10 hours).

- For Dose 2, after a 7-day washout period, participants will crossover and receive the alternate study medication, powder in solution or powder-filled capsules, again in the fasted state.

On days where participants are confined in the research clinic, standardized meals will be served to participants (e.g., lunch at approximately 4.5 hours and dinner at 10 hours post-dose) will be served and an evening snack will be offered, if desired by the participant. The mealtimes are approximately and may be modified so the meals do not interfere with study procedures (but should be kept generally consistent for all participants to the extent feasible).

The study medication oral powder in solution or powder-filled capsule doses must be completely ingested as described above. Participants will remain sitting upright and ambulation will be limited during the immediate 4 hour post-dose period, except for bathroom privileges if necessary. On the study drug dosing days, participants must not consume any liquids other than the study drug Tang orange drink or water ingested with the study medication within 1 hour before and 1 hour after dosing.

Water will be offered *ad libitum* after the 1 hour post-dose PK blood sample is collected. Soft drinks (sodas) or non-citrus fruit juices will be offered with meals and *ad libitum* beginning 4.5 hours post-dose. Caffeinated beverages, such as coffee or tea may be consumed in moderation. Participants must refrain from ingesting alcohol or excessive amounts of caffeine at screening and within 24 hours prior to each dose and until after the last PK blood sample is obtained.

8.2.3. Test Article Accountability

Investigational CYB003 study drug will be labeled with the following statement – Caution: New Drug--Limited by Federal (or United States) law to investigational use. The Principal Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much of each test article is dispensed to and used by each individual participant in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose and will be signed by the Principal Investigator at the conclusion of the study. To satisfy regulatory requirements regarding drug accountability and destruction, following instruction from the Sponsor, the Principal Investigator will arrange for return or destruction of all used, unused, empty and partially used study drug and containers to the Sponsor for final accountability and disposal.

8.2.4. Randomization

A randomization schedule for the double-blind study part and another for the open-label study part will be generated by a statistical programmer not directly involved in the analysis or conduct

of the study. The randomization schedules will be provided to an unblinded pharmacist at the research site who will implement the schedule as participants qualify for randomization.

Randomization to double-blind study medication in Cohorts 1-6 will occur on Day 1 after successful completion of the three preparatory psychotherapy sessions for MDD participants and the predose preparation session for NHV participants and eligibility re-confirmation of all participants by the Investigator prior to dosing on Day 1. Participants in each cohort will receive a dose of CYB003 or matched placebo in the first dosing session (Day 1), and a dose of CYB003 in the second dosing session (Day 8 or Day 22).

Randomization to open-label study medication in the relative BA cohort will occur on Day 1 after successful completion of the predose preparation session for NHV participants and eligibility re-confirmation of all participants by the Investigator prior to dosing on Day 1. Participants in this cohort will receive the first dose of CYB003 in the fasted state on Day 1 and the second dose in the fasted state on Day 8, unless the time between dosing intervals is extended by the Investigator.

8.2.5. Emergency Unblinding

For double-blind Cohorts 1-6, in the infrequent and unlikely event that a participant's study medication identity must be known for medical reasons for participant safety based on Investigator decision, this unblinding must be documented in writing. An emergency procedure will be written (or if already in place in the research unit will be followed per standard operating procedures) by the unblinded pharmacist or designee to allow for unblinding a participant in the event of a medical emergency where the identity of the study medication is deemed necessary by the Investigator. If a participant's study medication is unblinded, the events surrounding this unblinding will be communicated promptly to the Sponsor and to the IRB if required.

8.2.6. Psychotherapy Session Facilitators and On Call Physician

In consideration of this study evaluating an investigational psychedelic medicine and to address FDA requirements with respect to the professional credentials, training and experience of facilitators, the following requirements will be adhered to in this study for psychotherapy session facilitators.

The lead facilitator must be a licensed healthcare provider with professional training and clinical experience in psychotherapy and must be licensed to practice independently. Acceptable professional credentials are limited to the following: 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 second facilitator must have a bachelor's degree and at least one year of clinical experience in a licensed mental health care setting.

Additionally, a licensed physician must be on call and able to reach the clinical site within 15 minutes in the event of a physiological or psychiatric emergency during Day 1, Day 8 and Day 22 dosing sessions for Cohorts 1-6 and during Day 1 and Day 8 dosing sessions for the relative BA cohort. The physician should be available at least until 4 hours after all vital signs and mental status/neurological effects return to baseline.

8.3. Selection and Withdrawal of Participants

Participants for the study will be recruited from a research participant data base and/or general advertising and selected during screening based on the inclusion and exclusion criteria and clinical assessment listed below.

8.3.1. Inclusion Criteria

MDD and NHV Participants:

Participants meeting the following criteria will be included in the study:

1. Participant is assigned female or male at birth.
2. Participant is aged between 21 to 65 years, inclusive, at Screening.
3. Participant has a BMI of 18 to 30 kg/m^2, inclusive, at Screening.
4. Participant is ≥60 kg.
5. Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test at Screening and Day -1.
6. Participants capable of producing sperm must use a condom during the trial and for 3 months after their final dose of trial medication, if their partner is a person of childbearing potential. In addition, their partner of childbearing potential must use a highly effective method of contraception (i.e., failure rate less than 1% when used consistently and correctly) from first dosing until 3 months following final dosing.
7. Participants of childbearing potential must agree to use a highly effective method of contraception (i.e., failure rate less than 1% when used consistently and correctly) in combination with a partner who is capable of producing sperm must use a condom during the trial and for 3 months after their final dose of trial medication. Such participants must have a negative pregnancy test at Screening and Day -1.
8. Participants of non-childbearing potential who are or were capable of producing eggs (ova) must be postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy or bilateral oophorectomy. Postmenopausal is defined as spontaneous amenorrhea for at least 12 months, and a serum follicle stimulating hormone (FSH) level in

the menopausal range, unless the participant is taking hormone replacement therapy or is using hormonal contraception.

9. Provision of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

MDD Participants:

Participants meeting the following criteria will be included in the study:

1. Participant has a diagnosis of MDD (as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V] of moderate to severe degree (scoring ≥21 on the Montgomery-Åsberg Depression Scale [MADRS], established through a full psychiatric work up that includes the Mini-International Neuropsychiatric Interview [MINI]), who are otherwise healthy.
2. Confirmation of MDD diagnosis, a depression severity of moderate to severe based on MADRS score, inadequate response to current antidepressant medication, and absence of treatment-resistant depression, based on a diagnostic interview conducted by a clinician.
3. Participant has been on a stable dose of antidepressant medication (no more than 50% change) in the last month prior to Screening and has had an inadequate response, as judged by the Investigator.

8.3.2. Exclusion Criteria

MDD Participants:

Participants with the following will be excluded from study participation:

1. A reduction in the MADRS score of 25% or more between Screening and randomization.
2. Current or previous diagnosis of treatment-resistant MDD, defined as failure to respond to 2 or more antidepressant treatments given at an adequate dose for an adequate duration.
3. Current or previously diagnosed schizophrenia spectrum or other psychotic disorders, including schizophrenia, schizoaffective disorder, schizotypal disorder, schizophreniform disorder or brief psychotic disorder; current or previous history of bipolar disorder, or current personality disorder (as determined by MINI at Screening).
4. Currently receiving a monoamine oxidase inhibitor, tricyclic antidepressant, mirtazapine, an antipsychotic or a mood stabilizer.
5. Exposure to psilocin, or any other psychedelics, such as ayahuasca, mescaline, LSD or peyote more than 10 times in the last 10 years, or any psychedelic use within 6 months prior to Screening.
6. Use of a prescription medicine (except participants may take a stable chronic dose of antidepressant medication(s) and/or sedatives/hypnotics, and may take hormonal contraceptives, if applicable), certain herbal supplements (to be reviewed by the

Investigator), or over-the-counter (OTC) medicine, during the 28 days before dosing. Exceptions include the following medications:

a. Antianxiety medication, other than buspirone, is allowed if taken chronically (as needed or daily), provided that the participant must refrain from taking a dose of the antianxiety medication for at least 12 hours prior to a dose of study medication.
b. Preexposure prophylaxis (PrEP) medication for prevention of HIV infection, such as TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) or DESCOVY® (emtricitabine and tenofovir alafenamide), is allowed.
c. Acetaminophen/paracetamol (less or equal 4 g/day) may be taken for up to 48 hours prior to dosing.
d. Stable chronic therapy with hormone replacement medication is also allowed.

The Investigator and study team may review medication on a case-by-case basis to determine if its use would compromise participant safety or interfere with study procedures or data interpretation.

NHV Participants:

Participants with the following will be excluded from study participation:

1. Current or previously diagnosed mental health disorder as defined by DSM-V criteria.
2. Exposure to psilocin, or any other psychedelics, such as ayahuasca, mescaline, LSD or peyote or any psychedelic use within 6 months prior to Screening.
3. Use of any prescription medicine (except participants may take hormonal contraceptives, if applicable), certain herbal supplements (to be reviewed by the Investigator), or over-the-counter (OTC) medicine, during the 28 days before dosing or need to take any prescription or OTC medicine or herbal supplement during the study. Acetaminophen/paracetamol (less or equal 4 g/day) may be taken for up to 48 hours prior to dosing.

   The Investigator and study team may review medication on a case-by-case basis to determine if its use would compromise participant safety or interfere with study procedures or data interpretation.

MDD and NHV Participants:

Participants with the following will be excluded from study participation:

1. Clinically significant risk of suicidality, as determined through a comprehensive psychiatric interview that incorporates the Columbia Suicide Severity Rating Scale (CSSRS); a score of 4 or higher on the suicidal ideation subscale of C-SSRS (lifetime) or any suicidal behaviour (lifetime), would be exclusionary.

2. Clinically relevant history of abnormal physical health interfering with the study as determined by medical history and physical examinations obtained during Screening as judged by the Investigator (including [but not limited to], neurological, endocrine, cardiovascular, respiratory, gastrointestinal (including dyspepsia or gastroesophageal reflux disease), hepatic, or renal disorder).
3. Diagnosis of hypertension or an arrhythmia.
4. Clinically relevant abnormal results for heart rate (resting supine heart rate >100 bpm) or blood pressure (resting supine systolic blood pressure (SBP) above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg) at screening. Screening supine SBP, DBP and heart rate for evaluation will be the average of 3 readings obtained after at least 5 minutes rest.
5. History of hypothyroidism and/or current abnormal thyroid function tests. In case of uncertain or questionable screening thyroid function test results, the TSH test may be repeated once during screening. The TSH test must be reviewed to ensure that it is within normal limits before randomizing a participant into the study.
6. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at Screening. In case of uncertain or questionable results, tests performed during Screening may be repeated once to confirm eligibility or judged to be clinically irrelevant for healthy participants.
7. A family history of schizophrenia or schizoaffective disorder (first degree relatives), or bipolar disorder type 1 (first degree relatives).
8. Other eligibility considerations (i.e., participant personal circumstances, behavior, and/or any current problem that might interfere with participation or that is incompatible with establishment of rapport or safe exposure to psilocin), as judged by the Investigator.
9. Participants with abnormal vital signs which are out of range and deemed clinically significant by the Investigator at Screening or Day 1, following triplicate readings.
10. QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec at Screening, following triplicate ECG readings.
11. Presence of clinically significant ECG abnormalities at the Screening visit, as defined by medical judgement.
12. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion (ADME) of the study drug.
13. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.

14. Participant is not fluent in English.
15. Participant has a presence or relevant history of any of the following medical conditions: organic brain disorders (e.g., epilepsy, seizure, intracranial hypertension, intracranial bleed and aneurysmal disease, brain tumor or other medical conditions associated with seizures or convulsions).
16. Aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) or total bilirubin levels ≥1.5 x the upper limit of normal (ULN) at Screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the participant may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
17. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV) or human immunodeficiency virus I and II (anti-HIV I/II) at Screening.
18. Positive urine test for drugs of abuse (see Appendix 1) or alcohol breath test at Screening or Day -1. A positive test for cannabinoids (e.g., marijuana) at Screening may not exclude a participant if after discussion with and evaluation by the Investigator, the participant agrees not to use any marijuana or other cannabinoid products during the study, and if allowed to participate, the participant must test negative for cannabinoids on Day -1 (all participants), Day 7 (NHV participants, double-blind study part), Day 14 (NHV participants, open-label study part), and Day 21 (MDD participants).
19. History of substance use disorder within the last year, as assessed by a structured clinical interview (Mini International Neuropsychiatric Interview [MINI], Version 7.0.2) or determined by self-report, or intake of >21 units of alcohol weekly, and the inability to refrain from alcohol use from 48 hours before Screening and each scheduled visit until discharge from the study site. One unit is equivalent to a 285 mL glass of full-strength beer or 1 (30 mL) measure of spirits or 1 glass (100 mL) of wine.
20. Participant who consumes excessive amounts of caffeine (e.g., coffee, tea, caffeinated sodas) or (methyl) xanthines (e.g., chocolate) based on the Investigator's determination and discretion.
21. The participant has participated in a clinical study and has received a medication or a new chemical entity within 3 months prior to dosing of current study medication.
22. Known sensitivity to psilocin and/or any excipients present in the formulation. Known fructose malabsorption or intolerance, since the orange drink vehicle for study drug contains fructose.
23. Participant is taking or has taken any drugs known to inhibit monoamine oxidase within 28 days prior to study drug administration.

24. Participant is taking or has taken OTC doses of 5-hydroxytryptophan or St John's Wort within 28 days prior to study drug administration.
25. Strenuous exercise within 48 hours prior to each visit, and while at the study site.
26. Donation of blood or plasma of >400 mL within 1 month prior to first dosing until 4 weeks after final dosing.
27. Participants capable of producing sperm who will not abstain from sperm donation between first dosing and 3 months after final dosing.
28. Participants of childbearing potential who are pregnant, breastfeeding or planning to conceive.
29. Known difficulty with obtaining intravenous access.

8.3.3. Dose Stopping and Adjustment Criteria

8.3.3.1. Cohort Stopping Criteria

If any of the following safety concerns are observed in a cohort, dosing of all participants at the given dose level or higher may be suspended/halted and all available data will be evaluated by the Safety Review Committee (SRC). Dose continuation (remaining participants within a cohort) or escalation will not proceed, without SRC review, for any of, but not limited to, the following reasons:

1. One or more Hy's Law cases in participants who have been administered CYB003; Hy's Law is defined as AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN, in the absence of a significant increase in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that could explain the increase in bilirubin.
2. The occurrence of one serious adverse event (SAE) considered related to CYB003.
3. Two severe drug-related AEs in the same cohort, independent of within, or not within, the same system-organ class (SOC), considered related to CYB003.
4. Other findings that indicate dose escalation should be halted, e.g., if there is an unacceptable tolerability profile based on the nature, frequency and intensity of observed AEs and/or clinical safety monitoring in the opinion of the Investigator.
5. Two or more participants in a cohort find anxiety, fear, or distress caused by CYB003 to be intolerable during the dosing session, requiring rescue medication.
6. Two or more participants in a cohort develop clinically significant anxiety, fear, or distress following the dosing session that persists beyond the day of dosing, as assessed by the Investigator.
7. Psychedelic effects scales indicate either a complete mystical experience has been achieved in at least 75% of participants in two consecutive cohorts (MEQ30 scores > 60), or that scores on the oceanic boundlessness subscale of the 5D-ASC > 60 (percent of total maximum

score) have been achieved in at least 75% of participants in two consecutive cohorts, or scores on the Intensity subscale of the HRS > 2.79 have been achieved in at least 75% of participants in two consecutive cohorts or scores on the VAS "any drug effect" of 7 or higher have been achieved in at least 75% of participants in two consecutive cohorts0.

8. If the CYB003 doses administered in two consecutive cohorts are associated with ratings on the VAS – any drug effect of >9 in 75% of the participants, dose escalation will be stopped.
9. Clinically significant abnormalities in the laboratory parameters, vital signs or ECGs in 2 or more participants within the same cohort indicating dose-related intolerance, considered related to CYB003.
10. Two or more participants that receive CYB003 have QTc prolongation defined as an absolute QTcF value of >500 msec, or a change from baseline of >60 msec, that persists for at least 5 minutes following triplicate ECGs.
11. Two or more participants that receive CYB003 have tachycardia defined as resting supine heart rate >125 bpm, persisting for at least 10 minutes.
12. Two or more participants who receive CYB003 have symptomatic bradycardia defined as resting supine heart rate <45 bpm, or asymptomatic bradycardia defined as resting supine heart rate <30 bpm while awake persisting for at least 10 minutes.
13. Two or more participants who receive CYB003 develop hypertension defined as an increase in resting supine systolic blood pressure (BP) >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
14. Two or more participants who receive CYB003 develop more than one episode of symptomatic orthostatic hypotension, defined as a decrease of >20 mmHg for systolic BP, or asymptomatic systolic BP decrease of >30 mmHg which causes the systolic BP to fall below 100 mmHg, or >20 mmHg which causes the systolic BP to fall below 90 mmHg; or for single episodes associated with prolonged hypotension or a clinically significant event such as syncope, or other serious or severe cardiovascular signs or symptoms.
15. Two or more participants who are receiving CYB003 report treatment-emergent suicidality (an increase in Suicidal Ideation score to 4 or 5, or any Suicidal Behavior on the Since Last Visit of C-SSRS) that is considered related to the study drug.

8.3.3.2. Individual Stopping Criteria

Individual study participant stopping criteria will include:

1. Any participant who experiences severe nausea or vomiting that can't be controlled by medical and/or nursing support.
2. Any participant who experiences a severe headache or migraine that can't be controlled by medical and/or nursing support.

3. Any participant who experiences intolerable anxiety, panic, or suicidal thoughts that can't be controlled by medical and/or nursing and/or psychological support.
4. Any participant who experiences enduring perceptual distortions beyond the day of dosing.
5. Any participant who experiences tachycardia defined as resting supine heart rate >125 bpm, persisting for at least 10 minutes.
6. Any participant who develops hypertension defined as an increase in resting supine systolic blood pressure (BP) >40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
7. Investigator discretion based on clinical safety grounds.

For clarification, CYB003 is expected to cause commonly seen transient psychedelic drug effects, including auditory, visual, somatic, gustatory and olfactory hallucinations, synaesthesia, ideas of reference, mood elevation, time distortion, anxiety, agitation/ restlessness, confusion, connectedness, loosening of associations, mystical experiences and ego dissolution. CYB003 is also expected to produce some physical effects including nausea, vomiting, headache and transient HR and BP increases. The Investigator and SRC may take these expected class effects into consideration in their safety monitoring and decision-making with respect to whether to continue or discontinue a participant from the study.

8.3.3.3. Trial Stopping Rules

Dose escalation will be stopped if PK data indicates the predefined maximum exposure levels (i.e., C_{max} of 63.0 ng/mL or AUC_{0-24} of 123 hr*ng/mL, combined male and female data) based on toxicokinetic data from the 28-day toxicology study in dogs have been achieved or is predicted to be achieved or exceeded should the dose be increased as planned. The exposure limits will be applied on mean values within a cohort.

The Sponsor will terminate the study if the occurrence of AEs or other findings suggests an unacceptable risk to the health of the participants. The study may also be terminated by regulatory authorities for safety or administrative reasons.

8.3.4. Withdrawal Criteria

In addition to any participant meeting the individual stopping criteria specified in Section 8.3.3.2, participants will be discontinued from the study prematurely if:

1. The participant requests to be withdrawn from the study;
2. Unacceptable toxicity develops;
3. A need for a concomitant medication prohibited by the protocol arises;
4. The Principal Investigator decides that it is in the participant's best interest;
5. The participant is noncompliant with the protocol, including any participant found to be positive for alcohol and/or urine drug testing;

6. Participant becomes pregnant during the study;
7. Sponsor decides to discontinue study.

8.3.5. Handling of Withdrawals

If a participant withdraws from the study at any time, either at his or her request or at the Principal Investigator's discretion, the reason(s) for withdrawal will be recorded on the relevant page of the CRF. All final visit tasks (discharge procedures) will be completed for all participants who withdraw from the study. Participants withdrawn due to AEs will be monitored until resolution or stabilization of the AE. Withdrawn participants who withdraw for reasons other than for safety reasons and/or who meet stopping criteria may be replaced at the discretion and agreement between the Investigator and Sponsor.

9. STUDY MEDICATION DOSING AND CLINICAL ASSESSMENTS

9.1. Participant Screening

After providing written informed consent, participants will have a Screening visit between 28 and 17 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good general health. Some of the Screening procedures may be performed remotely, while others will be required on-site. All screening assessments must be completed and participants confirmed eligible by the Investigator based on inclusion and exclusion criteria review before the preparatory psychotherapy sessions described below can commence.

9.2. Psychological Support Sessions

For MDD participants: Participants will have at least three preparatory psychotherapy session A1, A2 and A3 employing the EMBARK method, with the first two preparatory sessions occurring any time after eligibility screening and the third preparatory session occurring on or about Day -1 (see Table 4-2 for time windows). Each preparatory session will last for 90 minutes. Flexibility is allowed for the scheduling of these sessions at the facilitator's discretion and coordination with the participant and Investigator provided that all three preparatory sessions are completed prior to any study medication dosing. All preparatory psychotherapy visits are preferred in person but psychotherapy session facilitators have the option to conduct any two of the three preparatory sessions and all of the integration sessions as remote/telemedicine visits.

For the last of three preparatory psychotherapy predose sessions, the preferred default schedule is the final preparatory session on Day -1 in the afternoon or evening before dosing, first dosing on Day 1, and the first postdose integration session on the morning of Day 2, so the participant completes these study activities during one extended visit.

For NHV participants: Participants will have at least one preparation session (prior to the first dose), a medicine session on Day 1 (first dose) and Day 8 (second dose), and at least one debrief session following each dose. The predose preparation sessions and debrief sessions can be done remotely. Additional preparation sessions or debrief sessions may be conducted by study facilitators at the Investigator's discretion.

Participants who are deemed eligible will be scheduled to return to the CRU for admission to the treatment period.

9.3. Double-Blind Treatment Period (Cohorts 1-6)

9.3.1. First Dosing Session

All participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter monitoring session.

Randomization to double-blind study medication will occur on Day 1 after successful completion of the three preparatory psychotherapy sessions (MDD participants) or one preparation session (NHV participants) and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

Participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 or matched placebo in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing (Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 1, 6, 8, 12 and 24 hours postdose for MDD participants and predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose for NHV participants. Other safety, efficacy and PD assessments will be performed as described in Table 4-1 for MDD participants and Table 4-3 for NHV participants.

The CYB003 medicine session may last up to 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session for all participants. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

For NHV participants, after the Day 1 dose, participants will have at least one debrief session done either in person or remotely.

For MDD participants, after the Day 1 dose, postdose integration psychotherapy sessions, Sessions B1, B2 and B3, will occur on approximately Day 2, 10 and 21 following the dose (see Table 4-2 for time windows). Each postdose integration session will last for 90 minutes. These

integration sessions are meant to be flexible and may occur on different days rather than a fixed weekly schedule depending on an assessment of an individual study participant by the facilitator, provided there are at least three postdose integration sessions following each study medication dose. Additional integration psychotherapy sessions may be conducted by study facilitators at the Investigator's discretion. All integration psychotherapy visits are preferred in person, but psychotherapy session facilitators have the option to conduct all of the integration sessions as remote/telemedicine visits.

Adverse event and concomitant medication monitoring will be performed while participants are in-clinic, during remote visits and outpatient visits. Participants will have approximately weekly telephonic assessments for the three weeks following study drug administration for MADRS assessments and for safety assessments (MDD participants) or for 1 to 2 weeks following study drug administration for safety assessments (NHV participants).

9.3.2. Second Dosing Session

All participants will be re-admitted to the research site on Day 7 (NHV participants) or Day 21 (MDD participants) for the collection of safety assessments and mood and psychological health questionnaires to assess their response to the first dosing session. The same study procedures will be performed on Day 7 through Day 9 (NHV participants) or Day 21 through Day 23 (MDD participants) as were done on Days -1 through Day 2. All participants will receive an oral dose of CYB003 in the morning of Day 8 (NHV participants) or Day 22 (MDD participants). Two trained facilitators will be present to support the participant throughout the dosing session. There will be a +7 day window allowed for the Day 7 or Day 21 visit to allow for review of safety data, if needed.

Participants will reside at the research site until the morning of Day 9 (NHV participants) or Day 23 (MDD participants) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

For MDD participants, after the Day 22 dose, postdose integration psychotherapy sessions, Sessions C1, C2 and C3, will occur on approximately Day 23, 31 and 38 following the dose (see Table 4-2 for time windows). Each postdose integration session will last for 90 minutes. These integration sessions are meant to be flexible and may occur on different days rather than a fixed weekly schedule depending on an assessment of an individual study participant by the facilitator, provided there are at least three postdose integration sessions following each study medication dose. Additional integration psychotherapy sessions may be conducted by study facilitators at the Investigator's discretion. All integration psychotherapy visits are preferred in person, but psychotherapy session facilitators have the option to conduct all of the integration sessions as remote/telemedicine visits.

For NHV participants, after the Day 8 dose, participants will have a debrief session done either in person or remotely.

Adverse event and concomitant medication monitoring will be performed while participants are in-clinic, during remote visits and outpatient visits. Participants will have approximately weekly telephonic assessments for the three weeks following study drug administration for MADRS assessments and for safety assessments (MDD participants) or for 1 to 2 weeks following study drug administration for safety assessments (NHV participants).

9.3.3. End of Treatment Visit (Day 42)

MDD participants will return to the research site for an outpatient visit on Day 42 for collection of safety assessments and completion of mood and psychological health questionnaires to assess their response to the second dosing session. Adverse event and concomitant medication monitoring will also be performed.

For participants who discontinue prematurely, this visit should be performed as an early termination visit and all assessments should be performed to the extent feasible.

9.3.4. End of Study Visit (Day 28 or Day 56)

Participants will return to the research site for an outpatient end-of-study visit on Day 28 (±3 days) (NHV participants) or Day 56 (±3 days) (MDD participants) for collection of end-of study safety. Adverse event and concomitant medication monitoring will also be performed.

9.3.5. Follow-Up Remote Assessments

Remote MADRS assessments will be completed at 4-, 8- and 12-weeks post-Day 42 visit. The allowable time window for these assessments is ± 3 days.

Optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO.

9.4. Open-Label Treatment Period (Relative BA Cohort)

9.4.1. First Dosing Session

NHV participants will be admitted to the research site in the morning of Day -1 for the collection of baseline safety assessments and mood and psychological health questionnaires. Participants will wear a Holter monitor for approximately 6 hours initiated in the morning which will serve as a baseline Holter session. This baseline Holter recording must be reviewed prior to dosing on

Day 1 to confirm that there are no abnormal findings that may preclude a participant's involvement in the clinical trial.

Randomization to open-label study medication sequence 1 or 2 (with study medication assignment as described in Table 8-3) will occur on Day 1 after successful completion of the predose preparation session and eligibility re-confirmation by the Investigator prior to dosing on Day 1.

Participants who are confirmed eligible and who are randomized will receive an oral dose of CYB003 powder in solution or powder-filled capsules in the morning of Day 1 in the fasted state. Participants will wear a Holter monitor for approximately 12 hours following dosing (Holter monitor should be placed approximately 1 hour prior to dosing and continue until approximately 12 hours postdose). Serial PK blood sampling will be collected predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose. Other safety and PD assessments will be performed as described in Table 4-4.

The CYB003 medicine session may last from 4 to 8 hours, and two trained facilitators will be present to support the participant throughout the dosing session. Participants will reside at the research site until the morning of Day 2 (until approximately 25 hours postdose) and will be discharged if the Investigator deems it safe to do so, following collection of safety assessments and PK blood samples, and completion of mood and psychological health questionnaires.

9.4.2. Second Dosing Session

Participants will be re-admitted to the research site on Day 7 for the collection of safety assessments and mood and psychological health questionnaires. The same study procedures will be performed on Day 7 through Day 9 as were done on Days -1 through Day 2. Participants will crossover to the alternate study medication (CYB003 powder in solution or powder-filled capsule) in the morning of Day 8 in the fasted state.

Two trained facilitators will be present to support the participant throughout each dosing session. Participants will have at least one debrief session following each study medication dose. Adverse event and concomitant medication monitoring will also be performed during each of these visits. The preferred schedule is for participants to receive the two doses 1 week apart (i.e., Days 1 and 8). However, the time interval may be extended up to 2 weeks between doses at the Investigator's discretion. If the time interval between doses is extended to 2 weeks, participants will have approximately weekly telephonic safety assessments.

9.4.3. End of Study Visit (Day 28)

Participants will return to the research site one week later for a final in-person Follow-up visit on Day 28 (±3 days) for collection of end-of-study safety assessments. Adverse event and concomitant medication monitoring will also be performed.

10. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

10.1. Efficacy (Pharmacodynamics) Assessments

In addition to standard screening assessments, including medical and medication history, participants will undergo a number of screening tests to confirm the diagnosis of Major Depressive Disorder and establish disease severity as it relates to eligibility criteria. These tests will include the MADRS, MINI, and remote diagnostic interview by the central rater clinician.

10.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale with ratings based on a clinical interview which moves from broadly phrased questions about symptoms to more detailed ones allowing a precise rating of severity. A rating scale from 0 to 6 is employed and the rater must decide whether the rating lies on defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). The MADRS can be used for any time interval between ratings, be it weekly or otherwise, and the time interval should be recorded. The symptoms that are rated include: 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. Scores for each symptom are recorded and tallied, and the total score can range from 0 to 60 (Montgomery, 1979).

For MDD participants, the MADRS will be completed as part of the eligibility assessment at the Screening visit and must be completed prior to the start of the preparatory psychotherapy sessions. MADRS is also the primary efficacy endpoint assessed at various scheduled timepoints in-clinic and remotely as described in Table 4-1.

10.1.2. Mini International Neuropsychiatric Interview (MINI 7.0.2)

The Mini International Neuropsychiatric Interview (MINI) for DSM-5, MINI 7.0.2 is a short, structured psychiatric interview that takes approximately 15 minutes to complete (Sheehan, 1998). The major depressive episode component of the MINI asks over the past week, how much did you: 1) feel depressed, sad, empty or hopeless, 2) feel less interested in things or less able to enjoy the things you used to enjoy, 3) have a change in appetite or weight, 4) have trouble sleeping (difficulty falling asleep, waking up in the middle of the night, early morning awakening or sleeping excessively), 5) talk or move more slowly than normal or feel fidgety, or restless, 6) feel tired or without energy, 7) feel worthless or guilty, 8) have difficulty concentrating, thinking or making decisions, 9) have thoughts of hurting yourself, feel suicidal or wish that you were dead or any intent, or plan or attempt to kill yourself. Responses are scored on a scale of 0 to 4 (0=not at all, 1=a little, 2=moderately, 3=very, 4=extremely). Scores are summed to give a total score and divided by 9 to give a standardized score.

For MDD participants, the MINI will be completed as part of the eligibility assessment at the Screening visit and must be completed prior to the start of the preparatory psychotherapy sessions.

10.1.3. Remote Diagnostic Interview

A remote diagnostic interview will be conducted by a central rater clinician for determination and confirmation of participant eligibility in conjunction with the Investigator's assessment. This interview will confirm confirmation of eligibility (i.e., diagnosis, severity, treatment history) and will include confirmation of MDD using the MADRS, and assessment of current antidepressant therapy, adequacy of duration and dose of prior and current antidepressant therapy, as well as degree of improvement.

For MDD participants, site staff will schedule the interview for the central rater, who will contact the participant as scheduled and conduct the interview. The remote diagnostic interview must be completed before the preparatory psychotherapy sessions are started.

10.1.4. Psychedelic-Assisted Psychotherapy (EMBARK)

EMBARK for MDD is a six-domain framework for psychedelic-assisted psychotherapy; the six domains are: Existential-Spiritual, Mindfulness, Body Aware, Affective-Cognitive, Relational, and Keeping Momentum. A Treatment Manual for EMBARK: A Six-Domain Framework of Psilocin-Assisted Therapy for Major Depressive Disorder", Version 1.0, 08 January 2022 describes this approach to psychotherapy in great detail and will be used as a reference manual for this clinical trial.

For MDD participants, supportive psychotherapy, EMBARK for MDD will be provided during three or more sessions of preparatory psychotherapy (predose) sessions, and three or more sessions of integration psychotherapy (postdose) following each dose administration. During these sessions, participants will be paired with a dyad of two facilitators who will have completed specialized training in EMBARK for MDD; one or both facilitators will be a licensed psychotherapist. These sessions will be audio and videotape recorded which will be explained to participants and must be agreed to by participants as part of the informed consent process.

Participants will have a preparatory psychotherapy session A1, A2 and A3, with the first two preparatory sessions occurring after eligibility confirmation and the third session occurring and Day -1. Each preparatory session will last for 90 minutes. Flexibility is allowed for the scheduling of these sessions at the facilitator's discretion and coordination with the participant and Investigator provided that all three preparatory sessions are completed prior to any study medication dosing.

For the last of three preparatory psychotherapy predose sessions, the preferred default schedule is the final preparatory session on Day -1 in the afternoon or evening before dosing, first dosing on

Day 1, and the first postdose integration session on the morning of Day 2, so the participant completes these study activities during one extended visit.

After each dose, a postdose integration psychotherapy session will occur on the morning after dosing and two additional postdose integration psychotherapy sessions will occur approximately 1 and 2 weeks after each study medication dose. Sessions B1, B2 and B3 will occur on approximately Day 2, 10 and 21 following the first dose and Sessions C1, C2 and C3 will occur on approximately Day 23, 31 and 38 following the second dose. Each postdose integration session will last for 90 minutes. These integration sessions are meant to be flexible and may occur on different days rather than a fixed weekly schedule depending on an assessment of an individual study participant by the facilitator, provided there are three postdose integration sessions following each study medication dose.

NHV participants will have at least one preparation session (prior to the first dose), a medicine session during each dose, and at least one debrief session following each dose. The predose preparation sessions and debrief sessions can be done remotely. Additional preparation sessions or debrief sessions may be conducted by study facilitators at the Investigator's discretion.

10.1.5. Mystical Experience Questionnaire (MEQ30)

The revised Mystical Experience Questionnaire (MEQ30) consists of 30 questions looking back on the entirety of a dosing session, participants are asked to answer each question according to one's feelings, thoughts, and experiences at the time of the session. A rating scale from 0 to 5 is used with the categories of: 0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong (equivalent in degree to any other strong experience); and 5=extreme (more than any other time in my life and stronger than 4).

The 30 questions are divided into grouped into factors or domains of mystical, positive mood, transcendence of time and space, and ineffability. The factor scores are computed by calculating the average response to individual questions within the factor. The MEQ30-total score is computed by taking the average response to all items.

The MEQ30 will be administered to all participants at the end of each study drug administration session, 4 to 10 hours postdose.

10.1.6. 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

The 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) consists of a set of 94 items that participants are asked to rate to what extent the statements apply to one's particular experience, compared to normal waking consciousness, by making a vertical mark on a line below each statement, whereby the mark to the far left of the line represents a response of "No, not more than usually" and the mark on the far right of the line represents a response of "Yes, much more than usually". The questions are organized into 11 subscales consisting of experience

of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synesthesia, , and changed meaning of percepts (Dittrich, 1998; Dittrich, 2010; Curic, 2021; Studerus, 2010).

The 5D-ASC will be administered to all participants at the end of each study drug administration session, 4 to 10 hours postdose.

10.1.7. Hallucinogen Rating Scale (HRS)

The Hallucinogen Rating Scale (HRS) is a questionnaire with up to 100 items, and the questionnaire is designed to assess the subjective effects of hallucinogenic substances. Participants rate responses to the majority of questions on a 5-point intensity scale: 0=not at all; 1=slightly; 2=moderately; 3=quite a bit; and 4=extremely. Some questions have a slightly modified scale, and one question asks to rate the amount of time between when the drug was administered and feeling an effect from: no effect, 0-5 minutes, 5-15 minutes, 15-30 minutes, 30-60 minutes, or more than one hour. Questions are grouped into factors or domains including: 1) somaesthesia, 2) affect, 3) perception, 4) cognition, 5) volition, and 6) intensity (Strassman, 1994).

The HRS will be administered to all participants at the end of the study drug administration session, 4 to 10 hours postdose.

10.1.8. Persisting Effects Questionnaire (PEQ)

The Persisting Effects Questionnaire (PEQ) is a 5-item questionnaire that assesses the meaningfulness, spiritual significance, psychological insightfulness, and how psychologically challenging was the experience during the study drug dosing session. Participants provide a response on an 8-point rating scale from ‘no more than routine’ experience to ‘single most meaningful experience’ for the first 3 items and from ‘no more than routine’ to ‘single most difficult or challenging’ experience to the fourth item above. In addition, participants rate the overall drug effect at peak intensity on a 0-4 point scale from 0=none, 1=possibly slight, 2=moderate, 3=strong, and 4=extreme (Griffiths, 2006).

The PEQ will be administered to all participants at the end of each study drug administration session, 4 to 10 hours postdose.

10.1.9. 36-Item Short Form Survey (SF-36)

The 36-Item Short Form Health Survey (SF-36, Rand Corporation) is a set of generic quality-of-life measures, covering a range of items, including items such as general health and attitude, activity level, physical health or emotional problems with work, social activities, or regular daily

activities, pain, energy level and mood. The SF-36 will be answered by MDD participants at various scheduled days in-clinic as described in Table 4-1.

10.1.10. Any Drug Effect Visual Analogue Scale

A visual analogue scale will be completed by all participants on each day of dosing (Day 1 and Day 8 or Day 22) and will consist of a 100 mm bipolar line with the far left side of the line marked not at all, and the far right side of the line marked extremely. Participants will be asked "Right now, do you feel any drug effects at all?" and participants in response will make a vertical mark on the line on study dosing days predose and at 0.5, 1, 2, 4, 6, 8 and 12 hours postdose.

10.1.11. Quick Inventory of Depressive Symptomatology (QIDS SR-16)

The self-report Quick Inventory of Depressive Symptomatology (QIDS SR-16) is a 16-item depression scale, yielding scores from 0-27, which covers the symptom domains of major depressive disorder, for the time frame of the past week: sleep disturbance (Questions 1-4), sad mood (Question 5), decrease or increase in appetite or weight (Questions 6-9), concentration (Question 10), self-criticism (Question 11), suicidal ideation (Question 12), interest (Question 13), energy/fatigue (Question 14), and psychomotor agitation/retardation (Questions 15-16) (Rush, 2003). For MDD participants, QIDS SR-16 assessments will be completed prior to each study medication dose (Day -1, Day 21 and Day 42) and optional follow up assessments using QIDS-SR16 will be delivered to and completed by participants at 4-, 8- and 12-weeks post-Day 42 visit using ePRO.

10.2. Pharmacokinetics

10.2.1. Blood Sample Collection and Processing

Serial blood samples (approximately 6 mL per sample will be collected into blood collection tubes containing K_2EDTA) for determination of plasma CYB003 concentrations.

For the double-blind part of the study, PK blood samples will be collected on Day 1 (first dose) and Day 8 or Day 22 (second dose) at predose (within 30 minutes prior to dosing, all participants) and at 1, 6, 8, 12 and 24 hours postdose (total: 12 PK samples per MDD participant) and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose (total: 18 PK samples per NHV participant).

For the open-label part of the study, PK blood samples will be collected on Day 1 (first dose) and Day 8 (second dose) at predose (within 30 minutes prior to dosing) and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postdose (total: 18 PK samples per NHV participant).

The plasma samples harvested will be stored at -70 ºC until shipment to the bioanalytical laboratory for analysis. The study site will obtain the blood collection tubes, crushed ice and all required shipping supplies.

For the double-blind part of the study, a total of 72 mL (6 mL x 6 samples x 2 dosing sessions) of blood for MDD participants and 108 mL (6 mL x 9 samples x 2 dosing sessions) of blood for NHV participants will be collected over the 2 dosing sessions for plasma determination of CYB003. Additional blood samples (approximately 120 mL) will be obtained for clinical laboratory, pregnancy and serology evaluations, for a total of approximately 192 mL (for MDD participants) and 228 mL (for NHV participants) of blood collected during the study.

For the open-label part of the study, a total of 108 mL (6 mL x 9 samples x 2 dosing sessions) of blood for NHV participants will be collected over the 2 dosing sessions for plasma determination of CYB003. Additional blood samples (approximately 120 mL) will be obtained for clinical laboratory, pregnancy and serology evaluations, for a total of approximately 228 mL of blood collected during the study. Detailed instructions for blood collection, processing, and sample shipment will be provided in a separate PK Manual.

10.2.2. Plasma PK Sample Shipment

Plasma samples will be shipped on dry ice by overnight courier to:

Pyxant Labs Inc.
Sample Coordinator
4720 Forge Road, Suite 108
Colorado Springs, Colorado 80907 USA
Tel: 719-593-1165

The research site personnel shipping the PK samples will communicate directly with the designated lab sample coordinator by phone, fax or e-mail to alert the bioanalytical laboratory that samples are being shipped. Sample shipment schedules and receipt of samples will be coordinated and communicated between the research site, bioanalytical lab, and Sponsor, as necessary, such that PK sample integrity and proper storage conditions are maintained.

10.2.3. Bioanalysis

Plasma samples will be extracted and analyzed for plasma CYB003 concentration determination using a validated LC/MS/MS analysis method at Pyxant Labs. Plasma samples and bioanalytical data will be archived at Pyxant Labs as per applicable regulations and as agreed upon with Cybin and will be provided to Clinilabs Drug Development Corporation through an agreed upon data transfer agreement.

11. ASSESSMENT OF SAFETY

The safety and tolerability of CYB003 will be assessed by the incidence of treatment-emergent adverse events, study discontinuation information, clinical laboratory test results, ECGs, Holter data, vital signs and physical examination findings.

11.1. Adverse Events

11.1.1. Reporting Adverse Events

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational product, whether or not considered related to the investigational product, shall be documented on the eCRF. All AEs reported by the participant or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, outcome, intensity, if SAE, action taken and follow-up procedures will be reported.

The start of the AE reporting for a subject will be the signing of informed consent for this study. Between the informed consent and the first study drug dose, any SAE and related AEs (i.e., related to study procedures) should be reported. After the first study drug dose, all AEs (serious and non-serious, related and non-related) should be reported. All AEs that are recorded during this clinical study, including during the washout interval, will be documented on the eCRF.

11.1.2. Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation participant administered a drug and does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Treatment-Emergent Adverse Event (TEAE) – Any adverse event that is new or worsens beginning from the time the first dose of study drug through the end of the study and AE reporting time period. For example, nausea that occurs minutes after a dose of any study drug is by definition a TEAE. A baseline sign or symptom that occurs from the time of consent to the (assuming it does not meet an exclusion criterion) that worsens (i.e., changes from mild to moderate or from infrequent to a greater frequency) becomes a TEAE.

Serious Adverse Event (SAE) – Any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly or birth defect or an important medical event or requires medical intervention to prevent one of the outcomes listed.

Unexpected Adverse Event – Any adverse event that is not identified in nature, severity, or frequency in the CYB003 Investigator's Brochure.

Additionally, the Principal Investigator will evaluate all AEs as follows:

Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, is a congenital anomaly or an important medical event.

Action taken: whether or not the AE caused the participant to discontinue the study drug, or use a concomitant medication.

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

It is important to distinguish between serious and severe AEs.

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.1.3.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Relationship to study drug, to be graded as:

Causality term	Assessment criteria
Definite	• Time sequence from taking drug is reasonable • Event corresponds to what is known of the drug • Event ceases on stopping drug (dechallenge) • Event returns on restarting drug (rechallenge)
Probable	• Time sequence reasonable • Corresponds to what is known of the drug • Ceases on stopping drug (dechallenge) • Effect of rechallenge not known
Possible	• Time sequence reasonable • Corresponds to what is known of the drug • Effect of dechallenge and rechallenge not known
Unlikely	• Event not meeting the above criteria
Not Related	• Reasonable certainty that the adverse event is not related to the drug

11.1.3. Serious Adverse Events (SAEs)

The Principal Investigator shall document all AEs. He must make an accurate and prompt special report for any SAE to the Sponsor or its designee and to any IRB (Institutional Review Board) that has reviewed and is continuing to review the investigation within 24 hours of the first knowledge of the occurrence.

For any SAE, the Principal Investigator must notify the Sponsor immediately:

Drug Safety Navigator:

E-mail: PVG@DrugSafetyNavigator.com

With a copy to:
Amir Inamdar, MBBS, DNB (Psych), MFPM
Chief Medical Officer
Cybin IRL Limited
E-mail: amir@cybin.com
Tel: +44 7796 198 857

11.1.4. Recording of Adverse Events

11.1.4.1. Time Period for Collection of Adverse Events

Adverse Events will be collected from the time of signing the informed consent, throughout the treatment period up to and including the Follow-up Visit.

11.1.4.2. Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the participant's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF/eCRF.

The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

11.1.4.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product

- AE caused participant's withdrawal from study (yes or no)
- Outcome.

Additional variables will be collected for all SAEs including treatment given for the event.

11.1.4.4. Causality Collection

The Investigator will assess causal relationship between investigational product and each adverse event, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

11.1.4.5. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in the CRF/eCRF.

When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms.

However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

11.1.4.6. Adverse Events Based on Examinations and Tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the clinical study report.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria, or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information.

Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

11.1.4.7. Potential Abuse-Related Adverse Events

As recommended in the 2017 FDA Guidance, CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes should be assessed in clinical trials. FDA guidance lists the following MedDRA preferred terms as potential abuse-related AEs:

- *Euphoria-related terms* - Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormally; Hallucination; Inappropriate affect
- *Terms indicative of impaired attention, cognition, and mood* - Somnolence; Mood disorders and disturbances
- *Dissociative/psychotic terms* - Psychosis; Aggression; Confusion and disorientation
- *Related terms not captured elsewhere* - Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders

As stated in the FDA guidance Section V.B (pages 21-22), "a positive signal from abuse-related AEs does not inherently mean that a test drug has abuse potential. However, evaluation of clinical AE data, in conjunction with nonclinical abuse-related data (chemistry, receptor binding, animal studies), will determine whether a human abuse potential study should be conducted.

The presence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential. If euphoria-related AE(s) are reported, it will be important to further characterize the profile of the abuse-related signals to determine if the drug is similar to other known drugs of abuse (a stimulant, sedative, hallucinogen, etc.). In the absence of euphoria-related signals, AEs such as hallucination and dissociative state may also be indicative of abuse potential."

The above listed potential abuse-related AEs should be considered AEs of special interest and should be monitored for in this trial and reported by the Investigator to the Sponsor in an expeditious manner (i.e., within 24 to 48 hours). Narratives describing potential abuse-related events may be required, including time to onset in relation to drug administration, duration of the event, dose of drug, severity, medical outcome, and disposition of the subject (e.g., if the AE resulted in discontinuation from the study). It also may be relevant to indicate if more than one event was observed simultaneously, and if other drugs were taken by subjects at the time of the event.

11.1.5. Adverse Event Follow-up

The Investigator should take all appropriate measures to ensure the safety of the participants, including referral to a specialist if indicated. The Investigator should follow up on the outcome

of any AE (including SAEs) until the event has resolved or stabilized, or until 30 days from the initial report of the AE, whichever occurs first.

Any SAE brought to the attention of the Investigator within 30 days after discontinuation of study drug should be reported through the SAE reporting process.

11.1.6. Pregnancy

Pregnancy test will be performed at screening and at visits specified in Section 4. Participants with a positive test at screening or during the study period will be excluded from the study. Participants of child-bearing potential will be instructed to practice an acceptable method of birth control for the duration of the study. However, if a participant becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure. Both 'Pregnancy reporting form' and 'SAE form' will be completed and submitted to stakeholders and within timelines defined in protocol Section 11.1.3. Pregnancy shall be followed until its outcome.

11.2. Columbia-Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. The C-SSRS lifetime version will be completed at the screening evaluation, and the C-SSRS$_{SLV}$ (since last visit) version will be completed at multiple time points during the study, before and after study medication dosing and at scheduled visits as described in Section 4.

11.3. Clinical Laboratory Assessments

Hematology, chemistry and urinalysis laboratory test evaluations will be performed at the specified visits as described in Section 4. A list of clinical laboratory assessments is included in Appendix 1. A treatment-emergent abnormal clinical laboratory test result that is considered clinically significant by the Investigator will be recorded as an adverse event and follow-up clinical laboratory evaluations may be performed at the discretion of the Investigator.

11.4. Vital Sign Assessments

Seated vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate will be recorded at specified timepoints as described in Section 4. Vital signs may be measured at other unscheduled times at the Investigator's discretion if needed to assess the clinical status of a participant. Any vital sign assessment may be repeated at the discretion of the Investigator in the interest of participant safety. Height and weight will be recorded at the screening visit and BMI will be calculated.

11.5. Physical Examinations

A full physical examination (PE) will be performed at Screening and at other visits as described in Section 4. PEs may be repeated as deemed necessary by the Investigator or in response to adverse events (AEs). A full physical examination includes assessment of general appearance and evaluation of dermatological system, head, eyes, ears/nose/throat, neck, lymph nodes, lungs, heart, abdomen, neurological and musculoskeletal system. An abbreviated physical examination includes evaluation of general appearance, lungs, heart and musculoskeletal system, and any other symptom-directed system.

11.6. Resting 12-Lead ECG

A resting 12-lead ECG will be performed at scheduled time points as described in in Section 4. Parameters assessed will include ventricular rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec) and QTcF interval (msec) and an overall ECG interpretation by the Investigator. ECGs may be performed at any time during the study in the interest of participant safety at the discretion of the Investigator. Clinically significant changes in ECGs will be documented as AEs.

11.7. 12-Lead Holter Monitoring

Twelve-lead Holter monitoring will be performed for 6 hours (± 10 minutes) on Day -1 beginning in the morning at approximately 08:00 hours and on Day 1 and Day 22 (MDD participants), Day 1 and Day 8 (NHV participants, double-blind study part), and Day 1 and Day 8 (NHV participants, open-label study part) for approximately 12.5 hours beginning approximately 1 hour predose to 12 hours (± 10 minutes) postdose. The Investigator will review any alarms or alerts during the Holter sessions for potential safety issues or exclusionary findings. Holter monitoring data will be sent to a core ECG laboratory for central analysis. The Holter data will be reviewed by the Investigator and paper printouts of any clinically important events will be stored as source data.

12. CONCOMITANT MEDICATIONS

Over-the-counter or prescription medications should not be taken during the study, including during the washout interval, unless approved by the Sponsor and Principal Investigator on a case-by-case basis. Participants will continue stable doses of antidepressants during the study and should not modify the doses unless medically necessary with physician's guidance and approval. Acetaminophen may be used sparingly (occasional prn use at the Investigator's discretion) if needed for mild analgesia. Participants may take sedative/hypnotic drugs (e.g. zopiclone, zaleplon or zolpidem) for sleep on an as needed basis, but not more than 3 times a week and not 12 hours before any scheduled assessment. MDD participants may take

antianxiety drugs (e.g., benzodiazepines, hydroxyzine) on a chronic or as needed basis, but not 12 hours before study drug administration. Buspirone is an excluded/prohibited medication during the study.

Preexposure prophylaxis (PrEP) medication for prevention of HIV infection, such as TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) or DESCOVY® (emtricitabine and tenofovir alafenamide), is allowed for MDD participants.

Participants are allowed to continue taking stable chronic doses of hormone replacement medications during the study. Participants using oral hormonal contraceptives should continue these medications during the study. Any prescription or over-the-counter medication taken during the study, including during the washout interval, will be recorded in the appropriate section of the CRF.

No other medication is allowed, including herbal remedies or vitamin supplements, without the consent of the Investigator.

Medication, which is considered necessary for the participant's safety and well-being, for example to manage intolerable and persistent anxiety, persistent elevations/ changes in blood pressure, etc., may be given at the discretion of the Investigator during the residential period. When any such medication is required, it should be prescribed by the Investigator. Following consultation with the Sponsor Lead Physician or the Medical Monitor, and the Investigator should determine whether or not the participant should continue in the study.

13. STATISTICAL METHODS

Details of the statistical and pharmacokinetic analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

13.1. General Considerations

Data collected in this study will be presented using summary tables and participant data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum and maximum. Categorical variables will be summarized by frequencies and percentages.

Statistical calculations will be done using SAS software (Version 9.4 or higher, SAS Institute, Cary, North Carolina, USA).

13.2. Sample Size Determination

Up to 64 participants are planned to be enrolled into up to 7 cohorts, with up to 48 MDD participants and 16 NHV participants planned. Given the exploratory nature of this study, the sample size is not based on power calculations. The number of participants to be included is typical for this kind of study, and the results give sufficient safety and tolerability data, in addition to adequate description of the PK and PD parameters.

13.3. Analysis Populations

Safety Population: All participants who receive at least one dose of study drug, CYB003 or placebo, will be included in the safety population and safety analyses.

Pharmacokinetic Population: All participants who receive at least one dose of CYB003 without any major protocol violations, who have sufficient plasma CYB003 concentration data for reliable estimates of the key pharmacokinetic variables, and who do not vomit within 4 hours of CYB003 study medication will be included in PK population and PK analyses.

Relative Bioavailability Population: All participants in the open-label part of the study who receive both powder in solution and powder-filled capsule formulations in the fasted state, who have sufficient plasma CYB003 concentration data for reliable estimates of the key pharmacokinetic variables, and who do not vomit within 4 hours of CYB003 study medication.

Pharmacodynamic (Efficacy) Population: All MDD participants who receive at least one dose of CYB003 who have at least one post-baseline MADRS assessment will be included in the PD population and PD (efficacy) analyses.

13.4. Efficacy (Pharmacodynamics)

These questionnaires and rating scales will evaluate the psychedelic effects of CYB003 administration:

- Mystical Experience Questionnaire (MEQ30)
- 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
- Hallucinogen Rating Scale (HRS)
- Visual Analogue Scale (VAS) ratings of ‘Any drug effect’
- Persisting Effects Questionnaire (PEQ)

This standard efficacy assessment tool will be used to evaluate the clinical efficacy of CYB003 in treating the symptoms of MDD:

- Montgomery-Åsberg Depression Rating Scale (MADRS) score

Between-group effects will use the MADRS baseline score after the 3 preparatory psychotherapy sessions (post-randomization) for change from baseline scores, and within-group effects for the entire treatment will use MADRS screening scores to reflect the entire course of treatment, including all the preparatory psychotherapy sessions, as well as post-randomization study drug dosing and integration psychotherapy sessions.

Descriptive statistics will be calculated for quantitative efficacy data and frequency counts will be compiled for classification of categorical efficacy data. Summary statistics will be calculated for each endpoint by treatment, time, and group.

Summary statistics will be calculated for each PD endpoint by treatment, time and group. Total values and changes from baseline will be calculated.

Pooled analyses across cohorts (pools consisting of cohorts 1-6, 2-6, 3-6, 4-6, 5-6) of within-group and between group effects will be calculated.

13.5. Pharmacokinetics

Plasma CYB003 concentrations will be listed at each time point by participant and summarized by treatment at each time point using descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum and maximum values). PK calculations will be performed based on actual time of blood sample collection, using noncompartmental methods, with the linear up-log down trapezoidal method, using Phoenix WinNonlin Version 8.3 or higher (Certara Inc, Princeton, New Jersey, USA).

PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, T_{max}, V_z/F, CL/F, K_{el}, and $T_{1/2}$) will be listed by participant and summarized by treatment. In addition to the descriptive statistics listed above, geometric means will be reported for the PK endpoints ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}).

All plasma concentrations below the lower limit of quantitation (BLOQ) for the assay will be treated as "missing" in the PK analyses and summary statistics, except those that occur prior to the first quantifiable concentration on the day of dosing, or after the last quantifiable concentration, which will be treated as "0".

No value of K_{el} (λz), $AUC_{0-\infty}$ or $T_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. If the adjusted R-squared value (Rsq_adjusted) is < 0.8, the analyst may evaluate if other time points are more appropriate and use those for the calculation of K_{el}, or no value of K_{el}, $AUC_{0-\infty}$ or $T_{1/2}$ will be reported.

For determination of $AUC_{0-\infty}$, if calculated AUC from last to infinity is greater than 20% of the calculated AUC from 0 to infinity, then $AUC_{0-\infty}$ will not be reported.

Planned Pharmacokinetic/Statistical Analyses: The primary PK endpoints will be $AUC_{0-\infty}$, AUC_{0-t} and C_{max}, and the secondary PK endpoints will be T_{max}, V_z/F, CL/F, K_{el}, and $T_{1/2}$.

Relative Bioavailability Comparison: The geometric mean ratios and associated 90% confidence intervals between the powder in solution (Reference) and powder-filled capsule (Test) formulations administered in the fasted state will be provided for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} and will be used to assess the relative bioavailability of the two dosage forms.

13.6. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all participants and for MDD and NHV participants using descriptive statistics. The presence/absence of any current medical condition and/or other significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0, or higher. Medical and surgical history conditions will be listed, including reported term, System Organ Class (SOC) and Preferred Term, and year of diagnosis.

13.7. Exposure to Study Drug

Each participant's exposure to study drug (CYB003 and placebo) will be presented in data listings.

13.8. Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2021 version or later). Prior medications will be those that start and end prior to first dose of study drug. Concomitant medications will be those that have a known end date after the first dose of study drug, or have a missing end date. Medications will be listed by participant including Anatomical Therapeutic Class (ATC) classification, preferred term and reported term; the start and end dates (or ongoing status); and dose, unit and indication. Medications taken by participants from 30 days prior to Screening until the end of treatment will be included in the listing.

Any non-drug therapies that are incurred during the course of the study will also be coded using MedDRA or WHO Drug Enhanced Dictionary, as appropriate, and will be listed by participant including start date, end date and indication.

13.9. Safety Analyses

The safety and tolerability of a CYB003 will be assessed by the evaluation of treatment-emergent adverse events, study discontinuation information, laboratory test results, vital signs and physical examination findings.

Safety variables will be tabulated and presented for all participants and for MDD and NHV participants in the Safety Population. Data will be summarized by treatment. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for preferred term and system organ class, and will be listed by participant. Treatment-emergent AEs (TEAEs) will be summarized by treatment, where treatment-emergent is defined as any event with a start date on or after the date and time of the first dose date and time of study drug within a treatment period. All TEAEs will be summarized by relationship to study drug and by intensity.

Potential abuse-related TEAEs as listed in Section 11.1.4.7 will be summarized by category (i.e., euphoria-related terms; terms indicative of impaired attention, cognition, and mood; dissociative/psychotic terms; and related terms not captured elsewhere) and individual MedDRA Preferred Term.

12-lead ECGs will be centrally evaluated and measured by the central ECG laboratory (Clario), using a standard semi-automated method with measurements in lead II on 3 beats in each of 3 recordings. For the purpose of decisions on dose escalation, descriptive statistics on the interval data will be reported.

An evaluation of ECG effects of CYB003 may also be undertaken using 12-lead ECGs extracted from the Holter recordings with the EPQT method. The primary analysis will then be based concentration-QTc (C-QTc) modeling of the relationship between the plasma concentrations of CYB003 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) > 10 msec at clinically relevant plasma concentrations. The effect of CYB003 on the placebo-corrected ΔQTcF, ΔHR (heart rate), ΔPR, and ΔQRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. In addition, an analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology and U-wave presence.

Deaths, SAEs, and AEs resulting in study discontinuation will be tabulated and detailed in narratives.

14. ETHICS

14.1. Participant Information and Consent

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each participant prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the participant. The Principal Investigator will submit a copy of the informed consent document to the IRB for review and approval before research participants are consented and screened. The Principal Investigator will provide a copy of the signed

informed consent to the participant and a copy will be maintained in the participant's medical record.

14.2. Institutional Review Board

The Principal Investigator will provide the IRB with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB and the Sponsor in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

14.3. Study Monitoring

A third party clinical monitor contracted by Sponsor will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

14.4. Study Records Retention

In accordance with FDA regulations and GCP guidelines, the Investigator must retain all study-related documents for at least 2 years after the last approval of a marketing application/new drug application for the indication investigated or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (e.g., the IND application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.5. Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing.

The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of participants are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

14.6. Confidentiality

All information provided to the Principal Investigator by the Sponsor or their designees, including non-clinical data, protocols, CRFs and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to the Sponsor or their designees or in confidence to the IRB, except if required by law.

14.7. Publications

Following completion of the study, the data from this study may be considered for reporting at a scientific meeting or for publication in a scientific journal at the sole discretion of the Sponsor. In the case whereby the results of this study are to be published, the Sponsor will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

15. PRINCIPAL INVESTIGATOR'S STATEMENT AND SPONSOR APPROVAL SIGNATURE

I agree to conduct the study as outlined in the protocol and in accordance with the Sponsor's guidelines and Good Clinical Practice requirements.

_____ _____
Principal Investigator Date

Printed Name: _____

Institution: _____

Sponsor Approval Signature

_____ _____
Amir Inamdar, MBBS, DNB (Psych), MFPM Date
Chief Medical Officer
Cybin IRL Limited

16. REFERENCES

Barrett FS, Johnson MW, Griffiths RR (2015). Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol 29(11): 1182-1190. doi:10.1177/0269881115609019.

Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PCR, Strassman RJ (2015). Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol, 29(3):289-99. doi: 10.1177/0269881114565144.

Brown RT, Nicholas CR, Cozzi NV, et al. (2017). Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. Clin Pharmacokinet, 56(12), 1543-1554.

Carhart-Harris RL, Leech R, Hellyer PJ, et al. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci, 8, 20.

Carhart-Harris RL, Bolstridge M, Day CM, et al. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. The Lancet Psychiatry, 3, 619-627.

Carhart-Harris R, Giribaldi B, Watts R, et al. (2021). Trial of psilocybin versus escitalopram for depression. N Engl J Med, 384, 1402–1411.

CYB003 Investigator's Brochure Edition 1, Issue Date: May 2022, Cybin IRL Limited, Dublin, One Spencer Dock, North Wall Quay, Dublin, 1D01 X9R7.

Cipriani A, Furukawa TA, Salanti G, et al. (2018). Comparative efficacy and acceptability of 21antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet, 391, 1357–1366.

COMPASS Pathways (2018). COMPASS Pathways receives FDA Breakthrough Therapy designation for psilocybin therapy for treatment resistant depression: Compass Pathways. https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment resistant-depression. Accessed 25 May 2021.

Cosgrove L, Mills C, Karter JM, et al. (2020). A critical review of the Lancet Commission on global mental health and sustainable development: Time for a paradigm change. Critical Public Health, 30(5), 624-631.

Curic S, Andreou C, Nolte G, Steinmann S, Thiebes S, Polomac N, Haaf M, Rauh J, Leicht G, Mulert C (2021). Ketamine Alters Functional Gamma and Theta Resting-State Connectivity in Healthy Humans: Implications for Schizophrenia Treatment Targeting the Glutamate System. Front. Psychiatry, https://doi.org/10.3389/fpsyt.2021.671007.

Dahmane E, Hutson PR, Gobburu JVS (2021). Exposure-response analysis to assess the concentration-QTc relationship of psilocybin/psilocin. Clin Pharmacol Dev 10(1):78-85.doi:10.1002/cpdd.796.

Davis AK, Barrett FS, May DG, et al. (2021). Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. JAMA Psychiatry, 78, 481-489.

Dittrich A (1998). The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry, 31(Suppl. 2):80–4. doi: 10.1055/s-2007-979351.

Dittrich A, Lamparter D, Maurer M (2010). 5D-ASC: Questionnaire for the assessment of altered states of consciousness. A short introduction. Zurich, Switzerland: PSIN PLUS (Translation from the original German by Felix Hasler and Rael Cahn).

FDA (2005). Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Available at: https://www.fda.gov/media/72309/download

FDA (2017). Guidance for Industry: Assessment of Abuse Potential of Drugs. Available at: https://www.fda.gov/media/116739/download

FDA (2018). Breakthrough Therapy | FDA. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy. Accessed 25 May 2021.

FDA (2019). Spravato (esketamine): Highlights of prescribing information. www.fda.gov/medwatch. Accessed 22 May 2021.

Griffiths RR, Richards WA, McCann U, Jesse R (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 187(3):268-83; discussion 284-92. doi:10.1007/s00213-006-0457-5.

Griffiths RR, Johnson MW, Carducci MA, et al. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol, 30, 1181-1197.

Griffiths RR, Johnson MW, Richards WA, et al. (2018). Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol, 32(1), 49-69.

Halberstadt AL, Koedood L, Powell SB, et al. (2011). Differential contributions of serotonin receptors to the behavioral effects of indoleamine hallucinogens in mice. Journal of Psychopharmacology (Oxford, England), 25(11), 1548–1561.

Hasler F, Bourquin D, Brenneisen R, et al. (1997). Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. Pharm Acta Helv, 72(3), 175-184.

Holze F, Ley L, Müller F, et al (2022). Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology, 47(6):1180-87.

Kraehenmann R, Pokorny D, Vollenweider L, et al. (2017). Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. Psychopharmacology, 234, 2031-2046.

Madsen MK, Fisher PM, Burmester D, et al (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology, 44:1328-34. https://doi.org/10.1038.s41286-019-0324-9.

Montgomery SA, Åsberg M (1979). A new depression scale designed to be sensitive to change. Br J Psychiatry, 134:382-389.

Moreno FA, Wiegand CB, Taitano EK, et al. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry, 67(11), 1735-1740.

National Institute of Mental Health, 2020 Statistics: Major Depression. Updated January 2022. https://www.nimh.nih.gov/health/statistics/major-depression; accessed: 22 April 2022.

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

Nielson EM, May DG, Forcehimes AA, et al. (2018). The psychedelic debriefing in alcohol dependence treatment: Illustrating key change phenomena through qualitative content analysis of clinical sessions. Front Pharmacol, 9(132), 1–13.

Noorani T, Garcia-Romeu A, Swift TC, et al. (2018). Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. J Psychopharmacol, 32(7), 756–769.

Nutt D (2019). Psychedelic drugs – a new era in psychiatry? Dialogues Clin Neurosci, 21(2), 139-147.

Nutt D, Erritzoe D, Carhart-Harris R (2020). Psychedelic Psychiatry's Brave New World. Cell, 181, 24-28.

Passie T, Seifert J, Schneider U, et al. (2002). The pharmacology of psilocybin. Addict Biol, 7(4), 357-364.

RAND Corporation. 36-Item Short-Form Survey. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html; accessed 22 April 2022.

Rizvi SJ, Grima E, Tan M, et al. (2014). Treatment-resistant depression in primary care across Canada. Can J Psychiatry, 59, 349–357.

Ross S, Bossis A, Guss J, et al. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. J Psychopharmacol, 30(12), 1165–1180.

Rush AJ, Trivedi MH, Ibrahim HM, et al. (2003). The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54(5):573-83. doi: 10.1016/s0006-3223(02)01866-8.

Rush AJ, Trivedi MH, Wisniewski SR, et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D Report. Am J Psychiatry, 163, 1905–1917.

Schindler EAD, Sewell RA, Gottschalk CH, et al. (2021). Exploratory controlled study of the migraine-suppressing effects of psilocybin. Neurotherapeutics, 18(1), 534-543.

Sewell RA, Halpern JH, Pope HG Jr. (2006). Response of cluster headache to psilocybin and LSD. Neurology, 66(12), 1920-2.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G (1998): The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 59(suppl 20): 22-33.

Staines R (2019). FDA tags psilocybin drug as clinical depression Breakthrough Therapy. In: Pharmaphorum. https://pharmaphorum.com/news/fda-tags-psilocybin-drug-as-clinical-depression-breakthrough-therapy/. Accessed 25 May 2021.

Strassman RJ, Qualls CR, Uhlenhuth EH, Kellner R. Dose-response study of N,N-dimethyltryptamine in humans: II. Subjective effects and preliminary results of a new rating scale (1994). Archives Gen Psychiatry, 51(2):98-108.

Studerus E, Kometer M, Hasler F, Vollenweider FX (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J Psychopharmacol, 25(11):1434-52.

Vigo D, Thornicroft G, Atun R (2016). Estimating the true global burden of mental illness. The Lancet Psychiatry, 3(2), 171-178.

Vollenweider FX, Leenders KL, Scharfetter C, et al. (1997). Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology, 16(5), 357-372.

Zhuk O, Jasicka-Misiak I, Poliwoda A, et al. (2015). Research on acute toxicity and the behavioral effects of methanolic extract from psilocybin mushrooms and psilocin in mice. Toxins (Basel), 7(4), 1018-1029.

17. APPENDIX 1 – CLINICAL LABORATORY TESTS

<table>
<tr>
<td>Blood Chemistry
Amylase
BUN
Creatinine
Glucose
Sodium
Potassium
Phosphate
Chloride
Calcium
AST
ALT
GGT
Alkaline phosphatase
Total bilirubin
Uric acid
Albumin
Total protein
Lactate dehydrogenase</td>
<td>Urinalysis (dipstick)
Glucose
Bilirubin
Ketone
Specific Gravity
Blood
pH
Protein
Urobilinogen
Nitrite
Leukocyte Esterase

Microscopic analysis if dipstick is abnormal</td>
</tr>
<tr>
<td>Haematology
Haemoglobin
Haematocrit
RBC count
RBC indices (MCV, MCH, MCHC)
Platelet count
White blood cell count with differential</td>
<td>Drugs of abuse
Amphetamines
Barbiturates
Benzodiazepines
Cocaine
Cannabinoids
Opiates</td>
</tr>
<tr>
<td rowspan="2">Coagulation
Prothrombin time (PT)
International normalized ratio (INR)
Activated partial thromboplastin time (aPTT)</td>
<td>Other Screens
Alcohol (breath)
COVID-19 test
Follicle stimulating hormone, for participants of non-childbearing potential who were capable of producing eggs (ova)
Urine/Serum pregnancy test, for participants of child-bearing potential</td>
</tr>
<tr>
<td>Serology
Anti-HIV I/II
Anti-HCV
HBsAg</td>
</tr>
</table>

Abbreviations: ALT – alanine aminotransferase; Anti-HIV I/II – Anti-human immunodeficiency virus I and II; Anti-HCV – anti-hepatitis C antibody; AST: aspartate aminotransferase; BUN – blood urea nitrogen; COVID-19 – Coronavirus disease 2019; GGT – gamma-glutamyltransferase; HBsAg – hepatitis B surface antigen; MCH - mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; MCV – mean corpuscular volume; RBC – red blood cell