RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CYB003, A DEUTERATED PSILOCYBIN ANALOG IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Introduction

- Available treatments for Major Depressive Disorder (MDD) have limited efficacy, remission and response rates. They require daily dosing, are associated with dose-limiting side effects, and do not address the maladaptive patterns of thinking and behavior underlying these conditions.
- Clinical studies have demonstrated that short-term administration of psilocybin has the potential for rapid and long-lasting antidepressant effects in MDD (Carhart-Harris 2021, Goodwin 2022), and may therefore meet a significant unmet clinical need.
- While psilocybin is efficacious and inherently safe, there is significant variability between patients in their psychedelic and side-effect experiences. This variability is likely due to psilocybin acting as a pro-drug that requires de-phosphorylation to the psychoactive metabolite, psilocin, that acts as an agonist at a variety of serotonin (5-hydroxytryptamine [5-HT]) receptors, including the 5-HT_{2A} receptor (Nichols 2004). CYB003 is a novel deuterated analog of psilocybin that may offer benefits over psilocybin.
- The aim of this clinical study was to determine safety, tolerability, and pharmacokinetics (PK) of ascending doses of CYB003 and to evaluate the efficacy of CYB003 in treating symptoms of MDD.

Aims

Primary:

- To determine the safety and tolerability of ascending oral doses of CYB003 in healthy participants with and without MDD

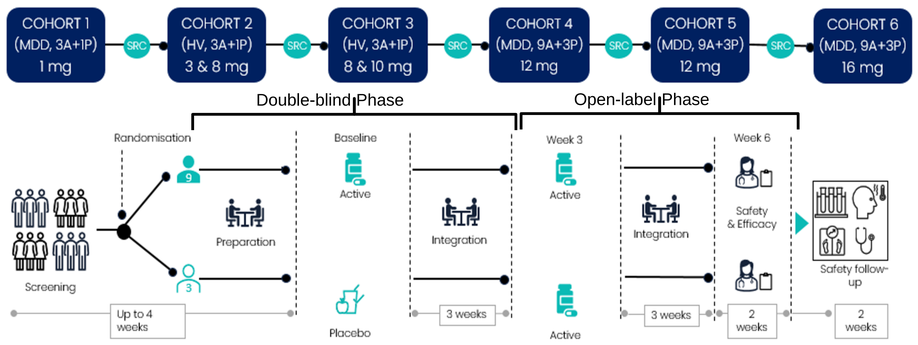
Secondary:

- To determine the PK of ascending oral doses of CYB003
- To evaluate the efficacy of CYB003 in treating symptoms of MDD (MADRS)
- To characterize the psychedelic effects of CYB003 administration (VAS any drug effect, MEQ-30, HRS, 5D-ASC , PDQ)

Methods

- A seamless Phase 1/2 study (www.clinicaltrials.gov; ID: NCT05385783) was designed to evaluate safety, tolerability, PK, psychedelic effects, and therapeutic efficacy of ascending doses of CYB003 (Figure 1).
- Three healthy control cohorts were initially examined to test the safety and pharmacokinetics (PK) of CYB003 at doses up to 10 mg (4 subjects per cohort).
- Three cohorts of patients with MDD were examined to test the safety, efficacy and PK of CYB003 at doses >10 mg. (12 subjects per cohort)
- Patients with MDD satisfied DSM-5 criteria for moderate to severe MDD and scored ≥ 21 on the Montgomery-Åsberg Depression Rating Scale (MADRS), were inadequately responding to their ongoing antidepressant treatment and were not treatment resistant. Patients were allowed to remain on a stable dose of their antidepressant medication during the trial.
- 36 MDD-Patients were randomized to Placebo or CYB003 at a 1:3 ratio for the first dose. 24 patients received 12 mg CYB003 or placebo and 12 patients received 16 mg CYB003 or placebo as the first dose. All patients received CYB003 as the second dose.
- Doses were administered one week apart for the healthy participants and 3 weeks apart for the MDD patients.
- All participants received psychological support based on Cybin's EMBARK™ psychological support framework.
- MADRS scores were collected at baseline and up to 12 weeks after the first dose to assess short and long-term efficacy. Dose escalations were based on PK-PD modelling (blinded data). Pharmacodynamic (PD) measures included the Visual Analogue Scale any drug effect (VAS), Revised Mystical Experience Questionnaire (MEQ-30), Hallucinogen Rating Scale (HRS), 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) and the Persisting Effects Questionnaire (PEQ).
- The primary endpoint for the efficacy assessment was the change from baseline at the end of the double-blind placebo-controlled phase (Day 21, MADRS total score). The effect of a second dose was assessed in an open label manner with efficacy measured at Day 42, three weeks after administration of a 2nd dose (everybody receiving an active dose of 12 mg or 16 mg).
- A responder analysis (improvement of at least 50%) and the number of subjects going into remission (MADRS scores of 10 or below) was performed.

Figure 1: Study Design



MDD: Participants with Major Depressive Disorder; HV: Healthy Volunteers
Primary efficacy assessed at Week 3, 12 week follow up to assess durability of effects

Results

Efficacy

Figure 2: Rapid improvement after a single dose of 12 mg

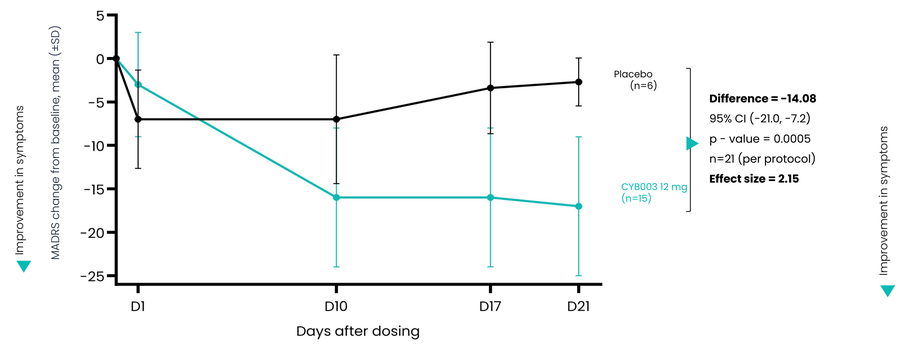


Figure 3: Rapid improvement after a single dose of 16 mg

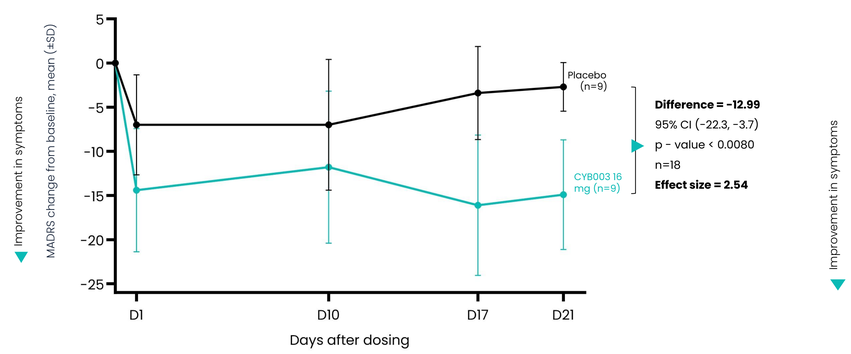
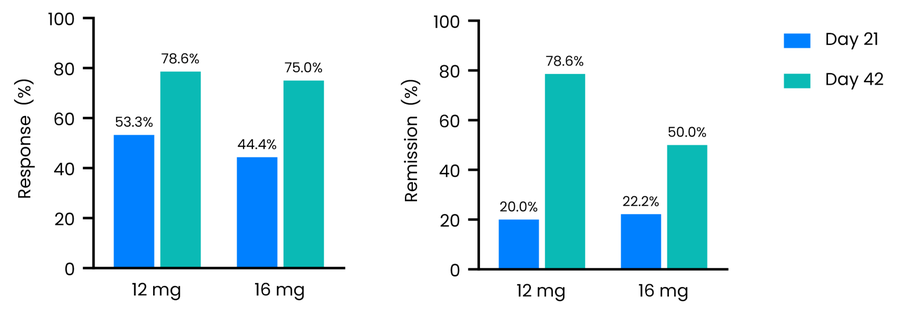


Figure 4: Remission* and Response**



*MADRS total score ≤10 points , **≥50% decrease in MADRS total score from baseline

Figure 5: 1st dose: large improvement after 3 weeks (pooled)

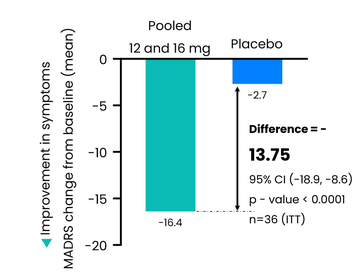
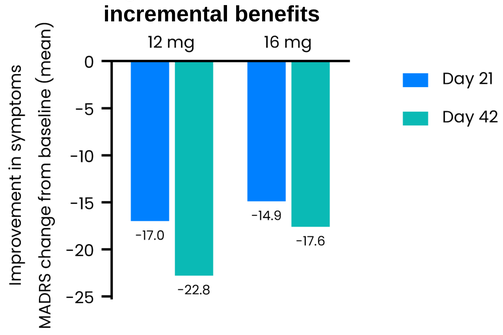


Figure 6: 2nd dose: Sustained and incremental benefits



Results

- CYB003 showed a rapid improvement with a clinically meaningful (Effect Size 2.15) and statistically significant (P=0.0005) difference of 14 points (MADRS) over placebo at the end of the double-blind phase (day 21) for the 12 mg dose (Figure 2). Similar results were obtained in the 16 mg group (Figure 3).
- This was also shown for a pooled analysis (all active versus all Placebo). A difference of -13.75 points was shown after three weeks (-16,4 versus -2,7, P<0.0001) (Figure 5).
- This resulted in a response rate of 53.3% and 44.4% and a remission rate of 20% and 22.2%, compared to 0% response and remission in the Placebo group for the 12 mg and 16 mg groups, respectively, at the end of the double-blind phase (Figure 4).
- A second dose of CYB003 also lead to further improvement in response and remission rates for the 12 mg (78.6% and 78.6%) and 16 mg (75% and 50%) groups respectively 3 weeks after a 2nd dose (Figure 4).
- A second dose of CYB003 given on day 22 resulted in additional numerical improvement with a total reduction from baseline in MADRS score on day 42 of -22.8 points for 12 mg (day 21: -17) and -17.6 points for the 16 mg group (day 21: -14.9) (Figure 6).

Safety

Table 1: Drug-related, treatment-emergent adverse events*

Drug-related, treatment-emergent adverse events*	CYB003 n (%)	Placebo n (%)
At least one AE	21 (60.0)	8 (61.5)
Nausea	6 (17.1)	3 (23.1)
Blood pressure increased	5 (14.3)	3 (23.1)
Headache	3 (8.6)	0
Vomiting	2 (5.7)	1 (7.7)
Eructation	1 (2.9)	0
Dizziness	1 (2.9)	0
Affect lability	1 (2.9)	0
Anxiety	2 (5.7)	1 (7.7)
Panic Attack	1 (2.9)	0
Confusional state	1 (2.9)	0
Nasal congestion	1 (2.9)	0
Tachycardia	1 (2.9)	0

*includes participants from all cohorts (CYB003 n=35, Placebo n=13)

- CYB003 was well tolerated with no Serious Adverse Events
- No Adverse Events (AEs) of suicidal ideation or behavior
- Most common AEs were nausea, elevated blood pressure and headache
- All AEs were mild or moderate in intensity and resolved without intervention
- Increases in blood pressure and heart rate were transient and resolved without intervention
- No clinically relevant changes in chemistry, hematology markers or ECG parameters

Conclusions

- Rapid and large improvements in symptoms of depression observed after single doses of CYB003 with a clear incremental benefit of a second dose.
- Effects translate into unprecedented effect size (Cohen's d > 2)
- Statically significant improvements were evident within 10 days after dosing with the 12mg dose
- The second dose of CYB003 was associated with a further incremental increase of 2.7 to 5.8 points for the 12mg and 16mg doses respectively, with antidepressant effects sustained at 6 weeks dosing.
- Response and remission rates of 53% and 20% respectively were seen with the 12mg dose (after the first dose at week 3) with further robust and significant improvements of > 75% with a 2nd dose at 6 weeks.
- CYB003 has demonstrated an excellent safety profile in doses tested so far – all reported AEs mild to moderate and self–limiting.
- These findings are very encouraging and support the continued development of CYB003 into Phase 3 clinical trials.

References

Carhart-Harris, R. et al. (2021) N Engl J Med, 384, 1402–1411.
Goodwin, G.M. et al. (2022) N Engl J Med, 387, 1637-1648..
Nichols D.E. (2004) Pharmacol Ther. 101(2):131-181.

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