CYB003 produces robust and enduring antidepressant effects in patients with Major Depressive Disorder (MDD)

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Introduction

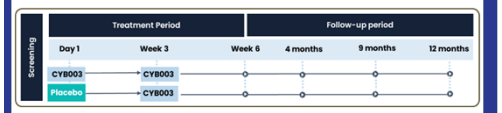
- Most of the available treatments for Major Depressive Disorder (MDD) have limited efficacy in terms of offering relief from symptoms and response or remission rates. Treatments also require daily dosing.
- Short-term administration of tryptamine serotonin receptor agonists (TSRAs) such as psilocybin has shown a potential for rapid and long-lasting antidepressant effects in MDD (Carhart-Harris et al., 2021, Goodwin et al., 2022) and could address a significant unmet need.
- An oft-cited concern with TSRAs is the potential for functional unblinding and the impact it may have on the interpretation of efficacy data. One way such concerns can be alleviated is by an assessment of durability of effects – however, long term follow up data are limited.
- CYB003 is a synthetic deuterated isotopomer of psilocin.
- We previously presented data from a 6-week evaluation of 2 doses of CYB003 in treating patients that were inadequately responding to their ongoing antidepressant treatment (Krempien et al., 2023).
- In this study, we evaluated long-term efficacy (up to 1 year) of 1 or 2 doses of CYB003 in maintaining improvement in symptoms of depression.

Aims

- CYB003-001b was a non-interventional, long-term observational study of patients with MDD who had previously participated in cohorts 4, 5 and 6 of the CYB003-001 study.
- The main aim of the study was to collect data to assess the long-term efficacy of CYB003 in treating symptoms of MDD.
- We also collected long-term data to evaluate potential adverse sequelae over a one-year period.

Methods

Figure 1: Study Design



- The primary study enrolled participants across 6 cohorts – cohorts 1-3 enrolled healthy volunteers, whereas cohorts 4-6 enrolled participants with MDD.
- The aim of the healthy volunteer cohorts was to establish preliminary safety and PK and identify a dose at which strong pharmacodynamic effects could be seen.
- Participants in cohorts 4-6 were patients with MDD who were on stable doses of antidepressants but were responding inadequately.
- Participants were allowed to remain on their background antidepressant medications throughout the study.
- Participants completing 6 weeks of treatment and the 4 month follow up in the CYB003-001 study were eligible to enroll in this long-term extension.
- Eligible participants that signed an informed consent were followed up over 2 visits, at approximately 9 and 12 months from Day 1. Visits could be remote or in person.
- At each visit, data on changes to medical history, background treatment (antidepressants or psychological therapies) and changes in symptoms were assessed.
- Changes in symptoms of depression were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS).
- Participants were also assessed for the occurrence of any adverse events, including potential abuse-related events.
- No treatment interventions were administered in this follow up.
- The study was approved by the relevant institutional review board (IRB).

Results

Figure 2: Sustained symptom improvement at 12 months with 2 doses of 12 mg CYB003

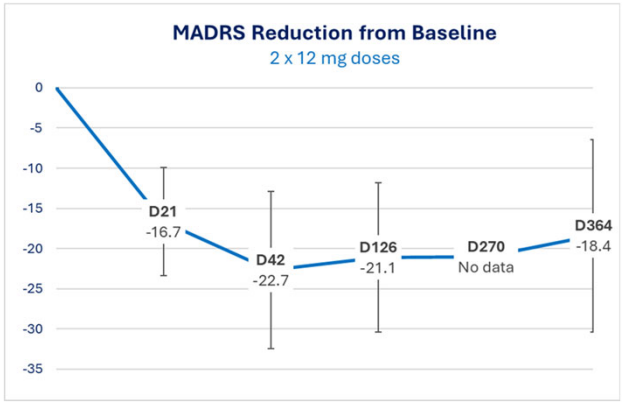


Figure 3: Sustained symptom improvement at 12 months with 2 doses of 16 mg CYB003

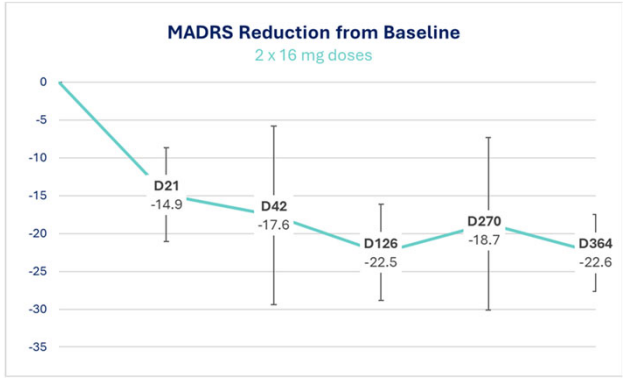
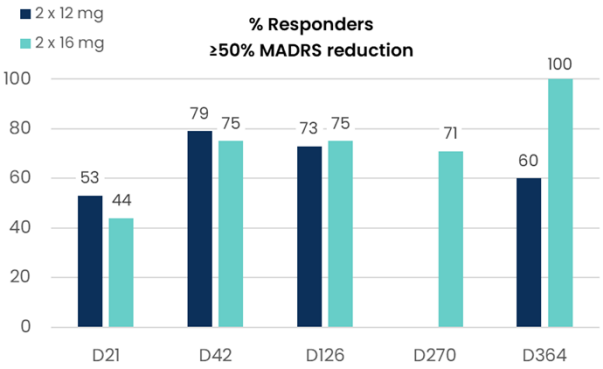
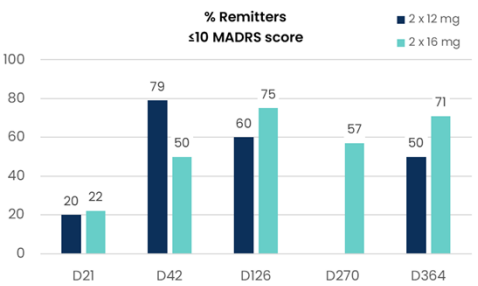


Figure 3: Response rates at 12 months with 2 doses of CYB003 (12 or 16 mg)



Results

Figure 4: Remission rates at 12 months with 2 doses of CYB003



- Of the 36 participants that were randomized to cohorts 4, 5 and 6, a total of 21 participants enrolled in the long-term follow up.
- These included 10 participants who had received 2 doses of 12 mg, 3 who had received 1 dose of 12 mg, 7 who had received 2 doses of 16 mg, and 1 who had received 1 dose of 16 mg.
- At 12 months, participants who had received 2 doses of 12 mg CYB003 showed a sustained benefit from treatment as indicated by persistent reduction from baseline in the total MADRS score of 18 points.
- Similarly, at 12 months, participants who had received 2 doses of 16 mg CYB003 continued to demonstrate a sustained benefit as evidenced by a change from baseline in the total MADRS score of 23 points.
- This translated into robust response and remission rates:
  - With 2 doses of 12 mg, 60% of the participants were still responders at 12 months, and 50% were in remission.
  - 100% of the participants who received 2 doses of 16 mg were still responders at 12 months, and 71% were in remission.
- The 2 patients on 16 mg that did not meet criteria for remission at 12 months had a score of 11, missing remission by just one MADRS point.
- Though based on limited numbers, two doses of CYB003 appeared to be better than a single dose. Three of the four completers who received a single dose of CYB003 were still symptomatic at 12 months.

Safety

- At the 12-month timepoint, no adverse events were reported, including no long-term sequelae of dosing.
- There were no reports of suicidality during the 12 month follow up, or at any point following dosing, as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).
- Participants that did not enroll in the 12-month follow-up did not do so because of an AE.
- Further, lack of response was not a reason for not enrolling in the 12-month follow up as the majority of patients that did not enroll in the follow up were in remission.

Conclusions

- Robust response and remission rates that were sustained for up to a year were observed after just 2 doses of CYB003.
- Almost all patients who received 2 doses of 16 mg of CYB003 were still in remission after a year of follow up.
- CYB003 was well-tolerated with no adverse long-term sequelae including no report of suicidality in the 12 months following dosing.
- With a favorable safety and efficacy profile, CYB003 is well positioned to enter Phase 3 development

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.
Krempien et. al .(2023) Neuropsychopharmacol. 48 (Suppl 1), 63–210 (2023); P226.

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