Development of Deuterated Analogues of Psychedelics for the Treatment of Mental Health Conditions

Submission ID 3005958

Submission Type Poster/Individual Research Report

Topic Depressive Disorders

Status Submitted

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SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract At Cybin, we are developing differentiated, next-generation therapeutics with the potential to improve clinical outcomes and address key unmet needs for people with mental health conditions. We are developing intermittent treatments with potential rapid-onset, long-lasting clinical efficacy in treating depression and anxiety. Unlike current treatments that only address symptoms, our therapies target underlying causes in neural circuitry that lead to mental health disorders.

The two clinical programs (CYB003 and CYB004) are currently being developed at Cybin.

CYB003 is a synthetic, deuterated isotopomer of psilocin, the active metabolite of psilocybin which is a natural product produced by numerous species of Psilocybe mushrooms. In humans, psilocin is an agonist of a variety of serotonin receptors, most importantly the 5-HT2A receptor, through which it is believed to exert it's therapeutic effects. CYB003 is being developed as an adjunctive to antidepressants in the treatment of patients suffering from major depressive disorder who are inadequately responding to their ongoing treatment. A seamless Phase 1/2 study (CYB003-001) was designed to evaluate safety, tolerability, and therapeutic efficacy of ascending doses of CYB003. In this study patients suffering from moderate to severe MDD (scoring ≥21 on the Montgomery-Åsberg Depression Rating Scale (MADRS)) who were inadequately responding to their ongoing antidepressant treatment, were enrolled in a double-blind, randomized, placebo-controlled manner across three cohorts with 12 patients per cohort. 36 MDD patients were randomized to placebo or CYB003 at a 1:3 ratio for the first dose, with all patients receiving CYB003 as the second dose. Doses were administered 3 weeks apart. MADRS scores were collected at baseline and up to 16 weeks after the first dose to assess acute and medium-term (Day 126) efficacy. To further evaluate the durability of effect of two doses of CYB003 up to 12 months, a follow-up study (CYB003-001b) was initiated for patients who had completed the CYB003-001 study.

The primary endpoint for the efficacy assessment was the change from baseline in MADRS total score. A responder analysis (improvement of at least 50%) and the number of subjects going into remission (MADRS scores of 10 or below) was performed after unblinding at Days 21, 42, and 126., 270 and 364.

CYB003 demonstrated a favorable safety profile. Adverse effects were mild or moderate and mostly self-limiting, and no severe or serious AEs occurred.
CYB003 showed a rapid improvement with a difference of 14 points on the MADRS total score compared to the placebo-group, leading to a clinically meaningful effect size of 2.15 (P=0.0005) at the end of the double-blind phase (Day 21) for the 12 mg dose. Similar results were obtained in the 16 mg dose group with a difference of 13-point improvement over placebo (Effect size 2.54, P=0.008).
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 (Day 21).
A second dose of CYB003 on Day 22 led to further improvement of the 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 (Day 42).
Based on these data, the FDA granted CYB003 a breakthrough therapy status.
Long term efficacy was assessed in the follow-up study (CYB003-001b) with clinical and safety assessments at Days 270 and 364. Of the 36 eligible participants, 21 provided informed consent and were followed up to 12 months from the time of initial dosing. Participants who had received 2 doses of 12 mg CYB003 demonstrated a reduction in total MADRS scores of 18 points at 12 months and those administered 16 mg CYB003 had a reduction of 23 points. Response rates were 60% and 100% at 12 months and remission rates were 50% and 71% for those receiving 2 doses of 12 mg and 16 mg, respectively. There were no AEs reported, nor any instances of suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale in the long term follow up.
A phase 3 development program for CYB003 has been initiated and is underway.
Our second program, CYB004, is a deuterated analog of dimethyl tryptamine (DMT) and we have conducted a series of clinical studies that have explored the PK, PD, and safety of DMT and CYB004 in healthy participants and patients with MDD.
CYB004E (Parts A, B, and C) explored the PK, PD, and safety of DMT and CYB004 in a series of studies.
CYB004E Part A evaluated safety, PK and PD of a 90-minute infusion of DMT in healthy smokers at dose levels of 0.12 mg/kg, 18.2, 36.4, and 72.8 mg DMT hemifumarate and recruited 38 participants across 4 cohorts. DMT was well tolerated; all adverse events (AEs) were mild and self-limiting. Statistically significant effects ($p<0.0001$) were observed at 72.8 mg on the Mystical Experiences Questionnaire-30 (MEQ-30) total score, visual analogue scale (VAS) feeling high, hallucinogen rating scale (HRS) subscales cognition, intensity, perception and somaesthesia. We concluded that the rate at which Cmax is attained contributes to the psychedelic effects.
CYB004E Part B evaluated DMT IV as a bolus over 5 min followed by an infusion over 55 min, in an open label, fixed order, 2-way crossover rising dose design in healthy participants. An infusion rate of 18.2 mg in 5 min + 44.5 mg in 55 min IV was selected to provide a mean steady state DMT concentration of approximately 40 ng/mL, a concentration level that was reported previously in the literature to be associated with robust psychedelic effects. Doses for the second treatment period (18.2 mg in 5 min + 71.2 mg in 55 min IV) were selected based on safety, PK and PD data from the first dosing period. 10 healthy non-smokers were enrolled in Part B. Intense psychedelic effects were reported by subjects during the 5-minute bolus and were sustained during the infusion, with

effects in Part B being more intense compared to Part A.
Part C was a first-in-human dosing of deuterated DMT (CYB004) in healthy volunteers (n=12) evaluating IV dosing regimens (5 min bolus ± 30 min infusion). Intense psychedelic effects were reported by subjects for about 40 min after the stop of the infusion and these effects correlated with the plasma concentrations of CYB004.
Based on these data, CYB004 is being evaluated in patients with generalized anxiety disorder. These data, the phase 3 plan for CYB003 and the development pipeline will be presented at the conference.

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