PHARMACOKINETIC PROFILE OF CYB003: A NOVEL, DEUTERATED PSILOCYBIN ANALOG FOR THE POTENTIAL TREATMENT OF MAJOR DEPRESSIVE DISORDER

Amir Inamdar, Michael Morgan, Joan Krakowsky, Amy Reichelt, Clinton Canal, Tina Mueller, Ken Avery, Pradip Pathare, Joshua Hartsel, Alex Nivorozhkin, Geoffrey Varty, Michael Palfreyman

Cybin Inc., 5600-100 King St West, Toronto, ON M5X 1C9, Canada

NYSE:CYBN
NEO:CYBN

Abstract

Background: Studies have demonstrated significant benefits of psilocybin in a range of psychiatric conditions such as major depressive disorder (MDD), anxiety and substance use disorders. While psilocybin is efficacious and inherently safe, there is significant variability between patients in their psychedelic and side effect experiences. This is likely due to psilocybin acting as a pro-drug that requires de-phosphorylation to the psychoactive metabolite, psilocin, which acts at the central serotonergic receptors, including 5-HT_{2A} receptors. Improving the absorption, distribution, and elimination of psilocybin, while retaining its therapeutic effects, may offer significant benefits to the patient. CYB003 is a novel deuterated analog of psilocybin that may offer such benefits. The aim of these studies was to compare the pharmacokinetic (PK) profile of CYB003 to psilocybin and psilocin.

Methods: To compare the PK profile, CYB003, psilocin and psilocybin were administered orally to male Sprague-Dawley rats. Plasma and brain samples were collected over a 4-hours post-dosing and were analyzed by LC-MS/MS for levels of CYB003 and psilocin. The PK profiles of CYB003 following both oral and intravenous administration to the mouse, rat and dog were also determined. PK parameters were determined using noncompartmental analysis (Phoenix WinNonlin v 8.3).

Results: In rats, the time to reach peak plasma exposure (T_{max}) was 30 min for CYB003, compared to 60 min for plasma psilocin following psilocybin administration. The half-life ($T_{1/2}$) for CYB003 was 45 min, compared to greater than 240 min for psilocin from psilocybin and was corroborated by a reduction in CYB003 Mean Residence Time of 36%. Furthermore, the inter-subject variability of CYB003 at the maximum achieved plasma concentration (C_{max}) was reduced by 53% compared to psilocin from psilocybin. The rank order for oral bioavailability (%F) across species was mouse = dog >> rat. The CYB003 brain:plasma ratio in the rat after an IV administration was 10.6, compared to 7.7 for psilocin from psilocybin, suggesting improved penetration into the CNS, and therefore, the potential to reduce the systemic dose of CYB003 needed to achieve a target therapeutic level in the brain. This trend was also observed in mice.

Conclusion: These findings suggest that the unique PK properties of CYB003 may provide a meaningful advantage over psilocybin for the treatment of an array of psychiatric disorders, including MDD.

Overview

Cybin's CYB003 program aims to develop a novel Second-Generation psychedelic compound based on psilocybin that will provide therapeutic benefits while addressing some of the limitations with psilocybin.

By leveraging Cybin's cutting-edge medicinal chemistry expertise, we have successfully generated CYB003, a proprietary deuterated psilocybin analog.

CYB003 may harness the therapeutic benefits of psilocybin while potentially reducing the duration of the clinical visit and diminishing side-effects associated with psilocybin.

CYB003 is designed to achieve less variability in plasma levels, faster onset of action, shorter duration of effect and potentially better tolerability versus oral psilocybin, for an overall better outcome for patients.

Here, we present the optimized pharmacokinetic (PK) profile of CYB003 used to predict safe and efficacious human doses for an on-going Phase 1/2a trial in Major Depressive Disorder (MDD) (NCT05385783).

Introduction

Psychedelic drugs, such as psilocybin, have emerging clinical potential for the treatment of psychiatric conditions including anxiety (Nutt 2019), depression (Carhart-Harris 2021, Goodwin 2022), OCD (Moreno 2006), cancer-related depression and anxiety (Griffiths 2016; Ross 2016), and substance use disorders (Nielson 2018, Noorani 2018).

Notably, psilocybin was recently granted '*breakthrough therapy*' designation by the US Food and Drug Administration (FDA) for MDD (Staines 2019), and treatment-resistant depression (TRD, Compass Pathways 2018) – recognizing the potential for substantial outcome improvements over current treatments (FDA 2018).

Psilocybin is a prodrug, which is dephosphorylated to produce its active form – *psilocin* – that acts as an agonist at a variety of serotonin (5-hydroxytryptamine [5-HT]) receptors, including the 5-HT_{2A} receptor (Nichols 2004).

Following dephosphorylation, the psychoactive effect of psilocybin occurs within 1 hr after dosing, peaks around 2-3 hr, and diminishes by 6 hr (Griffiths 2018). Based on this time course, in the clinical trial setting, protocols mandate observation until approximately 8 hr after dosing (Griffiths 2018).

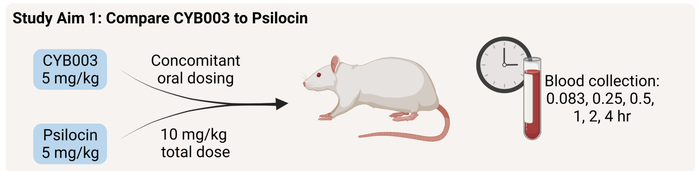
While psilocybin administration in a therapeutic setting represents a potential revolution in mental health therapy, the delayed onset of effects, patient-to-patient variability, long in-clinic times, and potential adverse reactions such as nausea, may present some development challenges.

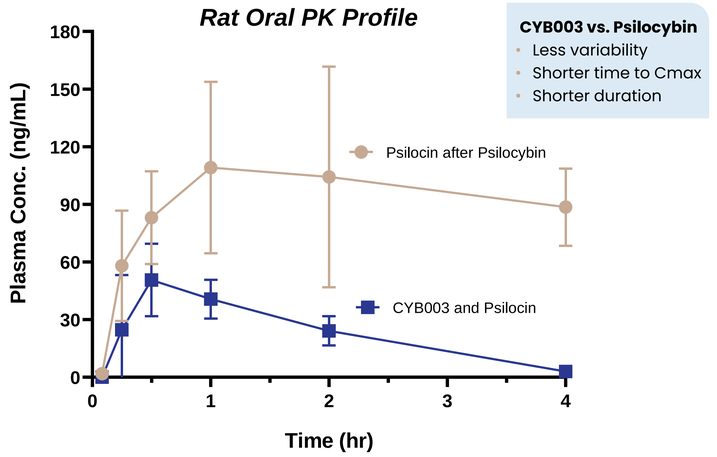
At Cybin, we have focused on developing a deuterated psilocybin analog, CYB003, with faster onset, reduced variability and a shorter duration of action in order to retain the therapeutic effects of psilocybin but improve patient and clinical experiences.

Aims and Hypothesis

- Aims: Determine the pharmacokinetic profile of CYB003, and compare to both psilocybin and psilocin
- Hypothesis: CYB003 will demonstrate improvements over psilocybin that could translate to better outcomes in the patient

Results

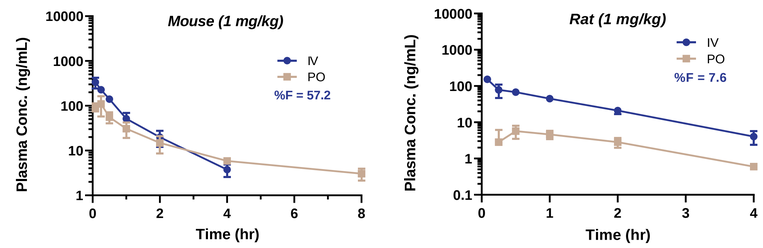


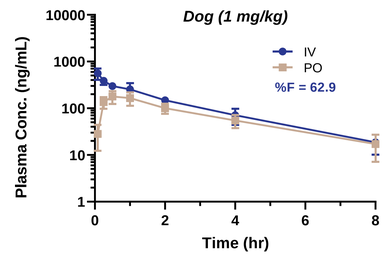


PK Parameter	CYB003	Psilocin	PK Parameter	CYB003	Psilocin
PO Route			**IV Route**		
C_{max} (ng/mL)	32.2	24.1	C_0 (ng/mL)	367	416
T_{max} (hr)	0.5	0.5	AUC (hr*ng/mL)	145	165
AUC (hr*ng/mL)	50.4	39.1	$T_{1/2}$ (hr)	0.86	0.79
$T_{1/2}$ (hr)	0.95	1.11	CL (mL/hr/kg)	6680	5910

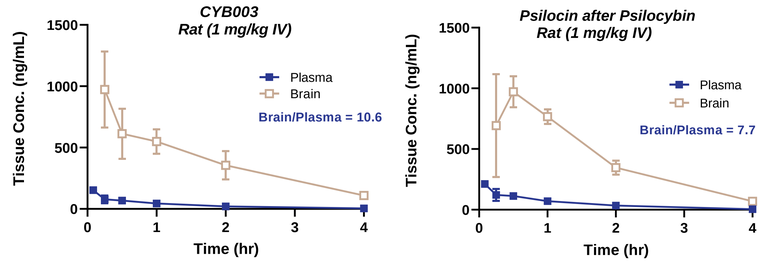
Results

CYB003 Plasma Exposure & Oral Bioavailability

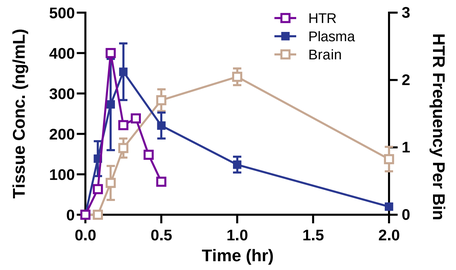




CYB003 Brain Penetration



CYB003 PK/PD in Mice



Conclusions

- The pharmacokinetic profile of CYB003 following either intravenous (IV) or oral (PO) administration is similar to psilocin, and both compounds are orally bioavailable.
- Compared to psilocybin, CYB003 exhibits less plasma level variability, a shorter time to peak levels (C_{max}), and a shorter duration in rodents.
- CYB003 brain penetration in the rat is greater than psilocin after the administration of psilocybin, 10.6 vs. 7.7, respectively.
- The CYB003 PK/PD relationship in mice suggests that the HTR closely follows the plasma concentration/time profile.
- CYB003 has excellent oral bioavailability in the dog, much higher than the rat.
- In conclusion, CYB003 demonstrates significant improvements in the plasma pharmacokinetic profile in rodents, compared to psilocin derived from psilocybin administration.
- These improvements may translate into a better clinical experience for the patient.

Further Investigations

- CYB003 completed IND-enabling safety pharmacology and toxicology studies in non-rodent and rodent species and was safe and well-tolerated.
- CYB003 has progressed into clinical studies for the treatment of MDD. **ClinicalTrials.gov Identifier: NCT05385783**

References

- Carhart-Harris R. et al. (2021) N Engl J Med, 384, 1402–1411.
- COMPASS Pathways. (2018). COMPASS Pathways receives FDA Breakthrough Therapy designation for psilocybin therapy for treatment resistant depression: Compass Pathways.
- FDA. (2018). Breakthrough Therapy | FDA. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.
- Goodwin G.M. et al. (2022) N Engl J Med, 387, 1637-1648.
- Griffiths R.R. et al. (2016) J Psychopharmacol, 30, 1181–1197.
- Griffiths R.R., et al. (2018) J Psychopharmacol, 32(1), 49-69.
- Nichols D.E. (2004) Pharmacol Ther. 101(2):131-181.
- Nielson E.M. et al. (2018) Front Pharmacol, 9(132), 1–13.
- Noorani T. et al. (2018) J Psychopharmacol, 32(7), 756–769.
- Nutt D. (2019) Dialogues Clin Neurosci, 21(2), 139-147.
- Ross S. et al. (2016) J Psychopharmacol, 30(12), 1165–1180.
- Staines R. (2019) In: Pharmaphorum. https://pharmaphorum.com/news/fda-tags-psilocybin-drug-as-clinical-depression-breakthrough-therapy/.

Cybin Inc @CybinInc cybininc