PHARMACOLOGICAL AND PHARMACOKINETIC PROFILE OF CYB003, A NOVEL, ORALLY ACTIVE ANALOG OF PSILOCYBIN

Geoffrey Varty, Amy Reichelt, Michael Morgan, Joan Krakowsky, Clinton Canal, Tina Mueller, Ken Avery, Pradip Pathare, Joshua Hartsel, Alex Belser, Aaron Bartlone, Doug Drysdale, Alex Nivorozhkin, Michael Palfreyman

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

NYSE:CYBN
NEO:CYBN

Overview

Cybin's CYB003 program aims to develop a novel Second-Generation psychedelic compound based on psilocybin that will provide therapeutic mental health benefits, with improved bioavailability and reduced duration of action.

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

CYB003 represents our ability to 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 efficacious and safe human doses, allowing the planned initiation of our Phase 1/2a trial in 2022.

Introduction

Serotonergic hallucinogens, such as psilocybin, have emerging clinical potential as a treatment strategy for psychiatric conditions including anxiety (Nutt 2019), depression (Carhart-Harris 2021), obsessive compulsive disorder (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 major depressive disorder (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 (Carhart-Harris 2014; Nichols, 2004).

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

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

At Cybin, we have focused on developing a 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 experience.

Aims and Hypothesis

- Compare the in vitro pharmacology and in vivo (behavior and pharmacokinetics) effects of CYB003 to both psilocybin and psilocin
- Determine if CYB003 offers any potential improvements over psilocybin that could translate to better outcomes in the patient

Results

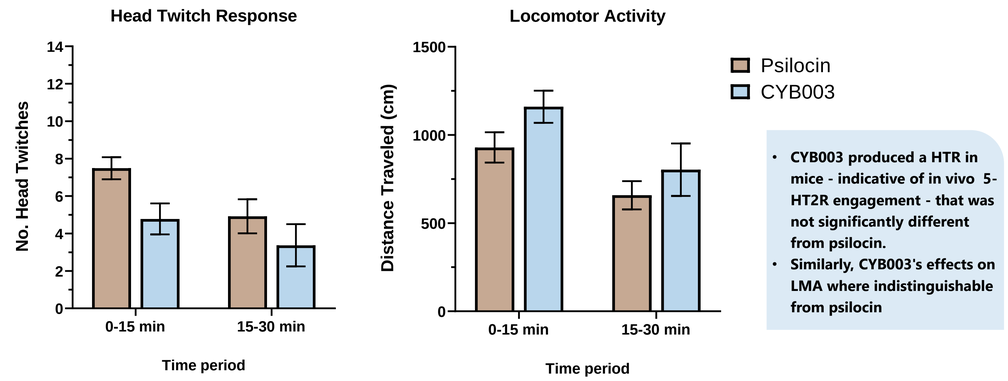
Experiment 1 – In Vitro Pharmacology & Toxicology

Serotonergic Receptors	% Inhibition @ 10 µM (Ki, nM)	
	CYB003	Psilocin
Human 5-HT_{1A}	96	96
Rat 5-HT_{1B}	80	82
Human 5-HT_{2A}	100 (37)	99 (31)
Human 5-HT_{2B}	100 (26)	100 (21)
Human 5-HT_{2C}	98 (92)	98 (95)
Human 5-HT_{5A}	99	99
Human 5-HT_{6}	98	98
Human 5-HT_{7}	98	102

Secondary Targets	% Inhibition @ 10µM	
	CYB003	Psilocin
Human adrenergic α_{2A}	70	63
Rat L-Type Ca^{2+} channel	54	56
Human histamine H_1	75	78
Human DA transporter	58	32
Human NE transporter	59	41
Human $Na_v1.5$ channel	6.6	6.6
Human $Ca_v1.2$ channel	No Inhibition	No Inhibition
hERG channel	25.62	43.54

- CYB003 and psilocin were tested in several in vitro toxicology assays and there were no issues with cell, genetic or cardiac toxicity

Experiment 2 – Mouse Head Twitch Response (HTR) & Locomotor Activity (LMA)



- **CYB003 produced a HTR in mice - indicative of in vivo 5-HT2R engagement - that was not significantly different from psilocin.**
- **Similarly, CYB003's effects on LMA where indistinguishable from psilocin**

Experiment 3 – Pharmacokinetic Profiling in the Rat

Study Aim 1: Compare CYB003 to Psilocin

Study Aim 2: Compare combined CYB003/Psilocin vs. Psilocin after Psilocybin
- 14 mg/kg dose of Psilocybin converts to 10 mg/kg psilocin combined

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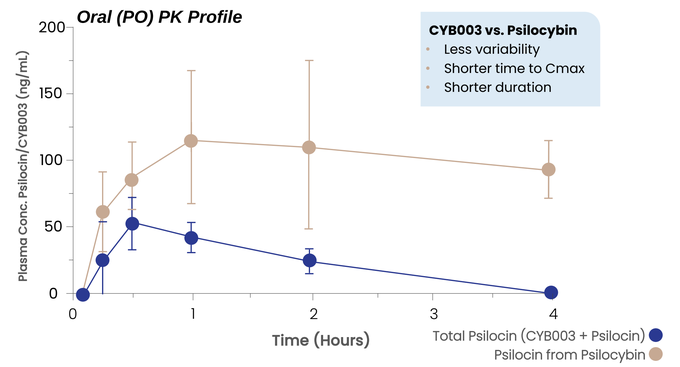
Experiment 3 – Pharmacokinetic Profile in the Rat



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

Conclusions

- CYB003 exhibits a psilocin-like serotonin receptor binding profile, as well as similar off-target activity.
- CYB003 induces head twitch responses and hyperactivity in mice and the effects are similar to psilocin.
- 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 (Cmax), and a shorter duration.
- In conclusion CYB003 maintains the in vitro binding profile and in vivo activity of psilocin, but demonstrates significant improvements in the plasma pharmacokinetic profile in the rat, compared to psilocin derived from psilocybin administration.
- These improvements may translate into a better clinical experience for the patient.

Further Investigations

- CYB003 has completed IND-enabling safety pharmacology and toxicology studies in non-rodent and rodent species and was well-tolerated.
- CYB003 to progress into clinical studies in 2022.

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