PRECLINICAL CHARACTERIZATION OF CYB004: A NOVEL, DEUTERATED N,N-DIMETHYLTRYPTAMINE (DMT) ANALOG FOR THE POTENTIAL TREATMENT OF GENERALIZED ANXIETY DISORDER (GAD)

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Introduction

CYB004, a deuterated isotopomer of DMT (N,N-dimethyltryptamine), is being developed by Cybin for the treatment of Generalized Anxiety Disorder (GAD).

DMT is the main active ingredient of ayahuasca, a traditional ceremonial beverage used by several indigenous Northwestern Amazonian cultures for ritualistic purposes dating back at least a millennium (Miller 2019). A relatively large number of placebo-controlled trials (Riba 2001; Dos Santos 2007; Palhano-Fontes 2019) and observational studies (Grob 1996; Fábregas 2010; Bouso 2012; Barbosa 2018; Argento 2019) have demonstrated that DMT per se, or as the active ingredient in ayahuasca, can improve various mental health outcomes, with positive effects on mood (Palhano-Fontes 2019; Sanches 2016; Zeifman 2019).

In humans, intravenous (IV), intramuscular (IM), or inhaled administration reveals DMT's effects on perception and consciousness within seconds, with profound and intense visual peak experiences occurring within 2 min. When given IV, the central nervous system (CNS) effects dissipate rapidly due to metabolism by monoamine oxidase (MAO) (Strassman 1994b).

Replacement of the hydrogen atoms with deuterium is postulated to slow oxidative metabolism while retaining DMT pharmacology and thereby afford greater clinical utility (Russak 2019; Stemmerich 2022). Cybin has synthesized a novel deuterated chemical entity, CYB004.

This poster compares the pharmacology and pharmacokinetics (PK) of CYB004 to DMT. We demonstrate that deuteration has no effect on the pharmacology of DMT but increases systemic CYB004 plasma exposure via reduced clearance.

Methods

CYB004 and DMT were compared as follows:

- Receptor pharmacological profiles compared using serotonin (5-HT) receptor binding and functional assays to evaluate potency, efficacy, and selectivity at serotonin receptors; both compounds were also screened for activity at over 160 proteins.
- In vivo activity in the mouse head twitch response (HTR) assay, a model of central serotonin 5-HT_{2A} receptor activation.
- Neurogenesis/neuroplasticity gene expression was evaluated.
- Pharmacokinetic (PK) studies were completed in the mouse, rat, and dog to assess the effect of deuteration on systemic exposure.
- Additional studies examined the PK profile of CYB004 administered via several different routes of administration, given the poor oral bioavailability of DMT.

CYB004 and DMT have similar effects on receptor binding and in vivo pharmacology

- Across the 5-HT and secondary receptors there is only a 6-10% difference between CYB004 and DMT.
- CYB004 and DMT induction of HTR were not statistically different.
- Acute SC administration CYB004 and DMT at 5.6 mg/kg resulted in changes in the mRNA levels of several proteins, compared to control.
- In the amygdala, c-Fos, Egr2, Fgf2, Iκβα, Sgk1 increases were similar for CYB004 and DMT.
- In the frontal cortex, differential effects on mRNA levels for CYB004 and DMT were observed.

CYB004 and DMT have different PK profiles

- Rat liver microsome and human recombinant MAO-A metabolism slows as hydrogen ions are replaced by deuterium.
- The systemic elimination $T_{1/2}$ was increased in mice, rats and dogs by 59, 62, and 62%, respectively, after SC/IV administration of CYB004.
- CYB004 brain penetration in the rat is greater than DMT, with brain:plasma ratios of 12.3 vs. 9.5, respectively.
- CYB004 exposure profiles can be modified by routes of administration including inhalation, and SC and IM injection.
- The absorption of CYB004 from a SC depot can be changed using a controlled release formulation.
- **CYB004 demonstrates significant improvements in the plasma pharmacokinetic profile in rodents and dog, compared to DMT, while maintaining similar pharmacological effects.**
- **These improvements may translate into a better clinical experience for the patient.**

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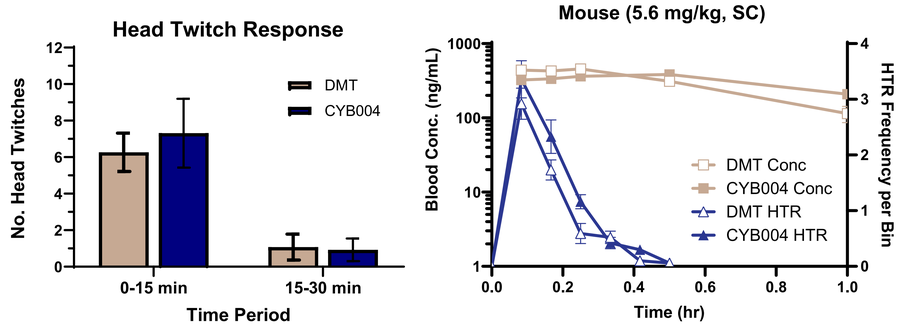
Serotonin Receptor & Off-Target Profile

Serotonergic Receptors	% Inhibition @ 10 μM (Ki, nM)	
	CYB004	DMT
Human 5-HT_{1A}	96	97
Rat 5-HT_{1B}	72	76
Human 5-HT_{2A}	94 (180)	96 (130)
Human 5-HT_{2B}	84 (450)	96 (520)
Human 5-HT_{2C}	93 (330)	99 (280)
Human 5-HT_{5A}	80	88
Human 5-HT_{6}	76	84
Human 5-HT_{7}	96	96

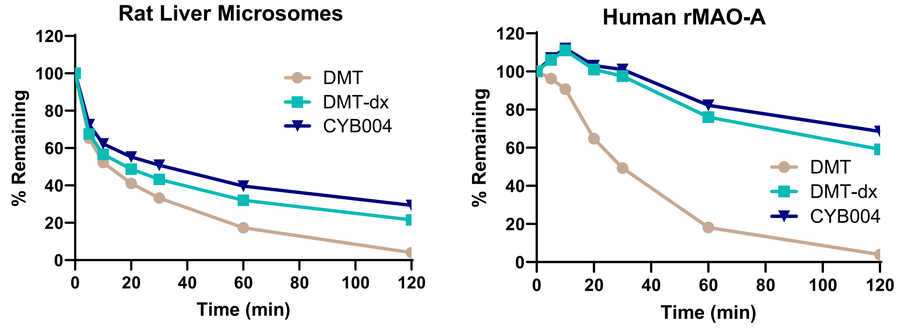
Secondary Targets	% Inhibition @ 10μM	
	CYB004	DMT
Human Adrenergic α_{2A}	65	76
Rat L-Type Ca^{2+} channel	62	64
Human Histamine H_1	92	93
Human DA transporter	45	27
Human NE transporter	53	46
Human $Na_v1.5$ channel	6.6	6.6
Human $Ca_v1.2$ channel	No Inhib	No Inhib
hERG channel	21	18

Mouse Head Twitch Response (HTR)

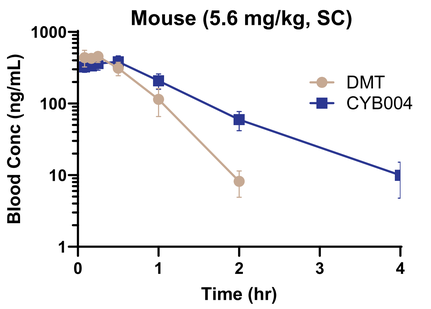


Deuteration did not affect DMT binding to 5-HT receptor subtypes
Deuteration did not affect DMT-induced HTR

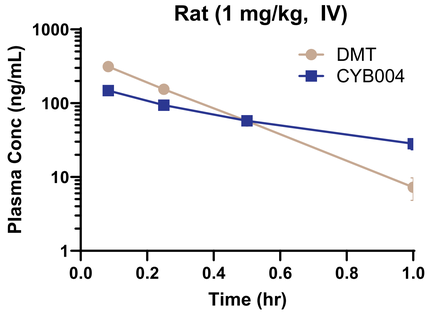
The Effect of Deuteration on In Vitro Metabolism



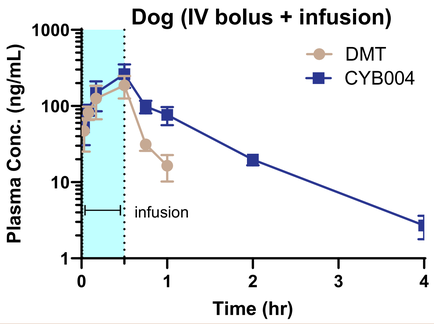
The Effect of Deuteration on Plasma Exposure



Mouse/ SC[a]	DMT	CYB004	%Change
Dose (mg/kg)[b]	5.6	5.9	CYB004/DMT
$T_{1/2}$ (hr)	0.28	0.69	59%↑
CL/F (mL/min/kg)	295	183	61%↓
Cmax (ng/mL)	460	561	18%↑
Tmax (hr)	0.083	0.500	83%↑
AUCinf (hr*ng/mL)	328	537	39%↑



Rat/ IV Bolus[a]	DMT	CYB004	%Change
Dose (mg/kg)[b]	1	1	CYB004/DMT
$T_{1/2}$ (hr)	0.17	0.45	62%↑
CL (mL/min/kg)	147	177	17%↑
C_0 (ng/mL)	424	185	129%↓
Tmax (hr)	NA[f]	NA	NA
AUCinf (hr*ng/mL)	113	94.0	20%↓

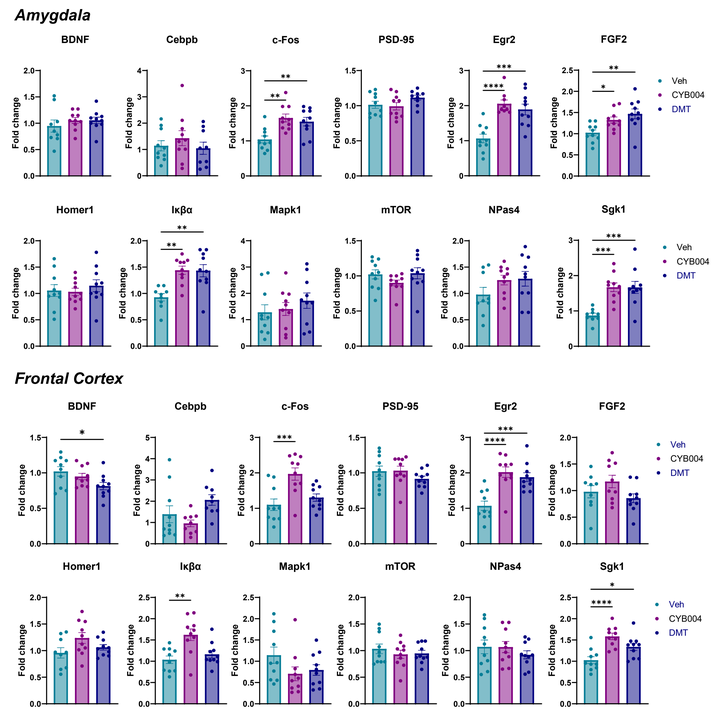


Dog/ IV Bolus+Infusion[a]	DMT	CYB004	%Change
Dose (mg/kg)[b]	0.35	0.35	CYB004/DMT
$T_{1/2}$ (hr)	0.13[d]	0.63	80%↑
CL (mL/min/kg)	4360[d]	1630	168%↓
Cmax (ng/mL)	187	263	29%↑
Tmax (hr)[c]	0.5	0.5	NC[e]
AUCinf (hr*ng/mL)	80.3[d]	223	64%↑

[a]n=3; [b]DMT and CYB004 co-dosed; [c]median; [d]n=1; [e]NC=no change; [f]NA=not applicable

Deuteration decreases metabolism

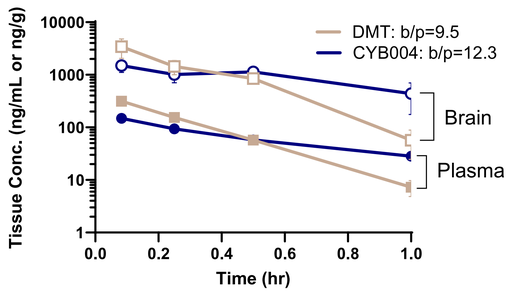
'Neurogenesis/plasticity' Gene Expression



CYB004- and DMT-induced changes in expression of genes associated with neurogenesis and neuroplasticity in mouse amygdala and frontal cortex. *Single dose at 5.6* mg/kg (SC), N=10 per group, tissue collected 2 hr after dosing. *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$ vs. vehicle (Veh).

CYB004- and DMT-induced changes in the expression of genes associated with neurogenesis and neuroplasticity

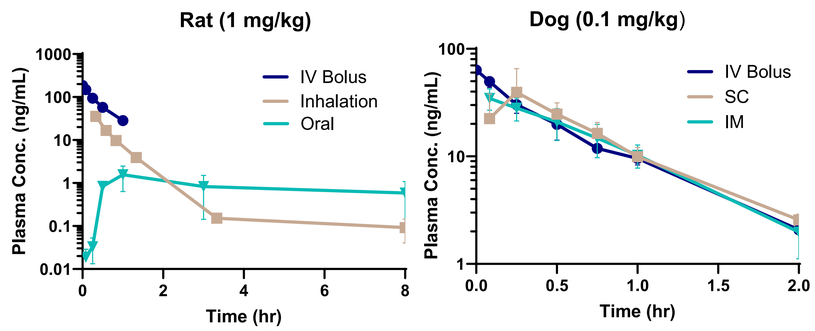
CYB004 vs. DMT (1 mg/kg, IV) Rat Brain Penetration



CYB004 brain levels higher vs. DMT

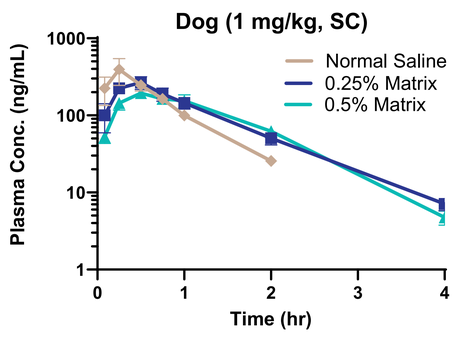
b/p: brain:plasma ratio

CYB004 Routes of Administration



Route of administration alters the time to Cmax

Subcutaneous Controlled Release Formulation



Dog/SC[a]	Normal Saline	0.25% Matrix	0.5% Matrix
Dose (mg/kg)[b]	1[d]	1	1
$T_{1/2}$ (hr)	0.48	0.79	0.59
CL (mL/min/kg)	59.7	48.2	54.0
Cmax (ng/mL)	395	289	195
Tmax (hr)[c]	0.25	0.5	0.5
AUCinf (hr*ng/mL)	306	357	324

[a]n=3; [b]DMT and CYB004 co-dosed; [c]median; [d]dose adjusted from 0.1 to 1 mg/kg for ease of comparison

CYB004 SC absorption profile can be modulated using a controlled release matrix