EARLY CLINICAL DEVELOPMENT OF A DEUTERATED N,N-DIMETHYLTRYPTAMINE (DMT) ANALOG FOR THE TREATMENT OF MENTAL HEALTH CONDITIONS

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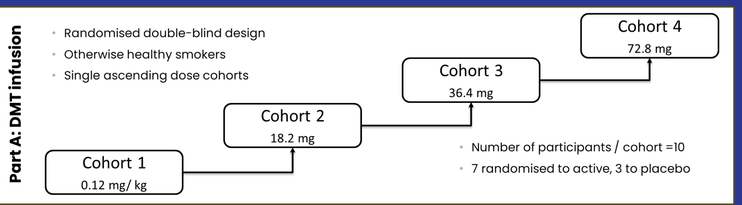
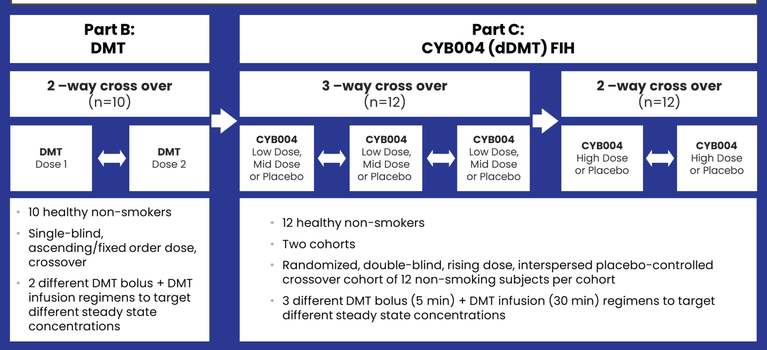
Introduction

- *N,N*-dimethyltryptamine (DMT) is a naturally occurring psychedelic and the main active ingredient of ayahuasca. Studies have shown that DMT/ayahuasca can improve various mental health outcomes.
- DMT is a potent agonist at the serotonin 5-HT_{2A} receptor, through which it exerts many of its subjective and potentially therapeutic effects.
- As DMT is not orally active, it is administered via intravenous (IV), intramuscular (IM), or inhaled routes. DMT's effects are evident within seconds to minutes but dissipate rapidly as it is quickly metabolised by monoamine oxidase.
- An optimal parenteral dosing regimen and pharmacokinetic / pharmacodynamic (PK/PD) relationship for DMT has not been accurately characterised, which limits the ability to generate large scale clinical data on the therapeutic utility of DMT.
- CYB004 is a deuterated analog of DMT. Selective deuteration has been shown to decrease metabolism, reduce pharmacokinetic variability and improve bioavailability. This could improve the PK profile of DMT while maintaining its desired PD effects.
- The current series of clinical studies (CYB004E Parts A, B, and C) explored the PK, PD, and safety of DMT and CYB004.

Methods





CYB004E Part A

- Investigated the safety, tolerability, PK and PD of a 90 min intravenous infusion of DMT hemi fumarate.
- Screening period lasting for up to 21 days
- Participants were randomised to either DMT or placebo infusion in a 7:3 ratio across 4 cohorts

CYB004E Part B

- Duration of infusion was selected to optimise the time of on-target effects.
- Dose 1 (18.2 mg in 5 min + 44.5 mg in 55 min IV) was selected to reach a target plasma concentration of approximately 40ng/ml
- Dose 2 (18.2 mg in 5 min + 71.2 mg in 55 min IV) was selected based on safety, PK and PD data from Dose 1.

CYB004E Part C

- First-in-human dosing of deuterated DMT (CYB004) in healthy volunteers.
- Randomized, double-blind, rising dose, interspersed placebo-controlled crossover design.
- Shorter infusion period based on PK and PD profile of CYB004 predicted using animal data.
- Cohort 1 was a double-blind, randomized, 3-way crossover design evaluating IV bolus + infusion dosing regimen (5 min bolus + 30 min infusion) to target steady state plasma DMT concentrations between 40-60ng/ml.
- Cohort 2 examined a bolus only regimen (5 min bolus)

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Results

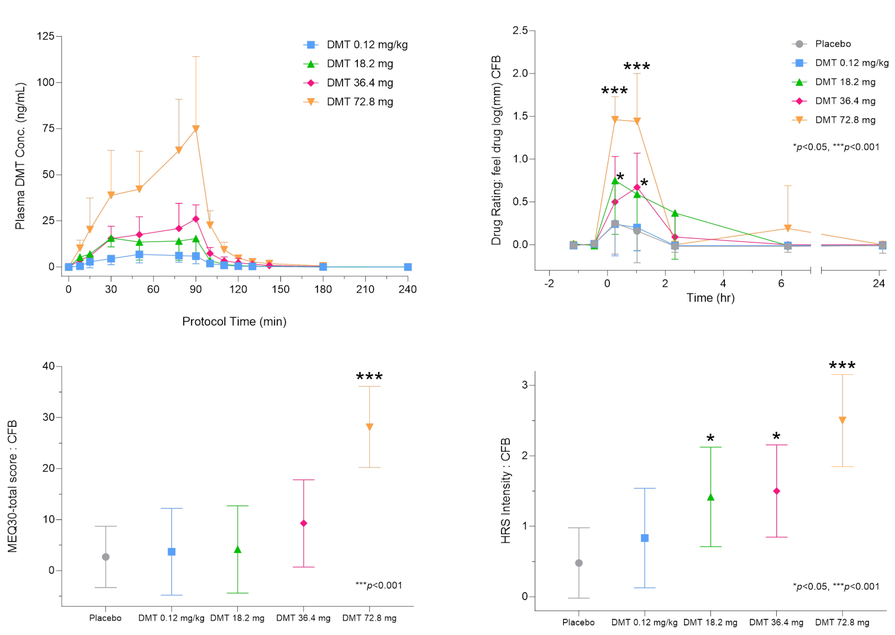
Part A

- DMT was well tolerated; all adverse events (AEs) were mild and self-limiting. Transient increases in blood pressure were noted at doses ≥36.4 mg.
- Statistically significant effects (p<0.0001) were only observed at the highest dose (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.
- Plasma concentrations of DMT increased in a dose proportional manner
- Maximum plasma concentrations of 81.5 ± 34.3 ng/mL (mean ± SD) were achieved at 72.8 mg, although, associated psychedelic effects remained moderate.

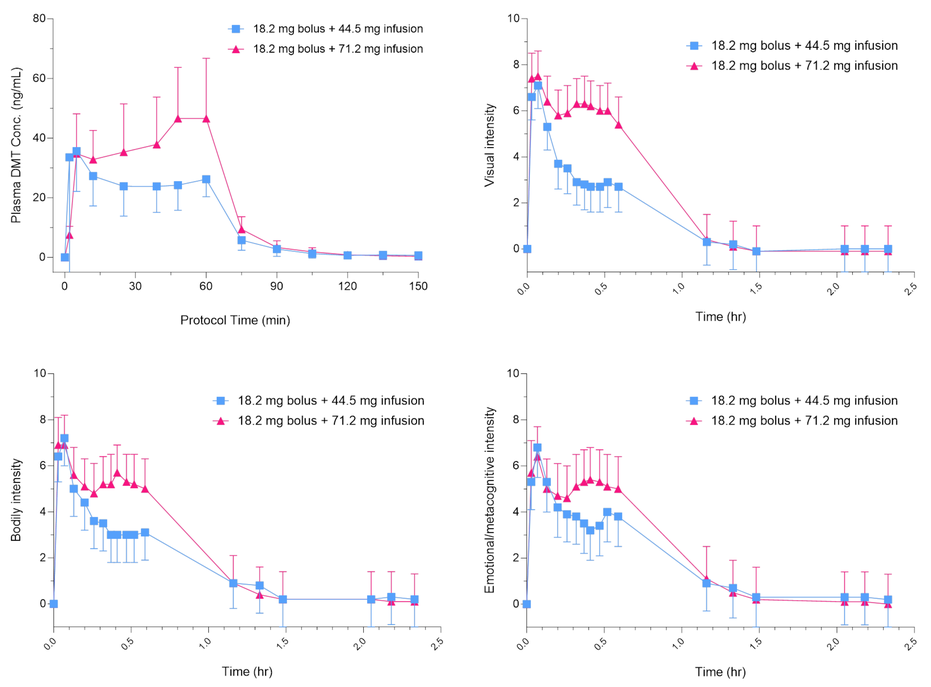
Part B

- All AEs were mild and self-limiting with transient increases in blood pressure and heart rate.
- Intense psychedelic effects were reported by subjects during the 5-minute bolus, changing to moderate intensity during the infusion. The time course of psychedelic effects followed the plasma concentration profile of DMT.
- For dose 1, the median plasma C_{max} was 37.7 ng/mL with a median T_{max} at 5 min, while AUC_{last} values ranged from 1006 to 2763 min*ng/mL. For dose 2, median plasma C_{max} was 55.1 ng/mL with a median T_{max} at 48 min, while AUC_{last} values ranged from 1602 to 3762 min*ng/mL.
- In general, psychedelic effects in Part B were more intense compared to Part A.

Pharmacokinetics and Pharmacodynamics of a 90 min IV infusion of DMT in Part A



Pharmacokinetics and Pharmacodynamics of an IV bolus + infusion of DMT in Part B

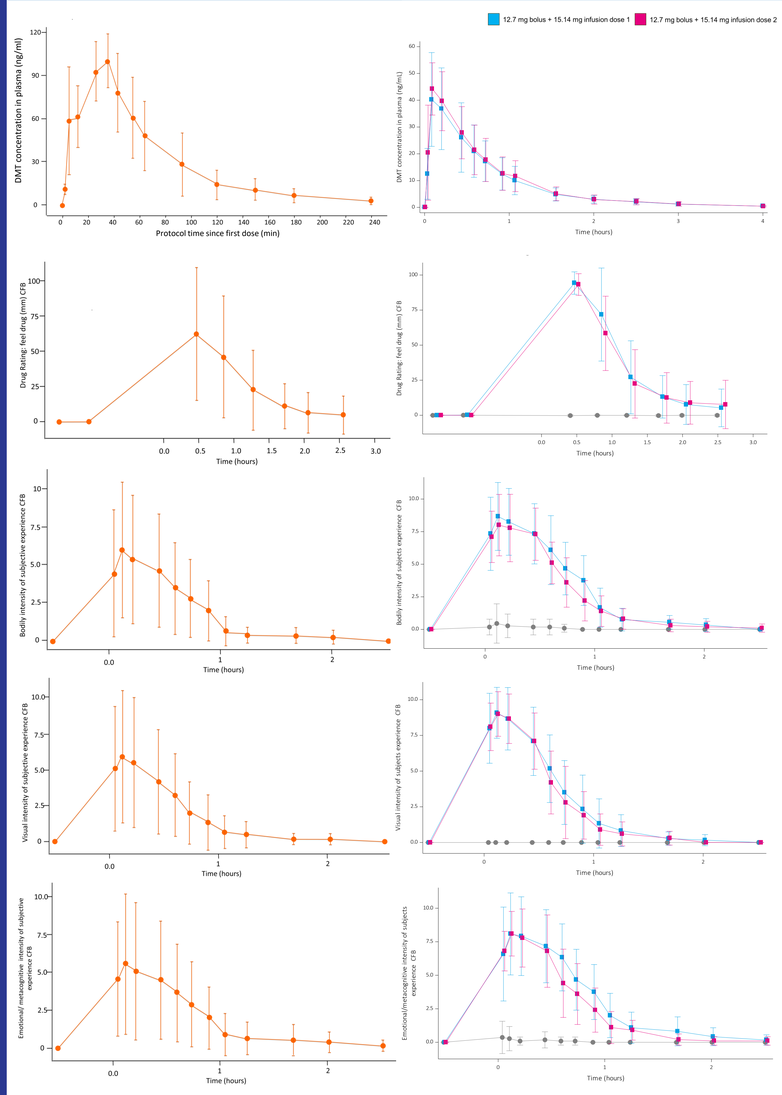


Results

Part C

- CBY004 was well tolerated following both the 35 min bolus + infusion and 5 min bolus only regimens.
- No serious adverse events were reported. Most of the AEs were mild to moderate in intensity. The most common AE was a transient increase in blood pressure which resolved without intervention in all cases.
- A bolus of 12.7 mg and infusion of 15.14 mg resulted in a median $_{Cmax}$ of 87.8 ng/mL and a median half-life of 37.33 min. AUC_{last} values ranged from 266 to 10861 min*ng/mL. A bolus of 12.7 mg administered over 5 minutes resulted in a median C_{max} of 37 ng/mL and a median half-life of 39.8 min. AUC_{last} values ranged from 832 to 3608 min*ng/mL.
- Intense psychedelic effects were reported by subjects for about 40 min after the stop of the infusion and these effects coincided with the plasma concentrations of CYB004.

PK/PD of 12.7 mg bolus + 15.14 mg infusion PK/ PD of CYB004 12.7 mg bolus only



Conclusions

- Escalating doses of DMT infusion over 90 minutes were well tolerated with high variability in plasma levels.
- Robust psychedelic effects were produced, and the intensity of effects was related to the rate at which C_{max} was achieved.
- A bolus + infusion dosing regimen for DMT may provide sustained therapeutically relevant psychedelic effects over an extended period.
- CYB004 was well tolerated with no serious adverse events with the majority of AEs reported being mild to moderate and self limiting
- Deuteration of DMT, as with CYB004, resulted in more robust psychedelic effects at lower plasma concentrations, compared with DMT.
- These were rapid in onset when administered as an IV bolus over 5 minutes and persisted for about 40 min after the 5 min bolus without the need for an extended infusion.
- This short duration of effects has the potential for CYB004 to be a scalable treatment that can be delivered in a short period of time compared with longer acting psychedelics.

Note: all data are preliminary and non-QC'ed