The effects of COMP360 (psilocybin formulation) on cognitive function: Results from a randomized, placebo-controlled trial in healthy participants

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Objective

- To explore the short- and longer-term effects of psilocybin on cognitive functions in healthy participants

Background

- Psilocybin belongs to a class of drugs referred to as psychedelics ('mind-manifesting'). Partial agonism of 5-HT_{2A} receptors is a key mechanism contributing to its biological effects[1]
- The effects of psilocybin on cognitive functioning have not been widely or systematically studied
- COMP360 is COMPASS Pathfinder Limited's proprietary synthetic psilocybin formulation optimized for stability and purity, and is in clinical development for treatment-resistant depression following encouraging indications of psilocybin efficacy, with minimal adverse events (AEs), in pilot studies in depressive states[1,2]
- Previous studies in healthy participants have indicated acute improvements in social cognition following psilocybin administration (non COMP360 formulation)[4-6]; however, it remains unclear whether these benefits persist post-acutely and whether the potential beneficial effects of psilocybin are limited to improving social cognition or if psilocybin may also benefit general cognitive abilities
- Here we report results on the effects of COMP360 on key domains of cognitive functioning from the largest randomized, placebo-controlled trial of psilocybin to date

Methods

Study design

- This was an exploratory, phase I, randomized, double-blind, placebo-controlled study to evaluate the effects of two doses of COMP360 (10 or 25mg) compared with placebo in healthy male and female participants, aged between 18-65 years
- Prior to dosing, participants took part in a preparatory group session
- The study drug was administered simultaneously to up to six participants, who received 1:1 psychological support

Assessments

- To assess the effects of psilocybin on cognition, participants completed a range of validated measures of cognition from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[7]
- **Figure 1** presents an overview of the scheduled study visits
- CANTAB assessments included the Paired Associates Learning-Total Errors Adjusted (PAL-TEA), measuring episodic memory, Spatial Working Memory-Between Errors (SWM-BE), measuring working memory, SWM-Strategy (SWM-S), measuring executive function and planning, and Rapid Visual Information Processing A-prime (RVP-A'), measuring sustained attention
- The effects of each outcome variable were evaluated on the basis of change from baseline scores using a mixed-model for repeated measures (MMRM) analysis
- This study was exploratory and therefore not adequately powered to detect statistical significance; as such p-values are not reported

Results

- In total, 89 healthy participants were randomized (mean [SD], age, 36.1[9.1] years, males; n=48 (53.9%), females; n=41 (46.1%).
- 33 (37.1%) participants had prior psilocybin experience
- **Figure 2** presents participant disposition

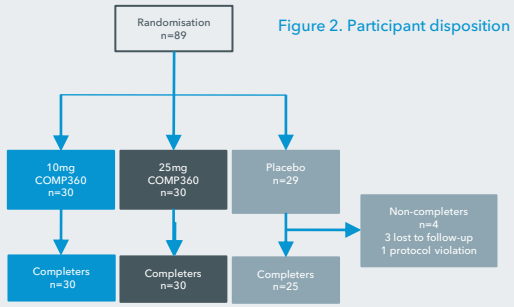


Figure 2. Participant disposition

Single doses of 10mg or 25mg COMP360 had no detrimental short-term or longer-term effects on cognitive functioning in a phase I study in healthy participants

Safety results

- COMP360 was generally well tolerated in healthy participants; there were no serious AEs and no AEs led to withdrawal from the study **(Figure 3)**

Figure 3. Most frequently reported treatment-emergent adverse event

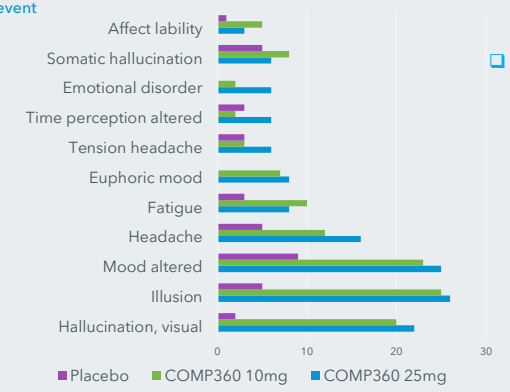


Figure 1. Schedule of events

	Visit 1 (Day -56 to -2) Eligibility screening	Visit 2 (Day -1) Baseline assessments	Visit 3 (Day 1) Randomisation and dosing	Visit 4 (Day 2) Follow-up at clinic	Visit 5 (Day 8) Follow-up by telephone	Visit 6 (Day 29) Follow-up by telephone	Visit 7 (Day 85) Follow-up by telephone
Informed consent form	✓						
Medical and psychiatric history	✓						
Preparatory session		✓					
Dosing session			✓				
Integration session				✓			
Vital signs	✓	✓	✓	✓	✓	✓	✓
Clinical laboratory tests	✓			✓			
Recording of adverse events	✓	✓	✓	✓	✓	✓	✓
PAL-TEA	✓	✓			✓	✓	
SWM-BE & SWM-S	✓	✓			✓	✓	
RVP-A'	✓	✓			✓	✓	

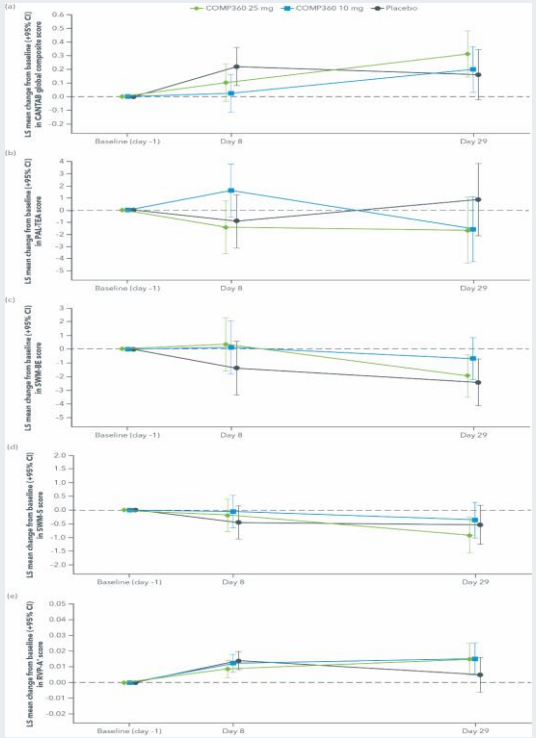
CANTAB results

- On the global composite measure (**Figure 4a**), there was an increasing trend in scores indicating better performance on average for the COMP360 10mg and 25mg doses by day 29 compared with baseline. No difference was observed for COMP360 10mg and 25mg when compared with placebo, and also between COMP360 25mg and 10mg by day 29
- For PAL-TEA (**Figure 4b**), a measure of episodic memory, there was no difference for any of the groups at day 29 compared with baseline, nor were any differences observed between the groups
- For Spatial Working Memory, SWM-BE (**Figure 4c**) and SWM-S (**Figure 4d**), there were trends indicating better performance on average for COMP360 25mg (and placebo for SWM-BE only) by day 29 compared with baseline, but no difference was observed for COMP360 10mg and 25mg when compared with placebo, nor between COMP360 25mg and 10mg
- For RVP-A' (**Figure 4e**), a measure of sustained attention, there were trends indicating better performance on average for COMP360 10mg and 25mg by day 29 compared with baseline, but no difference was observed for COMP360 10mg and 25mg when compared with placebo, nor between COMP360 25mg and 10mg

Conclusions

- Small differences in cognitive outcomes were seen between the groups, but no clinically-relevant negative findings were identified, suggesting that there were no consistent or differential performance changes between the placebo and the COMP360 groups
- For RVP-A', SWM-BE, SWM-S, and CANTAB global composite there were trends demonstrating better performance on average in the COMP360 groups by day 29 compared to baseline. The fact that participants were typically highly educated, and the small sample size, could have limited the generalisability of results. These findings warrant further investigation in clinical populations

Figure 4a-e. Mixed-model analysis of change from baseline in CANTAB outcome measures (safety population)



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Disclosures

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