Dose-dependent acute subjective psychedelic effects following COMP360 psilocybin across three clinical studies and its relationship to therapeutic response

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BACKGROUND

- Dose-dependent subjective psychedelic effects have been reported after psilocybin administration,[1] and a positron emission tomography study found positive correlations between 5HT2A receptor occupancy, subjective psychedelic experience, and plasma levels of psilocin (the active metabolite of psilocybin)[2]
- In developing COMP360 (COMPASS' proprietary, synthetic formulation of psilocybin) for treatment-resistant depression (TRD), a recent phase IIb trial (COMP 001) demonstrated statistically significant efficacy for a single 25 mg dose but not a single 10 mg dose in reducing depressive symptom severity scores over a period of 3 weeks compared with a single 1 mg dose[3]
- This dose-response relationship is an important finding that supports a central pharmacological effect of COMP360: It reduces depressive symptoms

OBJECTIVE

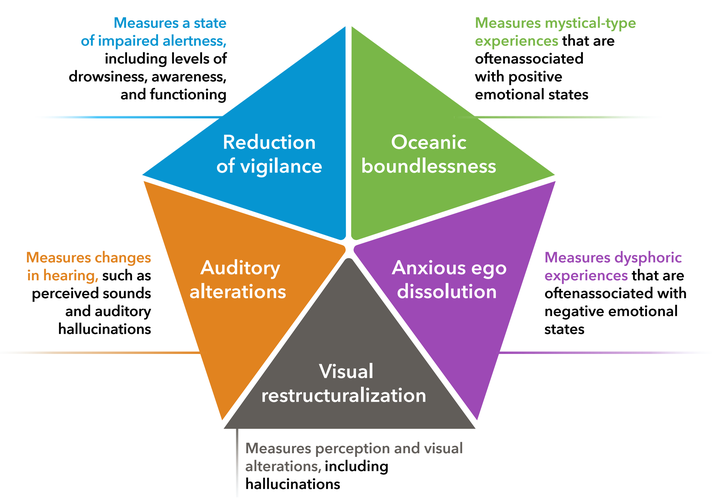
- We describe the Five-Dimensional Altered States of Consciousness (5D-ASC) questionnaire, which assesses subjective psychedelic experience, and the Emotional Breakthrough Inventory (EBI), which assesses emotional experience. Also, we report their relationships to changes in depressive symptom severity for the 3 COMP360 doses that were employed in COMP 001 and compare the results with those from COMP 002 and COMP 003:
  - COMP 002 investigated the subjective psychedelic effects of COMP360 25 mg, COMP360 10 mg, and placebo in healthy volunteers
  - COMP 003 investigated the effects of COMP360 25 mg administered adjunct to a selective serotonin reuptake inhibitor (SSRI) in adult participants with TRD
    - With previous reports that serotonergic drugs downregulate 5HT2A receptor number and function in rodents,[4] it was hypothesized that the action of psilocybin would be attenuated in participants from COMP 003

METHODS

Study design

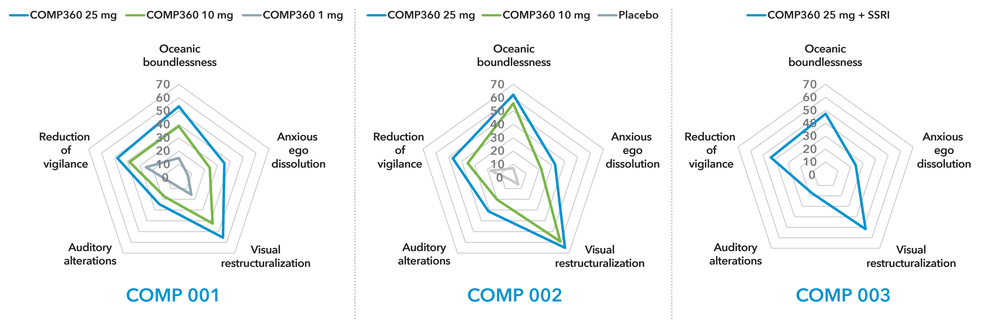
- In all 3 trials, COMP360 was administered alongside psychological support from trained therapists
- At the end of the COMP360 administration day, participants completed the 5D-ASC (**Figure 1**)
- In COMP 001, the EBI was completed the day after COMP360 administration. The EBI measures aspects relating to emotional release, trauma or interpersonal conflict resolution, and facing difficult emotions and feelings that are usually avoided
- In COMP 001 and COMP 003, the Montgomery-Åsberg Depression Rating Scale (MADRS) was completed at multiple timepoints. The primary efficacy endpoint was change from Baseline in MADRS total score at Week 3

Figure 1. 5D-ASC Dimensions



In the COMP 001 trial, improvement in depressive symptoms with COMP360 treatment was dose dependent, which suggested that this effect was unlikely to be the result of functional unblinding with a subjective psychedelic experience. Additionally, Emotional Breakthrough Inventory total score and several dimensions of the Five-Dimensional Altered States of Consciousness subjective psychedelic experience scale (oceanic boundlessness, visual restructuralization, and auditory alterations) correlated moderately with improvement in depressive symptoms on the Montgomery-Åsberg Depression Rating Scale total score at Week 3. In the COMP 002 trial, dose-dependent subjective psychedelic effects, as observed by the 5D-ASC, were also demonstrated. In the COMP 003 trial, COMP360 administered adjunct to a selective serotonin reuptake inhibitor did not block subjective psychedelic effects or antidepressant efficacy.

Figure 2. 5D-ASC dimension comparison across trials



SSRI: Selective serotonin reuptake inhibitor

RESULTS

- Participant disposition in the studies is shown in **Table 1**
- Clear dose-dependent subjective psychedelic effects were observed (**Figure 2**)
- In COMP 001, moderate correlations were observed in all dose groups between change from Baseline in MADRS total score at Week 3 and scores on 3 dimensions of the 5D-ASC (**Table 2**)
- Additionally, in COMP 001, moderate correlations were observed between change from Baseline in MADRS total score at Week 3 and EBI total score for all dose groups (**Table 2**)

Table 1. Baseline and clinical characteristics

	COMP 001 (N=233; TRD)			COMP 002 (N=89; Healthy volunteers)			COMP 003 (N=19; TRD)
	25 mg (n=79)	10 mg (n=75)	1 mg (n=79)	25 mg (n=30)	10 mg (n=30)	Placebo (n=29)	25 mg + SSRI (n=19)
Female, n (%)	44 (55.7)	41 (54.7)	36 (45.6)	14 (46.7)	14 (46.7)	13 (44.8)	13 (68.4)
Age at screening, years, mean (SD)	40.2 (12.19)	40.6 (12.76)	38.7 (11.71)	36.6 (10.29)	36.1 (9.25)	35.6 (7.69)	42.2 (10.80)
Race, White, n (%)	70 (88.6)	72 (96.0)	73 (92.4)	25 (83.3)	27 (90.0)	20 (69.0)	15 (78.9)
Baseline MADRS total score, mean (SD)	31.9 (5.41)	33.0 (6.31)	32.7 (6.24)	N/A	N/A	N/A	31.7 (5.77)

MADRS: Montgomery-Åsberg Depression Rating Scale; N: Number included in analysis; n: Number of participants; N/A: Not applicable; SD: Standard deviation; SSRI: Selective serotonin reuptake inhibitor; TRD: Treatment-resistant depression

Table 2. COMP 001 Pearson correlation coefficients of 5D-ASC dimensions and EBI total score versus change from Baseline in MADRS total score at Week 3

Measure	25 mg (n=79)	10 mg (n=75)	1 mg (n=79)
5D-ASC oceanic boundlessness	**-0.508**	**-0.485**	**-0.477**
5D-ASC anxious ego dissolution	0.048	0.061	-0.180
5D-ASC visual restructuralization	**-0.516**	**-0.431**	**-0.410**
5D-ASC auditory alterations	-0.293	-0.224	**-0.358**
5D-ASC reduction of vigilance	-0.064	-0.066	-0.305
EBI total score	**-0.614**	**-0.363**	**-0.424**

Moderate correlations are shown in bold and defined as 0.333≤ Pearson's rho <0.667 or -0.667< Pearson's rho ≤-0.333 5D-ASC: Five-Dimensional Altered States of Consciousness; EBI: Emotional Breakthrough Inventory; N: Number included in analysis; n: Number of participants

CONCLUSIONS

- Improvement in depressive symptoms correlated with higher scores on 3 dimensions of the 5D-ASC and EBI total score. Additionally, as observed in COMP 003, COMP360 administered adjunct to an SSRI did not seem to block the subjective psychedelic effects of psilocybin or its clinical benefit, which contradicts previous conjecture
- In COMP 001, a 10 mg dose produced a subjective psychedelic experience, but it was not significantly better in reducing depressive symptom severity compared with a 1 mg dose. This suggests that presuming that one received an active dose through having a subjective psychedelic experience, as evident from the 10 mg dose, is insufficient for improving symptoms; thus, this points to the potential validity of a pharmacological mechanism of action that separates the 25 mg dose from the other doses
- Although they were tested in different trials and populations, a 1 mg dose in COMP 001 resulted in some degree of subjective psychedelic experience that was notably greater than that of placebo in COMP 002. This result suggests that a 1 mg dose may serve as an adequate negative control in efficacy trials
- The correlations between changes in depressive symptom severity and 5D-ASC dimension scores and EBI total score warrant additional research to further understand the role that subjective psychedelic effects play in achieving therapeutic response

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DISCLOSURES

GMG, LM, SM, AN, CS, JT, SW, and EM are employees of COMPASS Pathfinder Ltd.

GMG is a National Institute for Health and Care Research Emeritus Senior Investigator, holds shares in P1vital and P1vital products, and has served as consultant, advisor, or CME speaker in the last 3 years for Beckley Psytech, Boehringer Ingelheim, Clerkenwell Health, COMPASS Pathfinder Ltd, Evapharma, Janssen, Lundbeck, Medscape, Novartis, Ocean Neuroscience, P1vital, Sage, and Servier.

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JJR has been on paid advisory boards for Clerkenwell Health, Beckley PsyTech, and Delica Therapeutics in the past. He has authored paid articles for Janssen, and has received grant funding from COMPASS Pathfinder Ltd, Beckley PsyTech, Multidisciplinary Association for Psychedelic Studies, National Institute for Health Research, Wellcome Trust, Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust. JJR has received travel and subsistence expenses for conferences from COMPASS Pathfinder Ltd to present data from trials.

AHY's research is funded by the National Institute for Health Research Biomedical Research Centre at King's College London and the South London and Maudsley NHS Foundation Trust. AHY has also received grant funding from COMPASS Pathfinder Ltd and honoraria for attending advisory boards and presenting lectures for Allergan, AstraZeneca, Bionomics, Eli Lilly, Janssen, LivaNova, Lundbeck, Servier, Sumitomo Dainippon Pharma, and Sunovion and has received consulting fees from Johnson & Johnson and LivaNova. AHY is on the editorial advisory board at the *Journal of Psychopharmacology.*

DF, VO, and JRK have nothing to disclose.

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