Predicting depression outcomes through the influence of therapeutic alliance and the psychedelic experience using path modeling in a phase IIb randomized controlled trial of COMP360 psilocybin therapy

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BACKGROUND

- Our recent phase IIb trial of COMP360 (COMPASS' proprietary, synthetic formulation of psilocybin) demonstrated efficacy in treatment-resistant depression (TRD) with significant improvement in depressive symptom severity after a single 25 mg dose[1]
- Therapeutic alliance and subjective psychedelic experience during psilocybin administration are potentially important elements of the treatment[2,3]; a recent systematic review reported a significant association of correlation, mediation, and/or prediction between the 2 variables[4]
- Understanding how these components relate to the COMP360 psilocybin therapy response is important for optimizing the treatment paradigm, clarifying underlying mechanisms, and identifying patients who may benefit from the treatment

OBJECTIVE

- Using data from the phase IIb trial, a post hoc analysis examined the relationship between therapeutic alliance, subjective psychedelic experience, and depressive symptom severity

METHODS

- COMP 001 was a phase IIb, international, multicenter, randomized, fixed-dose, parallel-group, double-blind trial that investigated the safety and efficacy of a single dose of COMP360 25 mg or 10 mg compared with a single dose of COMP360 1 mg (control)
- COMP360 was administered alongside psychological support from trained therapists to ensure the psychological and physical safety of participants. Psychological support was delivered before, during, and after COMP360 administration
- The primary efficacy endpoint was change from Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 3
- Subjective psychedelic experience was measured using the Five-Dimensional Altered States of Consciousness (5D-ASC) questionnaire, which was assessed at the end of the COMP360 administration day, and Emotional Breakthrough Inventory (EBI) total score, which was assessed the day after COMP360 administration. The 5D-ASC dimensions are oceanic boundlessness, anxious ego dissolution, visual restructuralization, auditory alterations, and reduction of vigilance (defined in **Figure 1**). The EBI measures aspects relating to emotional release, trauma or internal personal conflict resolution, and facing difficult emotions and feelings that are usually avoided

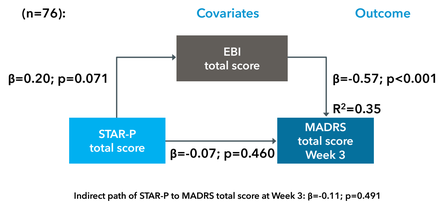
Table 1: Baseline and clinical characteristics

	COMP360			
	25 mg (n=79)	10 mg (n=75)	1 mg (n=79)	Overall (N=233)
Female, n (%)	44 (55.7)	41 (54.7)	36 (45.6)	121 (51.9)
Age at screening, years, mean (SD)	40.2 (12.19)	40.6 (12.76)	38.7 (11.71)	39.8 (12.19)
Race, White, n (%)	70 (88.6)	72 (96.0)	73 (92.4)	215 (92.3)
Prior psilocybin use, n (%)	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Lifetime depressive episodes, mean (SD)	7.3 (8.58)	7.8 (9.09)	5.7 (4.35)	6.9 (7.63)
Duration of current depressive episode, n (%)				
>2 years	34 (43.0)	37 (49.3)	36 (45.6)	107 (45.9)
Failed treatments for current depressive episode, n (%)				
2	66 (83.5)	62 (82.7)	63 (79.7)	191 (82.0)
3 or 4	12 (15.2)	11 (14.7)	14 (17.7)	37 (15.9)
Baseline MADRS total score, mean (SD)	31.9 (5.41)	33.0 (6.31)	32.7 (6.24)	32.5 (5.99)
Baseline STAR-P total score, mean (SD)	41.4 (5.28)	41.5 (4.97)	42.0 (5.60)	41.6 (5.28)

MADRS: Montgomery-Åsberg Depression Rating Scale; N: Number included in analysis; n: Number of participants; SD: Standard deviation; STAR-P: Scale to Assess Therapeutic Relationships - Patient version

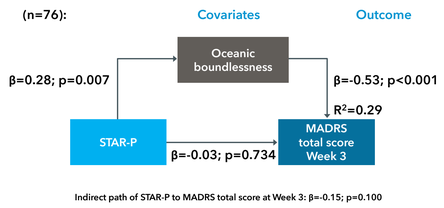
In patients with TRD who were treated with COMP360 psilocybin therapy, key elements of the acute subjective psychedelic experience but not therapeutic alliance predicted improvement in depressive symptom severity, which was assessed using the Montgomery-Åsberg Depression Rating Scale at Week 3

Figure 1A. Pathway 1: Path model that explores the relationship between STAR-P total score, EBI total score, and MADRS total score at Week 3



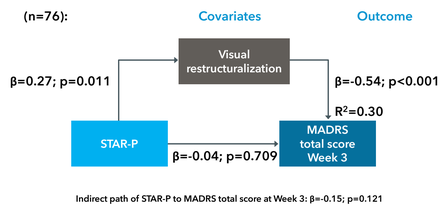
Indirect path of STAR-P to MADRS total score at Week 3: β=-0.11; p=0.491

Figure 1B. Pathway 2: Path model that explores the relationship between STAR-P total score, oceanic boundlessness, and MADRS total score at Week 3



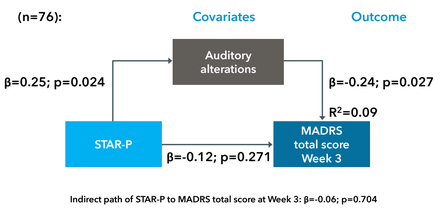
Indirect path of STAR-P to MADRS total score at Week 3: β=-0.15; p=0.100

Figure 1C. Pathway 3: Path model that explores the relationship between STAR-P total score, visual restructuralization, and MADRS total score at Week 3



Indirect path of STAR-P to MADRS total score at Week 3: β=-0.15; p=0.121

Figure 1D. Pathway 4: Path model that explores the relationship between STAR-P total score, auditory alterations, and MADRS total score at Week 3



Indirect path of STAR-P to MADRS total score at Week 3: β=-0.06; p=0.704

Auditory alterations: Changes in hearing, such as perceived sounds and auditory hallucinations; EBI: Emotional Breakthrough Inventory; MADRS: Montgomery-Åsberg Depression Rating Scale; Oceanic boundlessness: Mystical-type experiences that are often associated with positive emotional states; STAR-P: Scale to Assess the Therapeutic Relationship – Patient version; Visual restructuralization: Perception and visual alterations, including hallucinations

- Therapeutic alliance, which was measured by the Scale to Assess the Therapeutic Relationship – Patient version (STAR-P) and collected the day before COMP360 administration day, was hypothesized to predict depressive symptom severity at Week 3 (absolute MADRS total score) through its interaction with subjective psychedelic experience (5D-ASC dimension scores and EBI total score)
- Path analysis, which is a type of multiple regression that evaluates relationships between variables to assess causality, was conducted on data from the COMP360 25 mg group; COMP 001 found 25 mg to be the optimum therapeutic dose
- Saturated paths were modeled; each path included 3 variables:
  - STAR-P total score
  - Either EBI total score or 1 of the 5D-ASC dimension scores
  - MADRS total score at Week 3
- Due to expected multicollinearity between the subjective psychedelic experience variables, separate paths were fitted for EBI total score and each of the 5 dimension scores of the 5D-ASC. The path analyses used maximum likelihood estimation as the estimation method
- This analysis aimed to replicate what was previously reported in a pilot trial of participants with major depressive disorder (N=59) who were treated with COMP360 or escitalopram alongside psychological support. Reduction of depressive symptom severity was significantly predicted by acute subjective psychedelic effects, which were measured by EBI and Mystical Experience Questionnaire total scores[2]

RESULTS

- 233 participants were randomized (**Table 1**). Three 25 mg participants were excluded from the path analysis due to missing MADRS total scores at Week 3
- MADRS total score at Week 3 was predicted by EBI total score (**Figure 1A**) and the following 5D-ASC dimensions: Oceanic boundlessness (**Figure 1B**), visual restructuralization (**Figure 1C**), and auditory alterations (**Figure 1D**)
  - Anxious ego dissolution and reduction of vigilance did not predict MADRS total score at Week 3
- These variables were all related to a reduction in depressive symptoms, which was captured by MADRS total score at Week 3
- The absolute standardized effects and variance explained were largest for EBI total score, which indicated that this was the most reliable predictor of MADRS total score at Week 3
- The direct effect of STAR-P on depression outcomes was not significant for any path after applying a Bonferroni correction

CONCLUSIONS

- The outcomes of this path analysis, which used data from a larger, more robust TRD sample than in Murphy et al,[2] confirm some aspects of previous reports:
  - Subjective psychedelic effects were significant predictors of depressive symptom severity. If, as is very likely, intensity of subjective psychedelic experience reflects dose level, it also echoes the dose-related response in the primary analysis of COMP 001
  - In contrast with previous reports, indirect effects of therapeutic alliance were not significant; however, effects in smaller trials are often not confirmed in larger samples. Our therapy model may have less variance (as intended for a safety measure); thus, it has less potential to differentiate outcomes. This is an important advantage for trials to establish drug efficacy
- These findings may help us identify not only those patients who are likely to benefit from the treatment but also those patients who are not

REFERENCES

1. Goodwin GM, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med.* 2022;387(18):1637-1648.
2. Murphy R, et al. Therapeutic alliance and rapport modulate responses to psilocybin assisted therapy for depression. *Front Pharmacol.* 2022;12:788155.
3. Griffiths R, et al. Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology (Berlin).* 2011;218(4):649-65.
4. Ko K, et al. Psychedelics, mystical experience, and therapeutic efficacy: A systematic review. *Front Psychiatry.* 2022;13:917199.

DISCLOSURES

GMG, HS, LM, SM, DS, JT, 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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