The safety and efficacy of COMP360 psilocybin therapy as adjunctive treatment in treatment-resistant depression

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BACKGROUND

Treatment-resistant depression

- Treatment-resistant depression (TRD) is a major public health challenge that presents with greater severity, chronicity, disability, and risk of suicide than major depressive disorder (MDD). Many people with TRD do not benefit from currently available antidepressant treatments, which denotes a significant unmet need[1]

Psilocybin and depression

- Psilocybin is a tryptamine alkaloid found in numerous species of *Psilocybe* mushrooms[2]
- Psilocybin's potential antidepressant efficacy was suggested by preliminary studies in patients with life-threatening cancer. Subsequently, high rates of symptomatic response in pilot studies of MDD and, notably, TRD provided additional support for its therapeutic potential[2]
- COMP360 psilocybin (COMPASS Pathways' proprietary, synthetic formulation of psilocybin) therapy is being developed for TRD
- In a recent phase IIb, randomized, double-blind clinical trial, a single 25 mg dose of COMP360 given in conjunction with psychoeducation and support demonstrated a rapid and significantly greater decrease in depressive symptoms in antidepressant-treatment-free or withdrawn participants compared with a 1 mg dose of COMP360[3]
- Literature and anecdotal evidence have suggested that long-term treatment with serotonergic antidepressants might result in a weak or absent psychedelic experience.[4,5] Recent findings in healthy volunteers report that the psychedelic experience induced by psilocybin might not be largely impacted by the administration of a selective serotonin reuptake inhibitor (SSRI).[6] However, this has never been studied in a TRD population
- These encouraging results raise the question of how COMP360 psilocybin therapy acts adjunct to serotonergic antidepressants

OBJECTIVE

To evaluate the safety and efficacy of COMP360 administered adjunct to SSRIs for TRD

METHODS

Study design

- This was an open-label, phase II study that evaluated the safety and efficacy of a single administration of COMP360 25 mg adjunct to a single ongoing SSRI in adult participants with TRD (ClinicalTrials.gov Identifier: NCT04739865)
- COMP360 psilocybin therapy included 3 preparation sessions prior to the COMP360 administration session followed by 2 post-administration integration sessions. All preparation and integration sessions were 1:1 with a trained therapist
- COMP360 administration sessions could be carried out simultaneously with up to 6 participants who received 1:1 psychological support from their assigned therapist
- Participants were followed for 3 weeks post COMP360 administration. **Figure 1** presents an overview of the scheduled study visits and assessments performed

Figure 1. Schedule of assessments

	Visit 1 Screening	Visit 1a, 1b, 1c, etc Screening period	Visit 2 (Day -1) Baseline assessments	Visit 3 (Day 1) Administration	Visit 4 (Day 2) Follow-up at clinic	Visit 5 (Week 1) Follow-up at clinic	Visit 6 (Week 2) Follow-up at clinic	Visit 7 (Week 3) Follow-up at clinic
Informed consent form	✓							
Medical and psychiatric history	✓		✓					
Preparatory session		✓	✓					
Dosing session				✓				
Integration session					✓	✓		
Vital signs	✓		✓	✓	✓			
Clinical laboratory tests	✓				✓			
AEs, medications and C-SSRS	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG	✓				✓			
MADRS			✓		✓	✓	✓	✓
CGI-S			✓		✓	✓	✓	✓
5D-ASC				✓				

5D-ASC: 5-Dimensional Altered States of Consciousness scale; AE: Adverse event; CGI-S: Clinical Global Impressions - Severity scale; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: Electrocardiogram; MADRS: Montgomery-Åsberg Depression Rating Scale

Key inclusion criteria

- Aged 18 years and older
- Met *Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)* criteria for MDD based on clinical assessment, medical records, and Mini International Neuropsychiatric Interview (MINI, version 7.0.2) documentation
- Hamilton Depression Rating Scale (17-item scale; HAM-D-17) score ≥18 at Screening and Baseline visits
- Received treatment with an SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, vilazodone, vortioxetine, or escitalopram) at or above a minimum locally approved therapeutic dose for at least 6 weeks before Screening and Baseline visits
- Criteria for TRD
  - Current episode had not responded to an adequate dose and duration of 2 to 4 evidence-based antidepressant treatments based on the Massachusetts General Hospital Antidepressant Treatment History Response Questionnaire (MGH-ATRQ) with supplemental updates
  - Augmentation therapy counted as an independent treatment, provided the add-on drug was approved for adjunctive treatment of MDD in the study site country
  - Single-episode MDD with duration ≥3 months and ≤2 years

Key exclusion criteria

- Current or past history of any serious psychiatric comorbidity, including schizophrenia, psychotic disorder, bipolar disorder, delusional disorder, paranoid personality disorder, schizoaffective disorder or borderline personality disorder, or depression secondary to a medical condition

Safety outcomes

- 12-lead ECG
- Vital signs
- Clinical laboratory tests
- Suicidality (assessed using the Columbia-Suicide Severity Rating Scale [C-SSRS])
- Adverse events (AEs) and serious adverse events (SAEs)

Efficacy outcomes

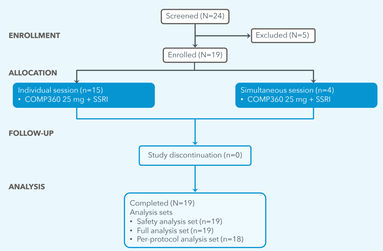
- Analyses of efficacy were performed on the full analysis set, which included all participants who received a single dose of COMP360 and had at least one post-Baseline efficacy assessment
- Primary efficacy endpoint: Change from Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 3
- Secondary efficacy endpoints
  - Change from Baseline in Clinical Global Impressions - Severity (CGI-S) scale score at Week 3
  - Proportion of responders at Week 3 (response criteria: ≥50% change from Baseline in MADRS total score)
  - Proportion of remitters at Week 3 (remission criteria: MADRS total score ≤10)
- Exploratory endpoint: summary of the 5-Dimensional Altered State of Consciousness (5D-ASC) questionnaire
- Results were summarized using descriptive statistics

RESULTS

Participant disposition

- Of the 24 participants who were screened, 19 were administered COMP360 25 mg adjunct to a single ongoing SSRI, and all completed the study at Week 3 with no study discontinuations (**Figure 2**)

Figure 2. CONSORT participant flow diagram



N: Number included in analysis; n: Number of participants; SSRI: Selective serotonin reuptake inhibitor

Baseline characteristics

- The majority of participants were females (68.4%), and of White race (78.9%)
- The mean body mass index at screening was 26.3 kg/m^2 (standard deviation [SD]=6.52)
- The majority of participants (63.2%) had 2 treatment failures in their current depressive episode, and the mean length of the current depressive episode was 23.5 months (SD=22.06)
- Stable ongoing SSRIs included escitalopram (n=6), sertraline (n=6), fluoxetine (n=3), vilazodone (n=2), paroxetine (n=1), or citalopram (n=1)

Safety results

- Eleven participants (57.9%) reported at least 1 treatment-emergent adverse event (TEAE); among these participants, there were 16 TEAEs up to Week 3 (**Table 1**). The most common TEAE was headache, which was reported by 6 participants (31.6%), with all events occurring on Day 1 (COMP360 administration) or on Day 2, and resolving in 1 to 2 days. Eight participants (42.1%), 2 participants (10.5%), and 1 participant (5.3%) reported TEAEs of mild, moderate, and severe maximum severity, respectively
- Eight participants (42.1%) experienced a TEAE on Day 1
- All 16 TEAEs resolved within a week from onset
- No treatment-emergent SAEs were reported up to Week 3
- Post Baseline, no participants reported any suicidal ideation or behavior more severe than nonspecific active suicidal thoughts at any time
- Aggregate review of changes in clinical laboratory tests, 12-lead ECG results, or vital signs did not reveal any clinically important changes

Table 1. Incidence and severity of TEAEs (safety analysis set)

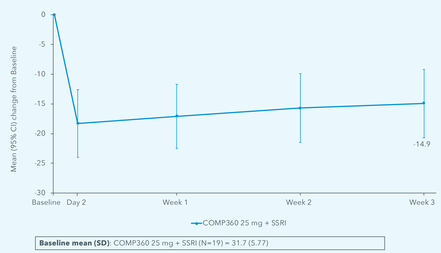
	COMP360 25 mg + SSRI (N=19)	
	n (%)	Severity
Headache	5 (26.3)	mild
	1 (5.3)	moderate
Blood pressure increase	1 (5.3)	mild
	1 (5.3)	severe
Depression	1 (5.3)	moderate
Diarrhea	1 (5.3)	mild
Dizziness	1 (5.3)	mild
Dry mouth	1 (5.3)	mild
Fall	1 (5.3)	mild
Palpitations	1 (5.3)	mild
Skin abrasion	1 (5.3)	mild
Vertigo	1 (5.3)	mild

N: Number included in analysis; n: Number of participants

Efficacy results

- There was a rapid decrease in depressive symptoms the day after COMP360 administration (Day 2) with a mean (SD) change from Baseline MADRS total score of -18.3 (11.85). For the primary efficacy endpoint, participants had a mean (SD) -14.9 (11.97)-point improvement in MADRS total score at Week 3 compared with Baseline (**Figure 3**)

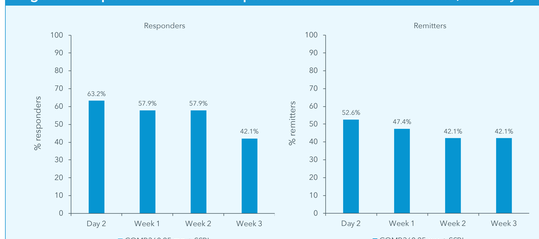
Figure 3. Change from Baseline in MADRS total score over time (full analysis set)



CI: Confidence interval; SD: Standard deviation; SSRI: Selective serotonin reuptake inhibitor

- At Week 3, 42.1% (n=8) and 42.1% (n=8) of participants were responders and remitters, respectively (**Figure 4**). Rapid response and remission were observed from Day 2

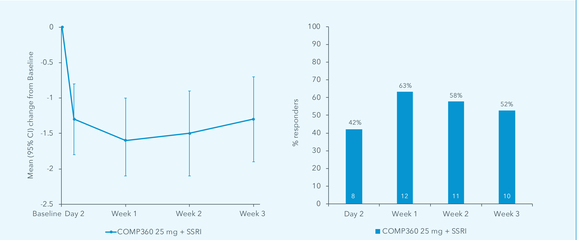
Figure 4. Proportion of MADRS responders and remitters over time (full analysis set)



Percentages are based on the number of participants in the full analysis set
MADRS: Montgomery-Asberg Depression Rating Scale; SSRI: Selective serotonin reuptake inhibitor

- Reduction in depressive symptoms was observed by the study clinician, as measured by the CGI-S. On the CGI-S, participants had a mean (SD) score of 4.3 (0.99), which was defined as "moderately ill," at Baseline and 2.9 (1.84), which was "mildly ill," at Week 3. On the CGI-S, 52.6% of participants (n=10) were responders at Week 3, which was defined as scoring 1 "normal, not at all ill" or 2 "borderline mentally ill" (**Figure 5**)

Figure 5. Change from Baseline in CGI-S score and proportion of CGI-S responders over time (full analysis set)

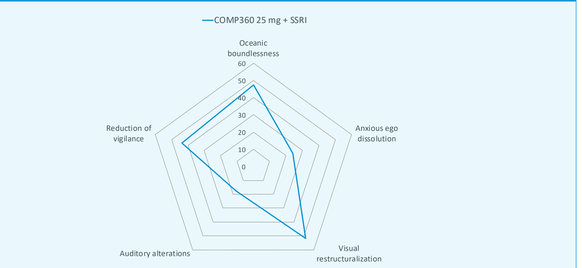


Mean change from Baseline CGI-S score was -1.3 at Week 3
CGI-S: Clinical Global Impression- Severity; CI: Confidence interval; SSRI: Selective serotonin reuptake inhibitor

Psychedelic effects

- Mean (SD) 5D-ASC dimension scores were indicative of a psychadelic experience (**Figure 6**)

Figure 6. Mean 5D-ASC dimension scores (full analysis set)



5D-ASC: 5-Dimensional Altered States of Consciousness questionnaire; SSRI: Selective serotonin reuptake inhibitor

CONCLUSIONS

- A single 25 mg dose of COMP360 adjunct to a single ongoing SSRI, administered with psychoeducation and support, was well tolerated in this exploratory study
- The subjective psychedelic effects observed were in line with the pharmacological profile of psilocybin observed in previous studies across all 5D-ASC dimensions
- The encouraging safety and efficacy results support further investigation of COMP360 psilocybin therapy adjunct to antidepressants as a treatment for TRD, especially in cases where antidepressant withdrawal may be challenging

References

1. Johnston KM, et al. *J Affect Disord.* 2019;242:195-210. **2.** Castro Santos H, et al. *Porto Biomed J.* 2021;6(1):e128. **3.** Goodwin GM, et al. The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: Results from a phase IIb randomized controlled study. Poster presented at the American Psychiatric Association Annual Meeting; 2022 May 21-26; New Orleans, US. **4.** Bonson KR, et al. *Neuropsychopharmacology.* 1996;14(6):425-436. **5.** Carhart-Harris R, et al. *N Engl J Med.* 2021;385(9):862-864. **6.** Becker AM, et al. *Clin Pharm Ther.* 2022;111(4):886-895.

Disclosures

GMG, JT, CS, SM, SW, and EM are employees of COMPASS Pathfinder Ltd; SCS was an employee at the time the study was conducted. DF, VO, and JRK have nothing to disclose.

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