The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: Results from a phase IIb randomized controlled trial

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BACKGROUND

Treatment-resistant depression

- Treatment resistance is a major public health challenge in the field of mental health
- STAR*D, the largest (N=3,671) prospective study of treatment outcomes in major depressive disorder (MDD), reported high rates of treatment resistance and found that remission rates became progressively lower from the first course of antidepressant treatment (36.8%) to the second course (30.6%), third course (13.7%), and fourth course (13.0%)[1]
- Limited drug tolerability and poor adherence to prescribed therapy further complicate the ability of clinicians to provide effective treatment
- Compared with patients with MDD, patients with treatment-resistant depression (TRD) have notably higher disease burden, including greater severity, chronicity, disability, rates of hospitalization, risk of suicide, and economic costs (both direct and indirect).[2,3] Thus, there is a substantial unmet clinical need for improved treatment

Psilocybin and depression

- Psilocybin is a tryptamine alkaloid found in numerous species of *Psilocybe* mushrooms[4]
- Its 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[5]

OBJECTIVE

To evaluate the safety and efficacy of a single dose of COMP360 (COMPASS Pathways' proprietary, synthetic formulation of psilocybin) (25 mg or 10 mg) compared with 1 mg in the treatment of depression in adult participants with TRD

METHODS

Study design

- After completing a ≥2-week washout of antidepressant treatments, eligible participants were randomized and double blinded in a 1:1:1 ratio to a single dose of COMP360 (25 mg or 10 mg or 1 mg)
- COMP360 administration session: The duration of the session was approximately 6-8 hours. The participant was supported by a trained therapist
- Participants were asked to remain off all antidepressant treatments for at least 3 weeks following the COMP360 administration
- Participants were followed for 12 weeks post COMP360 administration with visits on Day 2, Week 1, Week 3 (primary endpoint assessment), Week 4, Week 6, Week 9, and Week 12

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; HAM-D-17) score ≥18 at Screening and Baseline visits
- Criteria for TRD
  - Current episode had not responded to an adequate dose and duration of two to four 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
- Treatment with electroconvulsive therapy or ketamine/esketamine for the current episode or recent (≤3 weeks) initiation of cognitive behavioral therapy
- Use of a psychedelic compound in the past year or during current depressive episode, whichever was longer
- Met criteria (within past year) for *DSM-5* alcohol or substance use disorder or significant suicide risk
- Acute or unstable medical condition or clinically significant abnormal laboratory tests, electrocardiogram (ECG) results, vital signs, or physical examination findings

Efficacy outcomes

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Sustained response (criteria: Week 3 response maintained through Week 12; response criteria: ≥50% change from Baseline in MADRS total score). Note: Participants who initiated an adjunctive antidepressant treatment were considered non-responders

Efficacy analyses

- Analyses of efficacy were performed on the full analysis set, which included all participants who underwent randomization, received a single dose of COMP360, and had at least one post-Baseline efficacy assessment
- The primary efficacy endpoint (change from Baseline in MADRS total score at Week 3) was evaluated with a mixed model for repeated measures comparing COMP360 25 mg and 10 mg doses with the 1 mg dose
- The key secondary efficacy endpoint (sustained response) was analyzed using a logistic regression model

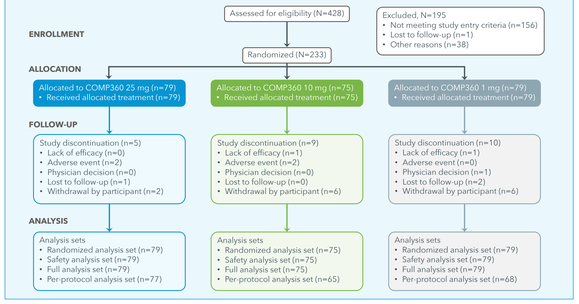
Safety analyses

- Analyses of safety were performed on the safety analysis set, which included all participants who underwent randomization and received single-dose COMP360
- Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were evaluated. Additionally, suicidality was assessed based on the Columbia-Suicide Severity Rating Scale (C-SSRS), and safety was assessed by vital signs, clinical laboratory tests, and 12-lead ECG

RESULTS

- Of the 428 participants screened, 233 were randomized to receive COMP360 treatment (**Figure 1**)
- There was a highly statistically significant and clinically relevant effect at the Week 3 primary endpoint for psilocybin at the 25 mg dose, but not at the 10 mg dose, compared with the 1 mg dose (**Figure 2**). The benefit of the 25 mg dose was fully evident at Day 2 and Week 1 following administration, confirming the rapid-acting character of the effect

Figure 1. CONSORT participant flow diagram



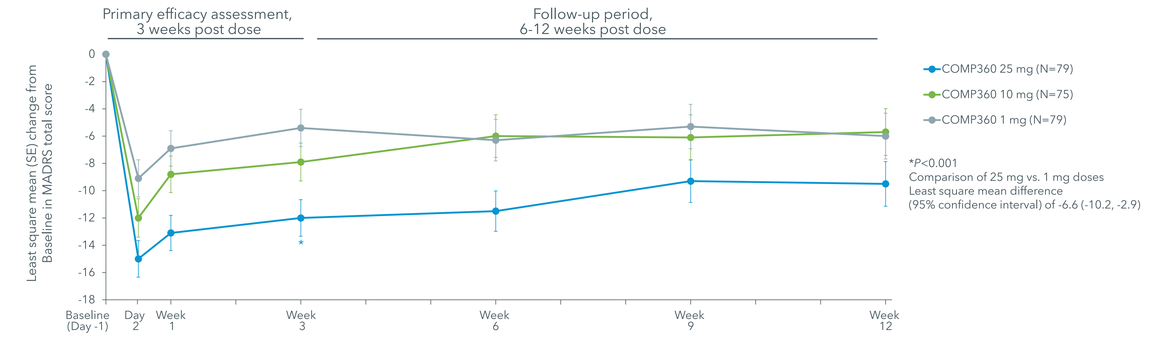
- The participants' baseline and clinical characteristics are summarized in **Table 1**

Table 1. Baseline and clinical characteristics (safety analysis set)

	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, 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)
Body mass index, kg/m², mean (SD)	26.52 (6.13)	28.26 (8.2)	27.26 (6.03)	27.34 (6.86)
Prior psilocybin use, n (%)	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Psychiatric history				
MDD, recurrent, n (%)	67 (84.8)	68 (90.7)	65 (82.3)	200 (85.8)
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 (%)				
<1 year	12 (15.2)	10 (13.3)	10 (12.7)	32 (13.7)
1 year to <2 years	33 (41.8)	28 (37.3)	33 (41.8)	94 (40.3)
>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)
Withdrawn from antidepressant at study entry, n (%)	49 (62.0)	50 (66.7)	50 (63.3)	149 (63.9)
Baseline depression scores				
MADRS total score				
Mean (SD)	31.9 (5.41)	33.0 (6.31)	32.7 (6.24)	32.5 (5.99)
Moderate (20-30), n (%)	33 (41.8)	19 (25.3)	18 (22.8)	70 (30.0)
Severe (≥31), n (%)	46 (58.2)	54 (72.0)	59 (74.7)	159 (68.2)
HAM-D-17 total score				
Mean (SD)	21.8 (3.04)	22.4 (2.77)	22.2 (2.93)	22.2 (2.92)
Moderate (18-23), n (%)	57 (72.2)	9 (65.3)	59 (74.7)	165 (70.8)
Severe (≥24), n (%)	22 (27.8)	26 (34.7)	20 (25.3)	68 (29.2)

HAM-D-17: Hamilton Depression Rating Scale - 17-item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major depressive disorder; SD: Standard deviation

Figure 2. Mean change from Baseline in MADRS total score over time (full analysis set)



Sustained response

- Sustained response rates at Week 12 to a single dose of COMP360 were 16/79 (20.3%) and 4/75 (5.3%) in the 25 mg and 10 mg groups versus 8/79 (10.1%) in the 1 mg group
- On the day of COMP360 administration, headache, nausea, and dizziness were the only TEAEs where a dose-related increase in incidence was evident (**Table 2A**). One participant in the 25 mg group was treated with lorazepam for acute anxiety

Table 2. Treatment-emergent adverse events (safety analysis set)

	COMP360		
	25 mg (N=79) n (%)	10 mg (N=75) n (%)	1 mg (N=79) n (%)
A. Day 1			
Any TEAE	48 (60.8)	35 (46.7)	30 (38.0)
Any severe TEAE	3 (3.8)	6 (8.0)	1 (1.3)
TEAEs ≥5%			
Headache	19 (24.1)	11 (14.7)	13 (16.5)
Nausea	17 (21.5)	5 (6.7)	1 (1.3)
Euphoric mood	4 (5.1)	5 (6.7)	3 (3.8)
Fatigue	5 (6.3)	2 (2.7)	4 (5.1)
Insomnia	2 (2.5)	3 (4.0)	5 (6.3)
Anxiety	3 (3.8)	6 (8.0)	0
Mood altered	4 (5.1)	3 (4.0)	0
Dizziness	5 (6.3)	1 (1.3)	0
Paresthesia	2 (2.5)	4 (5.3)	0
Thinking abnormal	0	4 (5.3)	0
Any TESAE	0	0	0
B. Day 2 up to Week 3			
Any TEAE	44 (55.7)	36 (48.0)	35 (44.3)
Any severe TEAE	7 (8.9)	5 (6.7)	1 (1.3)
TEAEs ≥5%			
Headache	9 (11.4)	5 (6.7)	9 (11.4)
Insomnia	4 (5.1)	5 (6.7)	8 (10.1)
Anxiety	4 (5.1)	6 (8.0)	3 (3.8)
Fatigue	6 (7.6)	2 (2.7)	3 (3.8)
Suicidal ideation	5 (6.3)	4 (5.3)	2 (2.5)
Depression	3 (3.8)	3 (4.0)	4 (5.1)
Mood altered	4 (5.1)	0	1 (1.3)
Any TESAE	4 (5.1)	4 (5.3)	0
Suicidal ideation	2 (2.5)	2 (2.7)	0
Intentional self-injury	2 (2.5)	1 (1.3)	0
Hospitalization	0	1 (1.3)	0
C. After Week 3 up to Week 12			
Any TEAE	23 (29.1)	24 (32.0)	24 (30.4)
Any severe TEAE	2 (2.5)	3 (4.0)	0
TEAEs ≥5%			
Headache	3 (3.8)	2 (2.7)	6 (7.6)
Any TESAE	4 (5.1)	3 (4.0)	1 (1.3)
Suicidal behavior	3 (3.8)	0	0
Intentional self-injury	0	1 (1.3)	1 (1.3)
Adjustment disorder with anxiety and depressed mood	1 (1.3)	0	0
Depression	0	1 (1.3)	0
Drug withdrawal syndrome	1 (1.3)	0	0
Suicidal ideation	0	1 (1.3)	0

TEAE: Treatment-emergent adverse event; TESAE: Treatment-emergent serious adverse event

- From Day 2 up to Week 3, the TESAEs reported in the 25 mg group were suicidal ideation (n=2) and intentional self-injury (n=2) and in the 10 mg group were suicidal ideation (n=2) and hospitalization (for severe depression, n=1). No TESAEs were reported in the 1 mg group (**Table 2B**)
- Treatment-emergent suicidal ideation and behavior were assessed using the MADRS item 10 (suicidal thoughts). The mean (standard deviation) change from Baseline in MADRS item 10 score showed a small reduction at Day 2 for the 25 mg, 10 mg, and 1 mg groups of -0.7 (1.28), -0.5 (1.28), and -0.4 (1.11), respectively, which were maintained at Week 3: -0.3 (1.57), -0.4 (1.33), and -0.3 (0.99)
- Three participants in the 25 mg group reported a TESAE of suicidal behavior. All three participants were MADRS non-responders at Week 3
- No clinically significant between-group changes in vital signs or clinical laboratory tests were observed during the study. In the 12-lead ECG, two participants in the 25 mg group had a change from Baseline in QTcF >60 msec on Day 2. In one of these participants, the QTcF interval on Day 2 was within normal range (403 msec) and the ECG overall interpretation was normal. The other participant had a QTcF interval duration >500 msec on Day 2 (QTcF was 515 msec). On Day 9, the QTcB and QTcF intervals had returned to screening levels (363 and 367 msec, respectively)

CONCLUSIONS

- In this international, multicenter, randomized, double-blind study of TRD, a single dose of the COMP360 formulation of psilocybin 25 mg, administered with psychoeducation and support, was associated with a clinically significant greater reduction in depression severity at Week 3, as assessed by the change from Baseline in MADRS total score, compared with the subtherapeutic 1 mg dose of COMP360
- Antidepressant efficacy for the 25 mg dose was statistically significant at Week 3 (primary efficacy endpoint) with rapid onset by Day 2 and sustained improvement to Week 6
- 20.3% of participants treated with the 25 mg dose met rigorous criteria for sustained response at Week 12
- TEAEs suggest that the treatment is acceptable and generally well tolerated, but vigilance for emergent suicidality will always be necessary in TRD
- Future clinical trials of COMP360 are needed for both replicating results and employing study designs that address unanswered clinical questions, most notably related to the optimal COMP360 treatment strategy for achieving a sustained treatment response in TRD

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Disclosures

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