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

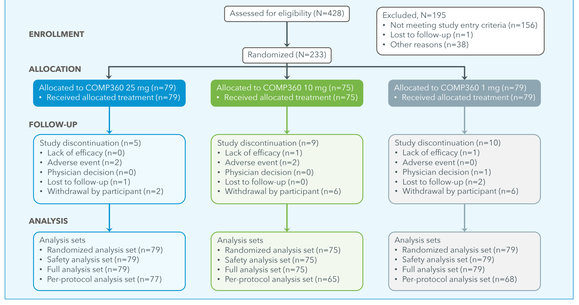
Safety analyses

- 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



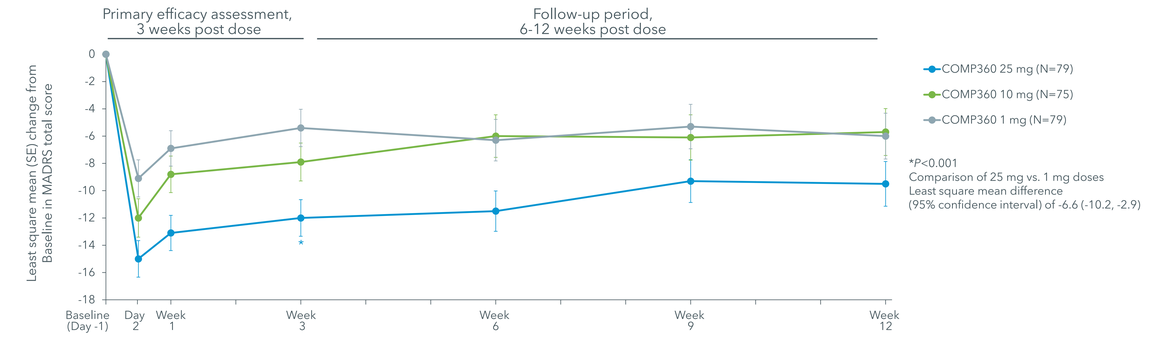
- The participants' baseline and clinical characteristics are summarized in **Table 1**

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

References: 1. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. **2.** Russell JM, et al. *J Clin Psychiatry*. 2004;65(3):341-347. **3.** Johnston KM, et al. *J Affect Disord*. 2019;242:195-210. **4.** Passie T, et al. *Addict Biol*. 2002;7(4):357-364. **5.** Castro SH, et al. *Porto Biomedical J*. 2021;6:128.

Disclosures

GG and EM are employees of COMPASS Pathfinder Ltd; SS was an employee at the time the study was conducted.

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DH has received research funding support from COMPASS Pathfinder Ltd for psilocybin studies and from Eli Lilly, GeneSight, IntraCellular Therapies, Marinus, Pfizer, Relmada, and Takeda for other studies. DH is also on the scientific advisory board for Reset Pharmaceuticals.

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A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Changes in affect, anxiety, and further exploratory endpoints

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Session Title: Poster Session 1

BACKGROUND

Treatment-resistant depression

- Treatment-resistant depression (TRD) is a major public health challenge in the field of mental health
- Compared with patients with major depressive disorder (MDD), patients with TRD have notably higher disease burden, including greater severity, chronicity, disability, rates of hospitalization, risk of suicide, and economic costs (both direct and indirect).[1,2] 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[3]
- 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[4]
- In the largest randomized, controlled, double-blind study of psilocybin therapy to date, a single 25 mg dose of COMP360 given in conjunction with psychoeducation and support resulted in rapid, significant, and clinically meaningful reductions in depression symptoms compared with a 1 mg dose. A 10 mg dose resulted in modest numerical reductions[5]
- In addition to its antidepressant effect, COMP360 psilocybin therapy has the potential to improve the functional impairment that is common in patients with TRD

OBJECTIVE

To evaluate the efficacy of COMP360 (COMPASS Pathways' proprietary, synthetic formulation of psilocybin) on exploratory measures of positive and negative affect, anxiety, quality of life, functioning, and cognition in adults with TRD

METHODS

This was a multicenter, international, phase IIb, randomized, fixed-dose, double-blind study that assessed the safety and efficacy of COMP360 25 mg or 10 mg compared with COMP360 1 mg in adult participants with TRD (ClinicalTrials.gov Identifier: NCT03775200)

Study design

- After completing a ≥2-week washout of antidepressant treatments, eligible participants were randomized in a 1:1:1 ratio to a single administration of COMP360 (25 mg or 10 mg or 1 mg)
- After psychological preparation with a trained therapist, participants received COMP360 in a therapist-supported session that lasted approximately 6 to 8 hours
- Participants were asked to remain off all antidepressant treatments for at least 3 weeks following COMP360 administration
- Participants were followed for 12 weeks post COMP360 administration

Key inclusion criteria

- Aged 18 years and older
- Met *Diagnostic and Statistical Manual of Mental Disorders 5th edition* 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
- 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

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

Exploratory outcomes

- Positive and Negative Affect Schedule (PANAS)
- Generalized Anxiety Disorder Scale – 7-Item Scale (GAD-7)
- Work and Social Adjustment Scale (WSAS)
- Sheehan Disability Scale (SDS)
- EQ-5D-3L and EQ Visual Analogue Scale (VAS)
- Digit Symbol Substitution Test (DSST)

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 exploratory efficacy endpoints (change from Baseline in PANAS, GAD-7, WSAS, SDS, EQ-5D-3L, EQ-VAS, and DSST total scores at Week 3) were evaluated with a mixed model for repeated measures comparing COMP360 25 mg and 10 mg doses with the 1 mg dose

RESULTS

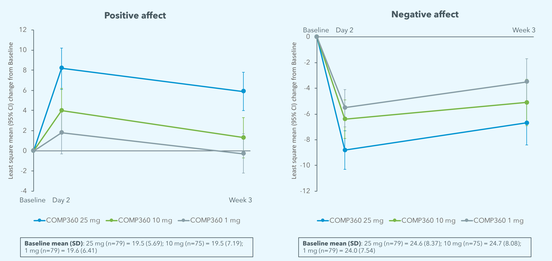
- 233 participants were randomized to COMP360 25 mg (N=79), 10 mg (N=75), or 1 mg (N=79). Baseline and clinical characteristics are summarized in **Table 1**
- At Week 3 post administration, change from Baseline in PANAS total score showed a least square mean difference (LSMD) that favored the COMP360 25 mg group for both positive (LSMD 6.2; 95% confidence interval [CI]: 3.5, 8.8) and negative (LSMD -3.2; 95% CI: -5.6, -0.8) affect compared with the 1 mg group (**Figure 1**)
- Similarly, at Week 3, change from Baseline in GAD-7 total score was greater in the COMP360 25 mg group (LSMD -1.8; 95% CI: -3.4, -0.2) compared with the 1 mg group (**Figure 2**)
- At Week 3, change from Baseline in WSAS total score was greater in the COMP360 25 mg group (LSMD -5.1; 95% CI: -8.4, -1.8) compared with the 1 mg group (**Figure 3A**)
- At Week 3, change from Baseline in SDS total score was greater in the 25 mg group (LSMD -6.5; 95% CI -9.5, -3.5) compared with the 1 mg group (**Figure 3B**)
- No differences were seen between the groups for quality of life (EQ-5D-3L and EQ-VAS) or cognition (DSST) with all groups showing an improvement over time on these measures (**Table 2**)

Table 1. Baseline and clinical characteristics (full 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 (8.20)	27.26 (6.03)	27.34 (6.86)
Prior psilocybin use, n (%)	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
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)
Baseline MADRS total score, mean (SD)	31.9 (5.41)	33.0 (6.31)	32.7 (6.24)	32.5 (5.99)
Severe depression at Baseline (HAM-D-17 total score ≥24), n (%)	22 (27.8)	26 (34.7)	20 (25.3)	68 (29.2)

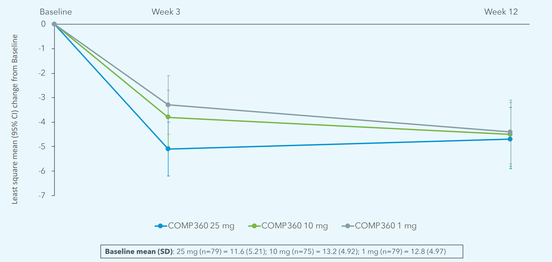
HAM-D 17: Hamilton Depression Rating Scale - 17-item scale; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: Major depressive disorder; n: Number of participants; SD: Standard deviation

Figure 1. Change from Baseline in PANAS positive and negative affect scores over time (full analysis set)



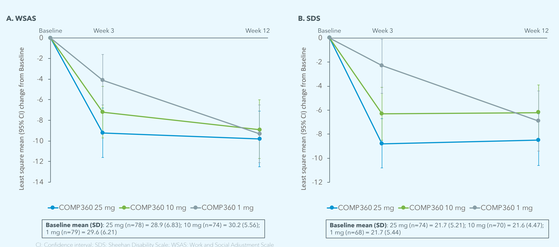
CI: Confidence interval; SD: Standard deviation

Figure 2. Change from Baseline in GAD-7 total score over time (full analysis set)



CI: Confidence interval; SD: Standard deviation

Figure 3. Change from Baseline in WSAS and SDS total scores over time (full analysis set)



CI: Confidence interval; SDS: Sheehan Disability Scale; WSAS: Work and Social Adjustment Scale

Table 2. Change from Baseline for additional exploratory efficacy endpoints at Week 3 (full analysis set)

	COMP360		
	25 mg (N=79)	10 mg (N=75)	1 mg (N=79)
EQ-5D-3L total score, LS mean change (SE)	0.20 (0.033)	0.14 (0.035)	0.14 (0.034)
LS mean difference vs. 1 mg (95% CI)	0.06 (-0.03, 0.15)	0.00 (-0.09, 0.09)	
EQ-VAS, LS mean change (SE)	11.1 (2.58)	8.7 (2.74)	4.4 (2.66)
LS mean difference vs. 1 mg (95% CI)	6.8 (-0.4, 13.9)	4.3 (-2.9, 11.5)	
DSST total score, LS mean change (SE)	6.8 (0.85)	5.7 (0.86)	5.5 (0.85)
LS mean difference vs. 1 mg (95% CI)	1.3 (-1.0, 3.6)	0.2 (-2.1, 2.5)	

CI: Confidence interval; DSST: Digit symbol substitution test; LS: Least square; SE: Standard error; VAS: Visual analog scale

CONCLUSIONS

- In combination with psychoeducation and support, COMP360 25 mg demonstrated additional participant benefits beyond reduction in depression symptoms
- These exploratory endpoint results support further development of COMP360 psilocybin therapy for TRD

References: 1. Russell JM, et al. *J Clin Psychiatry.* 2004;65(3):341-347. **2.** Johnston KM, et al. *J Affect Disord.* 2019;242:195-210. **3.** Passie T, et al. *Addict Biol.* 2002;7(4):357-364. **4.** Castro Santos H, et al. *Porto Biomed J.* 2021;6(1):e128. **5.** 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.

Disclosures

GMG, LM, SM, JT, SW, and EM are employees of COMPASS Pathfinder Ltd; SCS was an employee at the time the study was conducted.

SA has received research support from COMPASS Pathfinder Ltd and Neuronetics, and has served as a consultant for COMPASS Pathfinder Ltd, Sage Therapeutics, Biogen, Genomind, Janssen, LivaNova, and Neuronetics.

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DJH has received research funding support from COMPASS Pathfinder Ltd for psilocybin studies and from Eli Lilly, GeneSight, IntraCellular Therapies, Marinus, Pfizer, Relmada, and Takeda for other studies. He is also on the scientific advisory board at Reset Pharmaceuticals.

AHY's research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London. 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*.

SZ has received research funding support from COMPASS Pathfinder Ltd for psilocybin studies.

DF and MS have nothing to disclose.

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A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Response and remission rates

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ASCP: Abstract Number W21
Session Title: Poster Session 1

BACKGROUND

Treatment-resistant depression

- Treatment-resistant depression (TRD) is a common and debilitating condition that affects approximately 100 million people globally who are not helped by existing therapies[1]
- 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%)[2]
- Limited drug tolerability and poor adherence to prescribed therapy further complicate the ability of clinicians to provide effective treatment

Psilocybin and depression

- Psilocybin is a tryptamine alkaloid found in numerous species of *Psilocybe* mushrooms[3]
- 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[4]
- Safety and efficacy data from the largest randomized, controlled, double-blind study of psilocybin therapy to date recently demonstrated rapid, significant, and clinically meaningful reductions in depressive symptoms resulting from a 25 mg dose of COMP360 given in conjunction with psychoeducation and support[5]

OBJECTIVE

To evaluate the efficacy of COMP360 (COMPASS Pathways' proprietary, synthetic formulation of psilocybin) on response and remission rates and changes in self-reported depression scores in adults with TRD

METHODS

This was a multicenter, international, phase IIb, randomized, fixed-dose, double-blind study that assessed the safety and efficacy of COMP360 25 mg or 10 mg compared with COMP360 1 mg in participants with TRD

Study design

- After completing a ≥2-week washout of antidepressant treatments, eligible participants were randomized in a 1:1:1 ratio to a single administration of COMP360 (25 mg or 10 mg or 1 mg)
- After psychological preparation with a trained therapist, participants received COMP360 in a therapist-supported session that lasted approximately 6 to 8 hours
- Participants were asked to remain off all antidepressant treatments for at least 3 weeks following COMP360 administration
- Participants were followed for 12 weeks post COMP360 administration

Key inclusion criteria

- Aged 18 years and older
- Met *Diagnostic and Statistical Manual of Mental Disorders 5th edition* 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
- 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

Efficacy outcomes

- Montgomery-Åsberg Depression Rating Scale (MADRS)
  - Analyzed by blinded, remote assessor
  - Response criteria: ≥50% change from Baseline in MADRS total score
  - Remission criteria: MADRS total score ≤10
  - Sustained response criteria: Meeting MADRS response criteria at Weeks 3 and 12 and at least one other visit at Week 6 or 9
- Quick Inventory of Depressive Symptomatology - Self-Rated 16-Item Scale (QIDS-SR-16)

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
- Three key secondary efficacy endpoints (responders at Week 3, remitters at Week 3, and sustained responders at Week 12) were analyzed using a generalized linear mixed model (responders and remitters) or logistic regression model (sustained responders) comparing COMP360 25 mg and 10 mg doses with the 1 mg dose
- The exploratory efficacy endpoint of change from Baseline in QIDS-SR-16 total score at Week 3 was evaluated with a mixed model for repeated measures

RESULTS

- 233 participants were randomized to COMP360 25 mg (N=79), 10 mg (N=75), or 1 mg (N=79). Baseline and clinical characteristics are summarized in **Table 1**

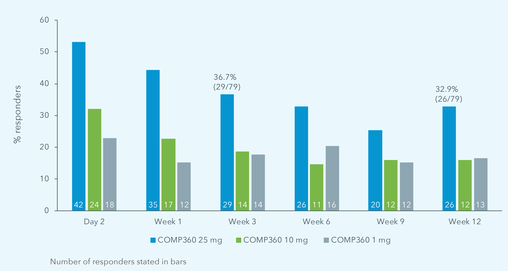
Table 1. Baseline and clinical characteristics (full analysis set)

	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; n: Number of participants; SD: Standard deviation

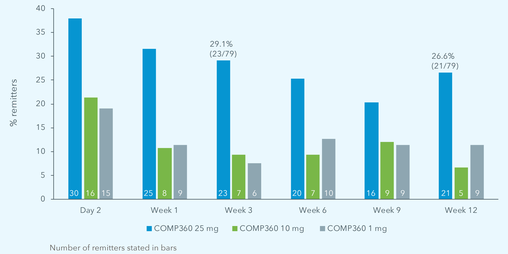
- At Week 3 post administration, 36.7% (n=29/79) of participants in the COMP360 25 mg group had responded compared with 17.7% (n=14/79) in the 1 mg group (**Figure 1**), and 29.1% (n=23/79) in the COMP360 25 mg group had remitted compared with 7.6% (n=6/79) in the 1 mg group (**Figure 2**)
- At Week 12 post administration, 24.1% (n=19/79) of participants in the COMP360 25 mg group were sustained responders compared with 10.1% (n=8/79) in the 1 mg group (**Figure 3**)
- Response and remission rates in the COMP360 10 mg group were comparable to those seen in the 1 mg group
- Change from Baseline in the QIDS-SR-16 total score was greater in the COMP360 25 mg group at Weeks 1, 2, and 3 compared with the 1 mg group with a least square mean treatment difference of -2.8 (95% confidence interval: -4.6, -0.9) at Week 3 (**Figure 4**)

Figure 1. Percentage of responders by visit (full analysis set)



Number of responders stated in bars

Figure 2. Percentage of remitters by visit (full analysis set)



Number of remitters stated in bars

Figure 3. Percentage of sustained responders at Week 12 (full analysis set)

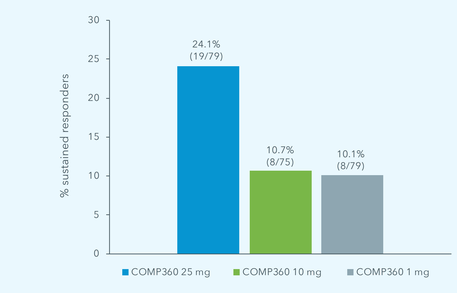
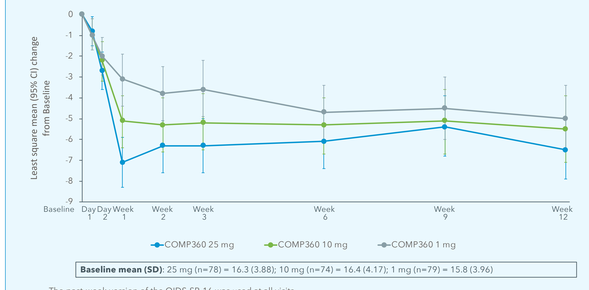


Figure 4. Change from Baseline in QIDS-SR-16 total score over time (full analysis set)



Baseline mean (SD): 25 mg (n=78) = 16.3 (3.88); 10 mg (n=74) = 16.4 (4.17); 1 mg (n=79) = 15.8 (3.96)

The past-week version of the QIDS-SR-16 was used at all visits.
CI: Confidence interval; QIDS-SR-16: Quick Inventory of Depressive Symptomatology - Self-rated 16-item scale; SD: Standard deviation

CONCLUSIONS

- In this international, multicenter, randomized, double-blind study of TRD, a single 25 mg dose of COMP360, administered with psychoeducation and support, generated a rapid antidepressant response that lasted up to Week 12 for almost a quarter of participants
- Response and remission rates in the 25 mg group were more than double the rates in the 1 mg group
- Self-reported outcomes of depression severity supported the primary endpoint results
- To further understand the durability of these effects beyond Week 12, a long-term study is underway
- 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

References: 1. Johnston KM, et al. *J Affect. Disord.* 2019;242:195-210. **2.** Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917. **3.** Passie T, et al. *Addict Biol.* 2002;7(4):357-364. **4.** Castro Santos H, et al. *Porto Biomed J.* 2021;6(1):e128. **5.** 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.

Disclosures

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DF and MS have nothing to disclose.

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COMP360 psilocybin therapy in treatment-resistant depression: Results of a large randomized controlled phase IIb monotherapy study and an exploratory uncontrolled adjunctive therapy study

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BACKGROUND

- COMP360 is COMPASS Pathways' proprietary, synthetic, and purified formulation of psilocybin that has received Breakthrough Therapy designation
- COMP360 was investigated in Study COMP 001, the largest randomized controlled study to date of psilocybin for the treatment of adult participants with treatment-resistant depression (TRD)
- COMP360 adjunct to a serotonergic antidepressant was also explored in Study COMP 003, a small open-label study on the treatment of adult participants with TRD

OBJECTIVES

- Study COMP 001: To evaluate the safety and efficacy of a single dose of COMP360 (25 mg or 10 mg) compared with 1 mg in the treatment of adult participants with TRD (ClinicalTrials.gov Identifier: NCT03775200)
- Study COMP 003: To evaluate the safety and efficacy of a single dose of COMP360 (25 mg) administered adjunctively to selective serotonin reuptake inhibitors (SSRIs) in the treatment of adult participants with TRD (ClinicalTrials.gov Identifier: NCT04739865)

METHODS

Study design

- Study COMP 001 was a randomized, double-blind, multicenter, international study in which participants with TRD washed out antidepressant medications (if applicable) for at least 2 weeks prior to Baseline. After a single COMP360 administration session on Day 1, participants were followed for 12 weeks. Initiation of antidepressant treatment prior to Week 3 was discouraged
- Study COMP 003 was an open-label study conducted at 2 sites in the United States and Ireland in which participants on a single serotonergic antidepressant received a single administration of COMP360 25 mg on Day 1 and were followed for 3 weeks
- The primary efficacy endpoint in both studies was change from Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score
- In both studies, COMP360 was administered with psychological support from a licensed and trained therapist to ensure psychological and physical safety. This included 3 preparation sessions prior to and 2 integration sessions after COMP360 administration
- In both studies, the MADRS was administered by blinded remote raters

Key inclusion criteria

- Aged 18 years and older
- Met *Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)* criteria for major depressive disorder (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
- 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
- Study COMP 003: Currently receiving 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

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

Outcome measures

- Analyses of efficacy were performed on the full analysis set, which included all participants who underwent randomization (Study COMP 001 only), received a single dose of COMP360, and had at least one post-Baseline efficacy assessment
- Primary efficacy endpoint: Change from Baseline in MADRS total score at Week 3 in both studies
- Key secondary efficacy endpoints
  - Proportion of participants with a response (criterion: 50% improvement [reduction] from Baseline in MADRS total score) at Week 3 in both studies
  - Proportion of participants with remission (criterion: MADRS total score ≤10) at Week 3 in both studies
  - Study COMP 001 only: Sustained response at Week 12 (criterion: Response at Weeks 3 and 12 and at least one other visit at Week 6 or 9)

Safety outcome measures

- Analyses of safety were performed on the safety analysis set, which included all participants who underwent randomization (Study COMP 001 only) and received a single dose of 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

Participant disposition

- Study COMP 001 (**Figure 1A**): 233 participants received double-blind COMP360 25 mg (N=79), 10 mg (N=75), or 1 mg (N=79)
- Study COMP 003 (**Figure 1B**): 19 participants received open-label COMP360 25 mg adjunctive to escitalopram (n=6), sertraline (n=6), fluoxetine (n=3), vilazodone (n=2), paroxetine (n=1), or citalopram (n=1)

Figure 1A. COMP 001 CONSORT participant flow diagram

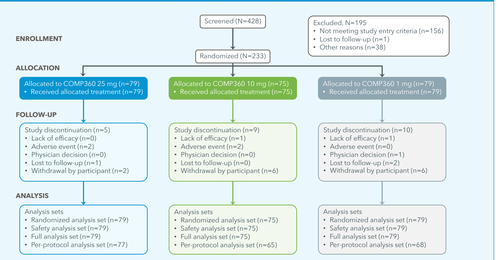
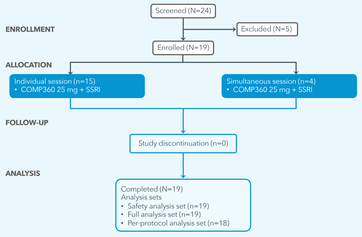


Figure 1B. COMP 003 CONSORT participant flow diagram



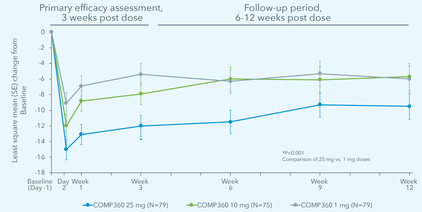
Baseline and clinical characteristics

- Majority of participants were female with a mean age of approximately 40 years
  - Study COMP 001: 51.9% female, mean (standard deviation [SD]) age of 39.8 (12.19) years
  - Study COMP 003: 68.4% female, mean (SD) age of 42.2 (10.80) years
- Baseline MADRS total scores were consistent with moderate-to-severe depression symptoms
  - Study COMP 001: Mean (SD) Baseline MADRS total score of 32.5 (5.99)
  - Study COMP 003: Mean (SD) Baseline MADRS total score of 31.7 (5.77)
- Majority of participants had 2 prior antidepressant treatment failures in the current episode
  - Study COMP 001: 82.0% had 2 prior treatment failures, 15.9% had 3 or 4 prior treatment failures
  - Study COMP 003: 63.2% had 2 prior treatment failures, 36.8% had 3 or 4 prior treatment failures

Efficacy

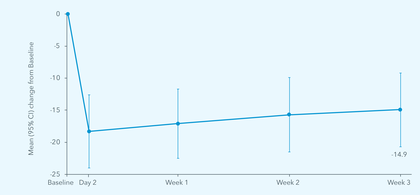
- Changes in MADRS from Baseline to Week 3 in Study COMP 001 and Study COMP 003 are shown in **Figures 2A** and **2B**, respectively.
- In both studies, a clinically meaningful improvement in MADRS total score was rapid and evident at Day 2 after administration of COMP360 25 mg
- Response and remission rates at Week 3 for COMP360 25 mg were 36.7% and 29.1%, respectively, in Study COMP 001 (**Figure 3A**) and 42.1% and 42.1%, respectively, in Study COMP 003 (**Figure 3B**)
- Study COMP 001: 24.1% of participants who received the COMP360 25 mg dose were sustained responders at Week 12. In the 10 mg dose group, the sustained response rate was 10.7%; in the 1 mg dose group, it was 10.1%

Figure 2A. COMP 001 change from Baseline in MADRS total score up to Week 12 (full analysis set)



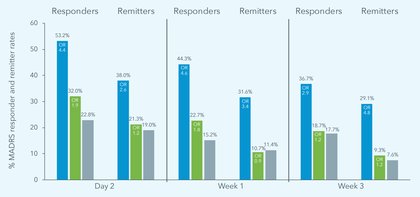
MADRS: Montgomery-Asberg Depression Rating Scale; N: Number included in analysis; SE: Standard error

Figure 2B. COMP 003 mean change from Baseline in MADRS total score up to Week 3 (full analysis set)



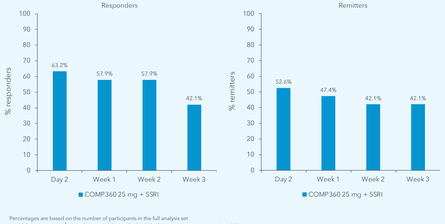
CI: Confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; SSRI: Selective serotonin reuptake inhibitor

Figure 3A. COMP 001 MADRS response and remission rates (full analysis set)



Percentages are based on the number of participants in the full analysis set
MADRS: Montgomery-Åsberg Depression Rating Scale; N: Number included in analysis; OR: Odds ratio (vs. COMP360 1 mg)

Figure 3B. COMP 003 MADRS response and remission rates (full analysis set)



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

Safety

- No clinically significant changes in vital signs, clinical laboratory tests, or 12-lead ECG results were observed in either study
- In each study, over 90% of TEAEs were mild or moderate in severity
- Study COMP 001
  - The proportion of participants with any TEAE during the full 12-week follow-up period was 83.5% in the 25 mg, 74.7% in the 10 mg, and 72.2% in the 1 mg groups. Rates of specific AEs by study time period are shown in **Table 1**
  - TESAEs were reported in 5 participants in the 25 mg, 6 in the 10 mg, and 1 in the 1 mg groups
  - Three non-responding participants at Week 3 in the 25 mg group had a TESAE of suicidal behavior; in all cases, the TESAE occurred >4 weeks after COMP360 administration
  - Mean change from Baseline in MADRS item 10 (suicidal ideation) did not show worsening in any group
  - Shift analyses from Baseline to worst post-Baseline C-SSRS score did not show a greater proportion of participants with worsening suicidal ideation in the 25 mg or 10 mg groups compared with the 1 mg group
- Study COMP 003
  - The proportion of participants with any TEAE during the 3-week follow-up period was 57.9%
  - No TESAEs were reported

Table 1: COMP 001 incidence of TEAEs ≥5% (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

n: Number of participants; TEAE: Treatment-emergent adverse event; TESAE: Treatment-emergent serious adverse event

CONCLUSIONS

- Single administration of COMP360 25 mg psilocybin appears to be a rapid, efficacious, and well-tolerated monotherapy for adult participants with TRD. The encouraging findings in the adjunctive setting warrant further investigation. The safety and efficacy of COMP360 25 mg should be further evaluated in large controlled, confirmatory studies

Disclosures

GMG, LM, SM, CS, JT, SW, and EM are employees of COMPASS Pathfinder Ltd; SCS was an employee at the time the study was conducted.

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