Results From a Long-Term Observational Follow-Up Study of a Single Dose of Psilocybin for a Treatment-Resistant Episode of Major Depressive Disorder

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Abstract

Background: The largest randomized study of psilocybin to date demonstrated the efficacy of COMP360 25 mg (Compass Pathways' investigational proprietary pharmaceutical-grade synthesized psilocybin formulation) in participants with treatment-resistant depression (COMP 001), compared with 10 mg and 1 mg doses. Here, we report findings from COMP 004, a 52-week observational follow-up of patients from COMP 001 and COMP 003, a small open-label study of the coadministration of 25 mg COMP360 with continuing antidepressant treatment.

Methods: Adverse events (AEs) were collected over the full 52-week period. The primary efficacy endpoint was time to a prespecified depressive event over the 52 weeks following COMP360 administration in COMP 001 participants, presented as Kaplan-Meier estimates. A post hoc analysis included only participants that entered COMP 004. Data were collected from July 2020 to July 2022.

Results: Sixty-six participants entered COMP 004 (COMP 001, n = 58 [25 mg group n = 22, 10 mg group n = 19, 1 mg group n = 17]; COMP 003, n = 8). Few AEs were reported post-entry into COMP 004, with 1 AE of mild suicidal ideation in the 1 mg group deemed possibly related to study drug. For all COMP 001 patients (n = 233), median time to depressive event was greater for the 25 mg group (92 days) compared to the 10 mg (83 days) and 1 mg (62 days) groups, with the majority of participants having had a depressive event by Week 12 (25 mg n = 37/75, 10 mg n = 38/79, 1 mg n = 44/75). The post hoc supplementary analysis of those who enrolled in COMP 004 from COMP 001 exhibited the difference between groups more strikingly (25 mg, 189 days; 10 mg, 43 days; 1 mg, 21 days); however, only 10 participants experienced a depressive event post-COMP 004 enrollment (25 mg n = 6, 10 mg n = 3, 1 mg n = 1) from COMP 001 and none from COMP 003. At COMP 004 entry, the 1 mg group had the highest number of participants on antidepressant medication (n = 10; 10 mg, n = 9; 25 mg, n = 6) and generally initiated treatment earlier.

Conclusion: Over 52 weeks, a single administration of 25 mg psilocybin suggested longer maintenance of antidepressant effect than both 1 mg and 10 mg. Larger long-term studies are required to confirm these findings and provide clarity on the longer-term effects of psilocybin.

Trial Registration: ClinicalTrials.gov identifier: NCT04519957.

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Treatment-resistant depression (TRD) is a major public health challenge, with more than 100 million people affected globally.[1] TRD is commonly defined as the absence of response after treatment with at least 2 antidepressant medications of adequate dose and duration during an episode of major depressive disorder (MDD).[2] In comparison to non-treatment-resistant MDD, TRD is associated with higher rates of relapse, suicidality, and residual symptoms.[3–6] A recent reanalysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study underscored the limited efficacy of existing antidepressant treatments.[7,8] Only 25.5% of participants experienced a remission of their MDD following initial treatment with citalopram, and the cumulative remission rate following up to four 12-week trials of antidepressant treatment was only between one- to two-thirds of participants. Furthermore, significant improvements in depression with traditional

Clinical Points

- Psilocybin has been explored as a potential new treatment for treatment-resistant depression; however, there is little research investigating the longer term safety and efficacy of this drug.
- Results presented here from the largest 52-week randomized controlled trial of psilocybin treatment to date suggest that a single administration of psilocybin treatment is safe in the longer term and may provide long-lasting clinical benefit.

antidepressant pharmacotherapies typically take 4–8 weeks.

In recent years, the short-term efficacy of the serotonin 2a receptor partial agonist, psilocybin, has been demonstrated in randomizedcontrolled trials (RCTs) for depression.[9–12] In the largest phase 2b RCT of psilocybin to date (N = 233), 29.1% of participants with TRD who received a single dose of 25 mg of psilocybin alongside psychological support achieved remission by 3 weeks post-administration.[9] Three months post-psilocybin treatment, over twice as many participants in the 25 mg group (20.3%) exhibited sustained response compared to the 10 mg (5.3%) and 1 mg (10.1%) groups. Additionally, the efficacy of 25 mg psilocybin compared to 1 mg was already evident the day immediately following administration. In terms of safety, psilocybin was deemed well-tolerated. Adverse events, including suicidal ideation and behavior, were reported in all dose groups.

However, data on long-term efficacy and safety outcomes of psilocybin on depression are limited. One open-label study following 20 participants with TRD out to 6 months after 2 administrations of psilocybin (10 mg and 25 mg, 7 days apart) reported pronounced reductions in symptoms of depression at both 3 and 6 months (Cohen $d = 1.5$ and 1.4, respectively, both $P < .001$).[13] Another open-label study using a waitlist controlled design followed 24 participants with MDD for 12 months after 2 doses of psilocybin and observed 75% response and 58% remission at the final time point.[14]

While the data from these MDD studies are promising, they are limited by their sample size and open-label design, and, to date, no RCTs have provided data on the long-term outcomes following psilocybin treatment of TRD—a harder-to-treat population in comparison to MDD.

This study assessed depression outcomes and treatment-emergent adverse events over 52 weeks in participants with TRD who had received Compass Pathfinder Ltd's investigational proprietary pharmaceutical-grade synthetic formulation of psilocybin, COMP360, administered with psychological support.[15]

MATERIALS AND METHODS

Participants

Participants who completed the final visit (ie, week 12 post-psilocybin administration) in COMP 001 (ClinicalTrials.gov ID: NCT03775200), the largest phase 2b RCT of psilocybin in participants with TRD to date (N = 233), were eligible to enroll in COMP 004, a 40-week observational follow-up study that began after week 12 of COMP 001 (ClinicalTrials.gov ID: NCT04519957). This included participants who had already experienced a depressive event in COMP 001. Participants were only excluded from entering COMP 004 if they had any condition for which, in the opinion of the investigator, participation would not be in the interest of the participant.

The COMP 004 protocol also allowed enrollment from COMP 003 (ClinicalTrials.gov ID: NCT04739865), a 3-week, phase 2, open-label study that explored the safety and efficacy of COMP360 25 mg as an adjunctive to ongoing selective serotonin reuptake inhibitors in participants with TRD[16] (N = 19).

Trial Design and Procedures

Participants who entered COMP004 were followed to 52 weeks post-COMP360 psilocybin treatment. No further pharmacological treatment or psychological support was provided. Training for the non-directive psychological support received alongside COMP360 administration in COMP 001 and 003 is described in Tai et al.[15] Stable psychotherapies that were initiated prior to entry into the COMP 001 lead-in study were permitted to be continued through COMP 001. In COMP 004, there were no restrictions on newly initiated treatments, including psychotherapies. Blinding from initial treatment allocation in COMP 001 was maintained through to week 52 (details from the COMP 001 study can be found in Goodwin et al[9]).

Safety and efficacy assessments were performed throughout the study. Investigator assessments, including the Montgomery-Asberg Depression Rating Scale (MADRS), were performed at weeks 16, 20, 24, 28, 40, and 52. COMP 003 also had assessments at weeks 6, 9, and 12. All visits were instructed to be remote, with in-person visits possible at the investigators' discretion. The MADRS was administered by a blinded independent rater. Full details of all assessments performed can be found in the Schedule of Assessments (Supplementary Table 1).

The protocol was approved by independent ethics committees or institutional review boards at each site, and the study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. All participants provided written informed consent.

Source of funding and role of the sponsor. This study was funded and designed by the sponsor, Compass Pathfinder Ltd (a subsidiary of Compass Pathways plc). It was conducted at 15 sites across North America and Europe.

Efficacy End Points

The prespecified primary end point was time to the first of any of the following depressive events, starting from baseline, which was 1 day prior to psilocybin administration in the previous lead-in study (COMP 001), in participants recruited from COMP 001 only.

Depressive events were defined a priori and included the following:

- Initiation of new antidepressant treatment, including pharmacologic, psychological, or somatic treatments;
- Hospitalization due to depression or suicidality;
- Suicide attempt, prevention of an imminent suicide attempt, or completed suicide;
- Increased suicidality measured by worsening on MADRS item 10, defined as either
  - a MADRS item 10 score of 5 or 6 or
  - a MADRS item 10 score of ≥3 that was an increase of at least 2 points compared to baseline
- Worsening on the MADRS defined as either
  - an increase of ≥5 points on the MADRS total score compared to baseline score at any time point post-baseline or
  - MADRS total score ≥15 and an increase of ≥5 points across 2 or more consecutive visits. In this case, the first date of the ≥5 point increase was classed as the time of event. If the ≥5 point worsening occurred at the final visit, it qualified as a depressive event without need for confirmation at a subsequent visit
- Discontinuation for an MDD-related adverse event (AE), eg, depression that led to withdrawal, or for lack of efficacy.

The criteria used here to characterize a depressive event are comprehensive in capturing clinically relevant aspects of depression, and thus, the time taken to experience one of these events is an appropriate measure.

These criteria were also used for the exploratory end point of COMP 003 participants only.

Safety End Points

Safety end points included the incidence and severity of AEs for participants enrolling from both COMP 001 and COMP 003.

Statistical Analysis

All analyses were based on the randomized groups receiving a single dose of 25 mg, 10 mg, or 1 mg psilocybin treatment received in COMP 001 and 25 mg open label in COMP 003. As participation in the study was optional and enrollment included the prerequisite of completing the COMP 001 or COMP 003 lead-in studies, we were unable to know the sample size in advance. Due to the low number of participants that did enroll into COMP 004 and the unpowered nature of the study, no formal significance testing was performed.

Primary end point analysis. The time to first depressive event was estimated for each treatment group using a Kaplan-Meier approach and informally compared across treatment groups. Thus, the prespecified primary analysis included all 233 participants enrolled in COMP 001 who completed at least 1 efficacy assessment in that study (modified full analysis set [mFAS]). Early depressive events that actually occurred in COMP 001 were therefore incorporated into this primary end point analysis. Participants who did not experience a depression-related event in COMP 001 and did not enroll in COMP 004 were censored at the time of study discontinuation or completion in COMP 001. Additionally, participants who enrolled into COMP 004 but completed or discontinued prior to experiencing a depressive event were censored at the time of study completion or discontinuation.

A post hoc supplementary analysis was performed for the primary end point that included only the participants from COMP 001 who enrolled in COMP 004 (FAS).

Safety end point analysis. Data regarding the type and frequency of AEs were summarized for safety end points. Types of AEs included treatment emergent AEs (TEAEs), serious AEs (SAEs), treatment-emergent serious AEs (TESAEs), and adverse drug reactions (ADRs), defined as an AE deemed to be related or possibly related to the drug by the Investigator.

RESULTS

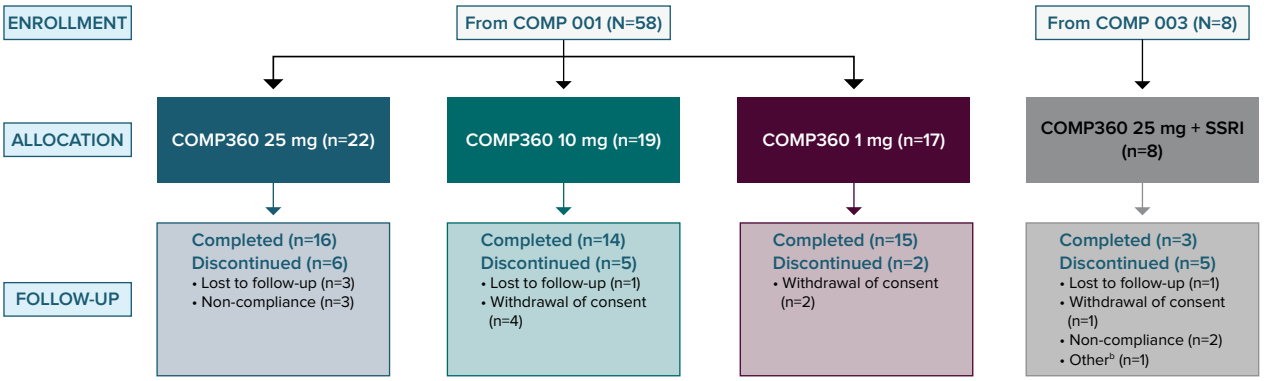
Participants

The current study was started partway through the COMP 001 study, and so not all completers from this study could enroll into COMP 004. Of the 126 completers from COMP 001 who were offered the opportunity to participate in COMP 004, 58 (46%) consented, with 45 of these participants completing the COMP 004 final study visit. For COMP 003, 8 (of the original 19) participants entered COMP 004. See Figure 1 for participant disposition.

From the full COMP 001 population, the number of participants (n) who had already experienced a depressive event in COMP 001 (ie, by week 12) were 25 mg group, n = 37; 10 mg group, n = 38; 1 mg group, n = 44.

Demographics and baseline clinical characteristics were similar between treatment groups (Table 1). These data were largely consistent with the characteristics reported in COMP 001,[9] with slight differences between

Figure 1.
Participant Disposition[a]



[a]Allocation to study drug was randomized at baseline of the COMP 001 study, and participants remained in these groups through to week 52. Noncompliance here describes participant noncompliance with protocol defined assessments.
[b]Participant withdrew consent and no longer wanted to continue in the study.
Abbreviations: N = number included in analysis, n = number of participants, SSRI = selective serotonin reuptake inhibitor.

Table 1.
Participant Demographics and Baseline Disease Characteristics

	COMP 004				
Parameter	COMP 001 psilocybin 25 mg (N = 22)	COMP 001 psilocybin 10 mg (N = 19)	COMP 001 psilocybin 1 mg (N = 17)	COMP 003 psilocybin 25 mg + SSRI (N = 8)	Overall (N = 66)
Sex, n (%)					
Female	10 (45.5)	10 (52.6)	9 (52.9)	3 (37.5)	32 (48.5)
Race, n (%)					
White	20 (90.9)	19 (100.0)	17 (100.0)	6 (75.0)	62 (93.9)
Age at screening (y)[a]					
Mean (SD)	38.7 (13.14)	40.7 (13.83)	42.6 (9.68)	45.8 (8.56)	41.1 (12.04)
Prior psilocybin experience, n (%)					
Yes	1 (4.5)	2 (10.5)	0	–	3 (4.5)
Length of current depressive episode, n (%)					
<1 y	3 (13.6)	3 (15.8)	3 (17.6)	2 (25.0)	11 (16.7)
≥1 to <2 y	7 (31.8)	6 (31.6)	4 (23.5)	4 (50.0)	21 (31.8)
≥2 y	12 (54.5)	10 (52.6)	10 (58.8)	2 (25.0)	34 (51.5)
HAM-D-17 baseline[b] severity categories, n (%)					
Moderate (18–23)	16 (72.7)	14 (73.7)	13 (76.5)	7 (87.5)	50 (75.8)
Severe (≥24)	6 (27.3)	5 (26.3)	4 (23.5)	1 (12.5)	16 (24.2)
Baseline[b] MADRS total score					
Mean (SD)	31.6 (4.69)	31.9 (5.14)	33.7 (4.28)	32.4 (6.84)	–

[a]Screening refers to the COMP 001 or COMP 003 screening visit.
[b]Baseline refers to the COMP 001 or COMP 003 baseline visit.
Abbreviations: HAM-D-17 = Hamilton Depression Rating Scale (17-item), MADRS = Montgomery-Asberg Depression Rating Scale, max = maximum, min = minimum, n = number, SD = standard deviation; , SSRI = selective serotonin reuptake inhibitor.

studies observed in recruitment region. Specifically, in COMP 004, a greater proportion of participants were recruited from North America (65.1%) compared to Europe (43.8%) than in COMP 001. Similar was seen for COMP 003, with differences in sex being most prominent (Supplementary Table 2A and 2B). However, MADRS endpoint scores at week 12 (the final study visit of COMP 001 and the point of enrollment for entry to COMP 004) for the subset of COMP 001 participants who entered into COMP 004 were not fully representative of the full COMP 001 population at the equivalent timepoint at completion of COMP 001. Specifically, for the 10 mg group in COMP 004, the mean MADRS total score change from baseline to week 12 was greater than that of the full COMP 001 population. Additionally, there was a higher percentage of 10 mg participants who demonstrated remission and sustained response at week 12 in COMP 004 than at week 12 in COMP 001 overall.

In the 1 mg group, the percentage of participants who were remitters at week 12 was lower for those entering COMP 004 than at week 12 in the full COMP 001 population (Supplementary Table 3).

In COMP 003, most participants were responders and remained so at most observation timepoints.

Efficacy

Time to first depression-related event. Among all participants from COMP 001, the proportion of participants with any depression-related event was similar across all treatment groups (25 mg, 54.4%, n = 43; 10 mg, 54.7%, n = 41; and 1 mg, 57.0%, n = 45). The most frequently reported events were initiation of new antidepressant treatment (25 mg, 48.1%, n = 38; 10 mg, 38.7%, n = 29; and 1 mg, 43.0%, n = 34) and worsening MADRS total scores (25 mg, 21.5%, n = 17; 10 mg, 18.7%, n = 14; and 1 mg, 22.8%, n = 18) (Supplementary Table 4).

In the primary analysis, which included all participants from the COMP 001 study, median time to depression-related event was longer for participants in the 25 mg and 10 mg groups compared with those in the 1 mg group; median (95% CI) of 92 days (49–199) for the 25 mg group compared with 83 days (39–142) for the 10 mg group and 62 days (28–NE) for the 1 mg group (Figure 2A).

The post hoc supplementary analysis that included only those completers from the COMP 001 study who entered COMP 004 indicated an even longer median time to depressive event in the 25 mg group (median [95% CI]: 189 days [24, -]) compared with the 10 mg (43 days [19–142]) and 1 mg (21 days [3–78]) groups (Figure 2B; Supplementary Table 5).

For participants from COMP 003, 2 participants experienced a depressive event (both MADRS worsening). Due to the low number of participants, the quartile estimates and corresponding CIs could not be calculated for this cohort.

New treatments for depression. The proportion of participants in the 1 mg group receiving new treatment for depression was numerically greater at 76.5% (n = 13). The 10 mg and 1 mg groups initiated treatments earlier post-COMP360 administration compared to the 25 mg group. Among the COMP 001 completers, at the time of entry into COMP 004 (ie, 12 weeks post-psilocybin administration), 58.8% (n = 10) of participants in the 1 mg group had started a new antidepressant treatment compared to 27.3% (n = 6) in the 25 mg group and 47.4% (n = 9) in the 10 mg group (Table 2). By Week 52, the proportion of participants who had started a new antidepressant treatment was similar between the 25 mg and 10 mg groups (54.5% [n = 12] vs 57.9% [n = 11], respectively).

Safety

There were 61 TEAEs in 27 participants in COMP 004 that were ongoing from the COMP 001 study or started after entry into COMP 004 (Table 3). The most common TEAE was COVID-19, reported in 13.8% (n = 8) of participants. All other reported TEAEs occurred in 2 or fewer participants. Safety and tolerability data from the first 12 weeks in COMP 001 has been reported in Goodwin et al, 2022.[1] No TEAEs were reported in COMP 003 participants after entry into COMP 004.

No participants experienced AEs that led to study withdrawal by participant or death.

In terms of ADRs, 9 events were reported as ongoing at or occurring after entry into COMP 004 by 4 participants. One 25 mg participant had ADRs of decreased appetite and altered mood (onset 4 days post-administration and ongoing), and anxiety (onset 5 days post-administration and ongoing). One 10 mg participant had the ADRs of affect lability and irritability (onset day of administration and ongoing). In the 1 mg group, 2 participants had ADRs. These were insomnia (onset 13 days post-administration and ongoing) for 1 participant and altered time perception (onset 4 days post-administration and ongoing) and suicidal ideation (onset 96 days post-administration and resolved by Day 108) for the second participant.

After entry into COMP 004, 4 TESAEs were reported by 3 participants, which were all deemed not related to study drug, as determined by investigator judgment (Table 3). In the 25 mg group, 1 participant had a TESAE of suicidal ideation and was hospitalized on Study Day 307. In the 1 mg group, 1 participant had a TESAE of breast cancer, and 1 participant had 2 TESAEs of therapy change requiring hospitalization, which were due to moderate suicidal ideation at both occurrences. No TESAEs were reported in COMP 003 patients.

A nonserious TEAE of mild suicidal ideation in the 1 mg group was reported as possibly related to study drug, occurring after entry into COMP 004. This AE began during the COMP 001 study at day 86 as moderate suicidal ideation, with the reduction in severity reported post-COMP 004 enrollment at day 96, and resolving within 2 weeks.

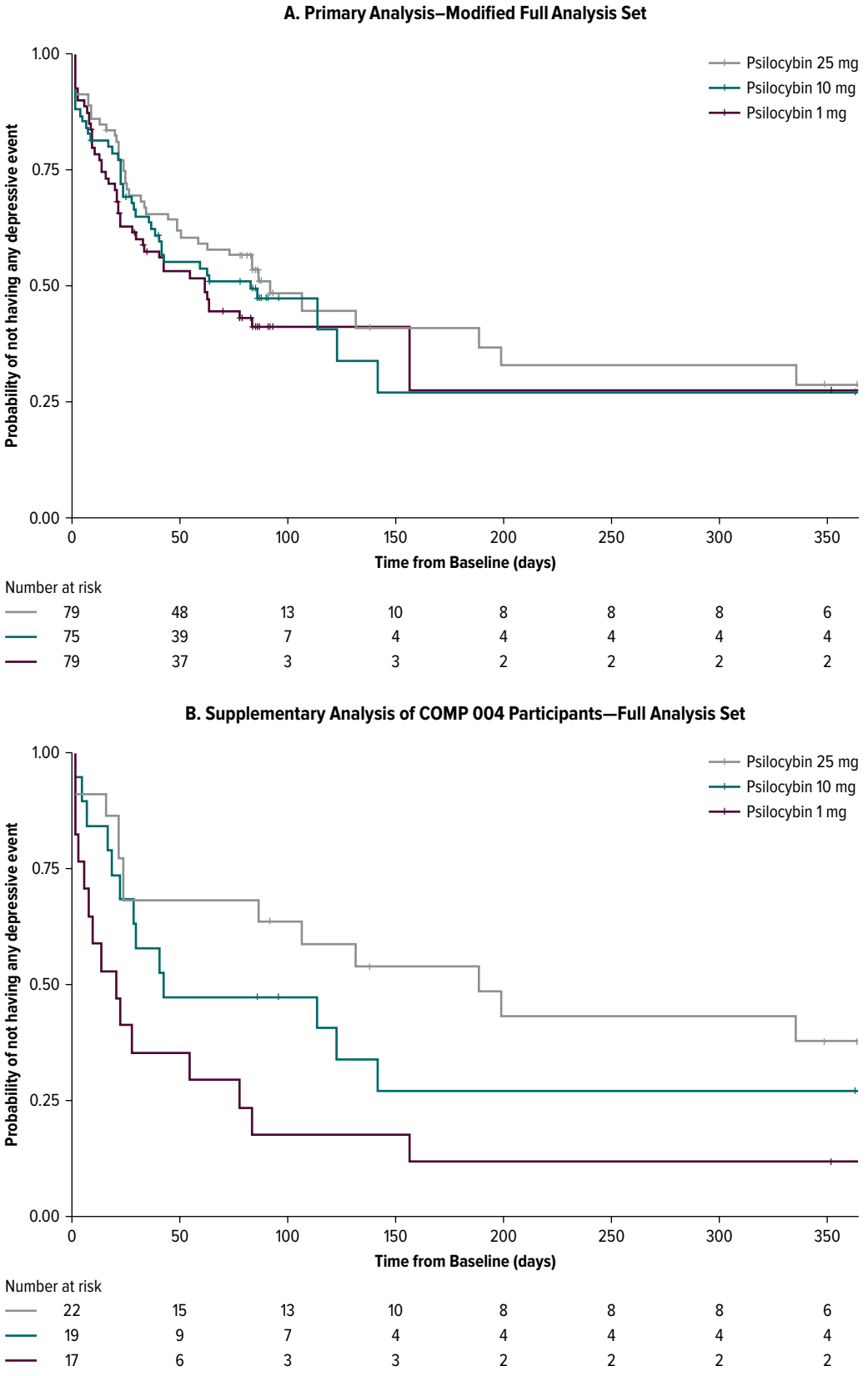
DISCUSSION

The current study investigated the long-term safety and efficacy of a single administration of 25 mg, 10 mg, or 1 mg COMP360 psilocybin monotherapy, or 25 mg COMP360 psilocybin adjunctive to an ongoing antidepressant, alongside psychological support, over a 52-week period in participants with TRD. The results should be regarded as simply descriptive.

In the primary analysis, which included all participants from the COMP 001 study (n = 233), those who received 25 mg psilocybin exhibited a longer median time from administration to depressive event compared to those who received 1 mg. However, 74 of the 114 participants who completed the 12-week COMP 001 study without experiencing a depressive event did not

Figure 2.

Kaplan-Meier Plots of Time to Any Depressive Event[a]



[a]Crosses on the figure represent participants who have been censored.

Table 2.

Timing of Initiation of New Treatments for Depression

Parameter visit	Psilocybin 25 mg (N = 22) n (%)	Psilocybin 10 mg (N = 19) n (%)	Psilocybin 1 mg (N = 17) n (%)	Overall (N = 58) n (%)
Had started new treatment for depression by visit:				
Day 2	0	0	0	0
Week 1	0	1 (5.3)	3 (17.6)	4 (6.9)
Week 3	2 (9.1)	4 (21.1)	6 (35.3)	12 (20.7)
Week 6	4 (18.2)	7 (36.8)	8 (47.1)	19 (32.8)
Week 9	6 (27.3)	9 (47.4)	8 (47.1)	23 (39.7)
Week 12	6 (27.3)	9 (47.4)	10 (58.8)	25 (43.1)
Week 16	8 (36.4)	9 (47.4)	12 (70.6)	29 (50.0)
Week 20	9 (40.9)	11 (57.9)	12 (70.6)	32 (55.2)
Week 24	9 (40.9)	11 (57.9)	13 (76.5)	33 (56.9)
Week 28	10 (45.5)	11 (57.9)	13 (76.5)	34 (58.6)
Week 40	10 (45.4)	11 (57.9)	13 (76.5)	34 (58.6)
Week 52	12 (54.5)	11 (57.9)	13 (76.5)	36 (62.1)

Table 3.

Summary of Treatment-Emergent Adverse Events Ongoing or Starting After Week 12—Safety Analysis Set

	Psilocybin 25 mg (N = 22)		Psilocybin 10 mg (N = 19)		Psilocybin 1 mg (N = 17)		Overall (N = 58)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	8 (36.4)	16	6 (31.6)	16	13 (76.5)	29	27 (46.6)	61
Any TESAE	1 (4.5)	1	0	0	2 (11.8)	3	3 (5.2)	4
Any ADR	1 (4.5)	3	1 (5.3)	2	2 (11.8)	4	4 (6.9)	9
Any SAR	0	0	0	0	0	0	0	0
Any severe TEAE	1 (4.5)	1	0	0	1 (5.9)	1	2 (3.4)	2

Abbreviations: ADR = adverse drug reaction, AE = adverse event, n = number, SAE = serious adverse event, SAR = serious adverse reaction, SSRI = selective serotonin reuptake inhibitor, TEAE = treatment-emergent adverse event.

continue into COMP 004. The post hoc supplementary analysis, which included only those participants who enrolled into COMP 004 (n = 58), reveals a more striking difference between the treatment groups in time to depressive event. However, this group may have been unrepresentative of the full cohort of patients from COMP 001. The number of depressive events was similar between the dose groups in the primary analysis, and for each type of depressive event.

Over 75% of participants in the 1 mg group had started a new antidepressant treatment by week 52 compared to approximately half in the 25 mg group, and at an earlier timepoint. While the 25 mg and 10 mg groups had similar proportions of new antidepressant treatment initiation, those in the 25 mg group tended to initiate later.

In those participants entering COMP 004, differences in TEAEs were evident between groups, with over 75% of participants (n = 13) in the 1 mg group experiencing an AE post-COMP 004 enrollment, compared to approximately a third of participants in the 25 mg (n = 8) and 10 mg (n = 6) groups. In terms of TESAEs, just 3 participants reported experiencing a TESAE post-enrollment to COMP 004, occurring more than 6 months after administration and all deemed unrelated to study drug.

We did not see persisting hallucinations (symptoms associated with hallucinogen persisting perception disorder [HPPD]), which have been associated with exposure to psychedelic drugs, usually in recreational settings.[17] Similarly, HPPD was not recorded during the COMP 001 study. Although the report of suicidal ideation in the 1 mg group was deemed possibly related to drug, the participant was taking antidepressant concomitant medications during this time.

Limitations

A key limitation was the modest sample size in COMP 004. This was due to the later study initiation relative to the COMP 001 study because of the COVID-19 pandemic, which limited the number eligible, and the low rate (46%) of participants who were offered enrollment providing consent.

Study entry was optional with no further treatment or compensation offered; therefore, there was little tangible incentive to continue. This low rate of enrollment into COMP 004 resulted in a high rate of censoring at the time of COMP 001 completion in the primary time to event analysis (31.8% of participants from COMP 001).

The analyses based solely on the participants that enrolled into COMP 004 are limited by the resulting selection bias; for example, the proportion of participants that were sustained responders in the 10 mg and 1 mg groups at entry into COMP 004, week 12, was lower than, and so not fully representative of, the COMP 001 population at that timepoint.

Due to the small sample size, statistical analyses formally comparing time to depressive event between the treatment groups were not performed.

CONCLUSION

Overall, results of this study have suggested the safety of a single administration of COMP360 psilocybin treatment in participants with TRD over a 52-week period. Clinical benefits were observed out to approximately 6 months post-administration. The long-term effects observed in this study are generally consistent with results from Carhart-Harris and colleagues,[13] which was a smaller, repeat-dose, open-label trial.

While these results are promising and begin to address the gap in the literature, their limitations mean that larger longer term studies are necessary to provide clarity on the effects of psilocybin in TRD. This study will help inform future longer term trial designs.

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Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Results From a Long-Term Observational Follow-Up Study of a Single Dose of Psilocybin for a Treatment-Resistant Episode of Major Depressive Disorder

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Supplementary Table 1: Schedule of Assessments for COMP 004

Visit	COMP 004 Enrolment Visit	Week 6[a]	Week 9[a]	Week 12[a]	Fortnightly online assessments[b]	Week 16	Week 20	Week 24	Week 28	Week 40	Week 52
Location of visit	**Clinic**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**	**Remote**
Allowable window **(Timepoints from baseline in COMP 001 and COMP 003)**	**Within 3 weeks of final COMP 001/COMP 003 visit**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**	**±14 days**
Clinic Assessments and Procedures											
Informed Consent	✓										
Inclusion/Exclusion Criteria	✓										
Activate/Deactivate Measure Health app (optional)	✓										✓
Set up and practice using the online assessment system	✓										
Participant Completed Assessments											
EQ-5D-3L				✓	✓						
QIDS-SR-16		✓	✓	✓	✓						
GAD-7				✓	✓						
WSAS				✓	✓						
TiC-P	✓			✓	✓						

Study Feedback Survey									✓
Investigator Assessments									
MADRS	✓	✓	✓		✓	✓	✓	✓	✓	✓
SDS			✓		✓	✓	✓	✓	✓	✓
Concomitant Medications/Therapies	✓	✓	✓		✓	✓	✓	✓	✓	✓
AEs/SAEs	✓	✓	✓		✓	✓	✓	✓	✓	✓

Abbr: EQ-5D-3L, EuroQol-5 Dimensions-3 Levels; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 Items; GAD-7, General Anxiety Disorder Questionnaire-7 Items; WSAS, Work and Social Adjustment Scale; TiC-P, Treatment Inventory of Costs in Patients with psychiatric disorders; MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; AE, adverse event; SAE, serious adverse event

[a] COMP 003 participants only

b From Week 14 onwards. The EQ-5D-3L, GAD-7, and WSAS will be rotated so the participants complete a total of two questionnaires digitally each week ie the QIDS-SR-16 and one of the following: EQ-5D, GAD-7 and WSAS. The EQ-5D will be asked at week 14, GAD-7 at week 16, WSAS at week 18 and this order will be repeated up to and including week 52

Supplementary Table 2a:

Participant Demographics and Baseline Disease Characteristics for all COMP 003 Participants

	COMP 001			
Parameter	**Psilocybin 25 mg (N=79)**	**Psilocybin 10 mg (N=75)**	**Psilocybin 1 mg (N=79)**	**Overall (N=233)**
Sex, n (%)				
Female	44 (55.7)	41 (54.7)	36 (45.6)	121 (51.9)
Race, n (%)				
White	70 (88.6)	72 (96.0)	73 (92.4)	215 (92.3)
Age at screening (years)[a]				
Mean (SD)	40.2 (12.2)	40.6 (12.8)	38.7 (11.7)	39.8 (12.2)
Prior psilocybin experience, n (%)				
Yes	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Length 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)
HAM-D-17 Baseline[b] severity categories, n (%)				
Moderate (18-23)	57 (72.2)	49 (65.3)	59 (74.7)	165 (70.8)
Severe (≥24)	22 (27.8)	26 (34.7)	20 (25.3)	68 (29.2)
Baseline[b] MADRS total score				
Mean (SD)	31.9 (5.4)	33.0 (6.3)	32.7 (6.2)	32.5 (6.0)

HAM-D-17=Hamilton Depression Rating Scale (17-item); MADRS=Montgomery-Åsberg Depression Rating Scale; max=maximum; min=minimum; n=number; SD=standard deviation

[a] Screening refers to the COMP 001 screening visit.

[b] Baseline refers to the COMP 001 baseline visit

Supplementary Table 2b:

Participant Demographics and Baseline Disease Characteristics for all COMP 003 Participants

	COMP 003
Parameter	**Psilocybin 25 mg + SSRI (N=19)**
Sex, n (%)	
Female	13 (68.4)
Race, n (%)	
White	15 (78.9)
Age at screening (years)[a]	
Mean (SD)	42.2 (10.80)
Length of current depressive episode, n (%)	
<1 year	3 (15.8)
≥1 year to <2 years	13 (68.4)
≥2 years	3 (15.8)
HAM-D-17 Baseline[b] severity categories, n (%)	
Moderate (18-23)	17 (89.5)
Severe (≥24)	2 (10.5)
Baseline[b] MADRS total score	
Mean (SD)	31.7 (5.77)

HAM-D-17=Hamilton Depression Rating Scale (17-item); MADRS=Montgomery-Åsberg Depression Rating Scale; n=number; SD=standard deviation

[a] Screening refers to the COMP 003 screening visit.

[b] Baseline refers to the COMP 003 baseline visit

Supplementary Table 3: Comparison of MADRS-related Endpoints Between Participants Enrolled in COMP 001 and Participants Enrolled in COMP 004

	COMP 001 (mFAS)[3]			COMP 004 (FAS)		
Parameter	**Psilocybin 25 mg (N=79)**	**Psilocybin 10 mg (N=75)**	**Psilocybin 1 mg (N=79)**	**Psilocybin 25 mg (N=22)**	**Psilocybin 10 mg (N=19)**	**Psilocybin 1 mg (N=17)**
Change from baseline to Week 12 in MADRS total score, Mean (SD)	-12.4 (13.05)	-10.9 (12.80)	-10.5 (13.07)	-12.6 (13.52)	-12.6 (13.13)	-10.2 (11.10)
MADRS responders at Week 12, n (%)[1], (%)[2]	34 (45.9), (43.0)	16 (25.0), (21.3)	22 (31.4), (27.8)	9 (40.9), (40.9)	5 (26.3), (26.3)	6 (35.3), (35.3)
MADRS remitters at Week 12, n (%)[1], (%)[2]	26 (35.1), (32.9)	8 (12.5), (10.7)	17 (24.3), (21.5)	7 (31.8), (31.8)	4 (21.1), (21.1)	3 (17.6), (17.6)
MADRS sustained responders at Week 12 – primary definition*, n (%)[1], (%)[2]	18 (24.0), (22.8)	5 (7.1), (6.7)	8 (10.8), (10.1)	6 (27.3), (27.3)	4 (22.2), (21.1)	0
MADRS sustained responders at Week 12 – relaxed definition**, n (%)[1], (%)[2]	21 (28.0), (26.6)	9 (12.7), (12.0)	9 (12.3), (11.4)	7 (31.8), (31.8)	5 (26.3), (26.3)	0

FAS=full analysis set; mFAS=modified full analysis set; SD=standard deviation.

The FAS includes all participants enrolled in COMP 004 with at least one efficacy assessment, whereas the mFAS includes all participants enrolled in COMP 001 that completed at least one efficacy assessment.

[1] Percentages are based on the number of participants with non-missing data in the respective analysis set by treatment group.

[2] Percentages are based on the number of participants in the respective analysis set by treatment group.

[3] Results are based on the number of participants in the respective analysis set by treatment group regardless of new treatment for depression.

[*] Primary Definition: Sustained responders were participants meeting the MADRS response criteria (a > 50% reduction from Baseline in MADRS total score) at any visit up to and including Week 3 and also at all visits after Week 3 until Week 12.

[**] Relaxed Definition: Sustained responders are defined as participants meeting the MADRS response criteria (a > 50% reduction from Baseline in MADRS total score) at any visit up to and including Week 3 and also at Week 12 and at least one visit out of Week 6 and Week 9.

Supplementary Table 4: All depressive events across groups, Primary Analysis- Modified Full Analysis Set

	Statistic	Psilocybin 25 mg (N=79)	Psilocybin 10 mg (N=75)	Psilocybin 1 mg (N=79)
Number of Participants with:				
Any depressive event or discontinuation	n (%)	43 (54.4)	41 (54.7)	45 (57.0)
Initiation of new antidepressive treatment	n (%)	38 (48.1)	29 (38.7)	34 (43.0)
MADRS worsening	n (%)	17 (21.5)	14 (18.7)	18 (22.8)
Increased suicidality (MADRS based)	n (%)	11 (13.9)	14 (18.7)	11 (13.9)
Active suicidal ideation (C-SSRS)	n (%)	4 (5.1)	2 (2.7)	0
Hospitalization due to depression/suicidality	n (%)	2 (2.5)	2 (2.7)	0
Suicide attempt/prevention/completion	n (%)	2 (2.5)	0	0
Discontinuation[a]	n (%)	0	2 (2.7)	1 (1.3)

C-SSRS=Columbia–Suicide Severity Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale;

[a] Only discontinuation reasons of ‘Adverse Event (MDD-related)’ and ‘Other: Lack of Efficacy’ are included in the definition of the time-to-event variable.

Supplementary Table 5: All depressive events across groups, Supplementary Analysis of COMP 004 Participants – Full Analysis Set

	Statistic	COMP360 25 mg (N=22)	COMP360 10 mg (N=19)	COMP360 1 mg (N=17)
Number of Participants with:				
Any depressive event or discontinuation	n (%)	13 (59.1)	13 (68.4)	15 (88.2)
Initiation of new antidepressive treatment	n (%)	12 (54.5)	11 (57.9)	13 (76.5)
MADRS worsening	n (%)	6 (27.3)	4 (21.1)	4 (23.5)
Increased suicidality (MADRS based)	n (%)	4 (18.2)	2 (10.5)	6 (35.3)
Hospitalization due to depression/suicidality	n (%)	1 (4.5)	0	0
Suicide attempt/prevention/completion	n (%)	1 (4.5)	0	0
Active suicidal ideation (C-SSRS)	n (%)	1 (4.5)	0	0
Discontinuation[a]	n (%)	0	0	0

CI=confidence interval; C-SSRS=Columbia–Suicide Severity Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder.

[a] Only discontinuation reasons of 'Adverse Event (MDD-related)' and 'Other: Lack of Efficacy' are included in the definition of the time-to-event variable.