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Research paper

Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life

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ABSTRACT

Background: COMP360 is a proprietary, synthetic formulation of psilocybin being developed for treatment-resistant depression (TRD), a burdensome, life-threatening illness with high global impact. Here, we expand upon the previous report of primary outcomes from a phase 2 study of COMP360 in individuals with TRD—the largest randomised controlled clinical trial of psilocybin—to discuss findings of the exploratory efficacy endpoints.

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Methods: In this phase 2, double-blind trial, 233 participants with TRD were randomised to receive a single dose of psilocybin 25 mg, 10 mg, or 1 mg (control), administered alongside psychological support from trained therapists. Efficacy measures assessed patient-reported depression severity, anxiety, positive and negative affect, functioning and associated disability, quality of life, and cognitive function.
Results: At Week 3, psilocybin 25 mg, compared with 1 mg, was associated with greater improvements from Baseline total scores in all measures. The 10 mg dose produced smaller effects across these measures.
Limitations: Interpretation of this trial is limited by the absence of an active comparator and the possibility of functional unblinding in participants who received a low dose of psilocybin.
Conclusions: Three weeks after dosing, psilocybin 25 mg and, to a lesser degree, 10 mg improved measures of patient-reported depression severity, anxiety, affect, and functioning. These results extend the primary findings from the largest randomised clinical trial of psilocybin for TRD to examine other outcomes that are of importance to patients.

Abbreviations

CI	confidence interval
DSST	Digit Symbol Substitution Test
EQ-5D-3L	EuroQol–5-Dimensions 3-Levels
EQ-VAS	EuroQol-Visual Analogue Scale
GAD-7	Generalised Anxiety Disorder-7 item
HAM-D-17	Hamilton Depression Rating Scale-17 item
LSM	least-squares mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MRMM	mixed model for repeated measures
N	number included in analysis
n	number of participants
PANAS	Positive and Negative Affect Schedule
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-16 item
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
TRD	treatment-resistant depression
WSAS	Work and Social Adjustment Scale

1. Introduction

Major depressive disorder (MDD), which is experienced by some 280 million people globally, is a leading cause of prolonged suffering, disability, and premature death (WHO, 2021). Approximately one-third of people with MDD progress to treatment-resistant depression (TRD), which is often defined as failing to respond to at least 2 antidepressant treatments of adequate dose and duration within a major depressive episode (Brown et al., 2019). Roughly 3 in 4 people with TRD are treated with 4 or more lines of medication prior to achieving a tolerable response (Cipriani et al., 2018; Kubitz et al., 2013), with broad heterogeneity in treatment approaches due to limited evidence-based guidelines on stepwise approaches to treatment (Voineskos et al., 2020). The lack of consistently effective treatment approaches is particularly problematic because the rate of resistance and risk of relapse progressively increase with successive courses of treatment (Rush et al., 2006).

The limitations of current pharmacotherapies present an urgent and unmet need for people with MDD. People with TRD have notably higher disease burden (i.e., greater severity, chronicity, and suicide risk) and lower quality of life than people with MDD who do respond to first- or second-line treatment (Fekadu et al., 2009; Johnston et al., 2019; Rybak et al., 2021). TRD has a wide societal impact and incurs twice the cost of non-treatment-resistant MDD. Furthermore, people with TRD have a higher likelihood of unemployment, are less productive at work, and lose a significantly higher number of life years to disability (Zhdanava et al., 2021). Thus, despite the availability of numerous antidepressant drugs new treatment approaches are needed for individuals with TRD. Given the added burden and major social cost of resistance to existing treatments, recent advances in antidepressant therapies have focused on novel mechanisms of action and greater rapidity of response to outcomes related to quality of life and psychosocial functioning, as well as core MDD symptoms. This has renewed interest in the therapeutic potential of drugs producing a psychedelic experience (Reiff et al., 2020).

Psilocybin is a tryptamine alkaloid found in several species of *Psilocybe* mushrooms (Passie et al., 2002). The antidepressant effect of psilocybin has been supported by several small studies in patients with cancer-related depression and patients with MDD or TRD (Carhart-Harris et al., 2016; Carhart-Harris et al., 2021; Davis et al., 2020; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), and recently in a large randomised double-blind trial of psilocybin for the treatment of TRD (Goodwin et al., 2022a). In that trial, psilocybin 25 mg, but not 10 mg, demonstrated significantly better efficacy compared with the 1 mg control on the primary efficacy endpoint, change from Baseline to Week 3 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Notably, antidepressant effects were rapid, occurring as early as Day 2, and one-fifth of participants who received psilocybin 25 mg sustained response from Week 3 through Week 12 (Goodwin et al., 2022a).

Although improvement in key symptoms of depression is central to supporting the efficacy of a proposed antidepressant, the experience of MDD extends beyond the depression symptoms evaluated by a clinician. In addition to clinician-rated evaluations of symptomatic response, patient-reported outcomes can provide important details about the effects of a treatment on a patient's life and well-being. Patient perspectives and improvement in anxiety, functioning, and quality of life are all key components of overall improvement and recovery and could have impact on global burden of disease (Baune and Christensen, 2019; Kan et al., 2020; Morton et al., 2022; Zimmerman et al., 2006).

To characterise fully the nature of psilocybin's antidepressant effects, we report findings regarding other important, exploratory efficacy endpoints of the Goodwin et al. (2022a) trial to further elucidate the role of psilocybin in the treatment of people with TRD. These measures include self-reported depression severity, anxiety, positive and negative affect, functioning, quality of life, and cognitive function.

2. Methods

2.1. Trial design and psilocybin administration

The design and methodology of this phase 2, multicentre, international trial are reported in detail in the primary study report (Goodwin et al., 2022a). The psilocybin used in this study was the investigational drug COMP360: a proprietary, pharmaceutical-grade, synthetic formulation of psilocybin, which was developed and optimised for stability and purity by COMPASS Pathways. Participants were aged 18 years and older; met Diagnostic and Statistical Manual of Mental Disorders 5th

edition criteria for MDD based on clinical assessments, medical records, and Mini International Neuropsychiatric Interview (version 7.0.2) documentation; and had Hamilton Depression Rating Scale-17 item total scores ≥18 at the Screening and Baseline visits. TRD was defined as failure to respond to 2 to 4 evidence-based antidepressant drugs. Eligible participants completed 3- to 6-week run-in periods during which antidepressant drugs and other prohibited central nervous system active medications were tapered and discontinued at least 2 weeks prior to the Baseline visit (the day before psilocybin administration). During this time, a trained therapist met with the participant during 3 preparatory sessions to explain the trial design and procedures, build trust, provide psychoeducation, and help the participant prepare for the psychedelic experience. A total of 428 participants were screened, and 233 participants were randomly assigned to psilocybin 25 mg, 10 mg, or 1 mg in a 1:1:1 ratio. The single-dose administration lasted 6 to 8 h with the lead therapist who had prepared the participant and an assisting therapist in attendance. During the administration session, the therapist ensured psychological and physical safety, maintained the participant's attention on the experience, and allowed the participant's subjective experience to unfold naturally. The therapists were encouraged not to actively guide the participant or interfere with the natural trajectory of their experience, meaning that interaction between therapist and participant was minimal. A trial psychiatrist was available on site for consultations. Administration rooms were designed to provide a nonclinical and calming setting. Throughout the duration of the administration session, participants listened to a specially designed music playlist through headphones while wearing eyeshades to help direct their attention inward. Participants returned home after a minimum of 6 h post-dosing, when the effects of the drug had dissipated.

The trial followed participants for 12 weeks post-psilocybin administration. Participants underwent 2 integration sessions with the same lead and assisting therapists on the Day 2 visit (the day after psilocybin administration) and with the lead therapist on the Week 1 visit. Participants were requested to remain off antidepressant treatments during the first 3 weeks post-administration; however, if deemed clinically necessary by a physician investigator, these treatments could be started at any time during the trial.

2.2. Exploratory efficacy endpoints

Exploratory efficacy measures included the following participant-rated measures: the Generalised Anxiety Disorder-7 item (GAD-7) (Spitzer et al., 2006), which reflects anxiety severity; the Quick Inventory of Depressive Symptomatology-16 item (QIDS-SR-16) (Rush et al., 2003), which gauges depression severity; the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), which assesses emotional states from a list of adjectives; the Sheehan Disability Scale (SDS) (Sheehan, 1983) and Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002), which are measures of function; and the EuroQol–5-Dimensions 3-Levels (EQ-5D-3L) (The EuroQol Group, 1990; Herdman et al., 2011), which assesses quality of life. Participants also completed a computer-based Digit Symbol Substitution Test (DSST) (Jaeger, 2018), a measure of global cognitive function incorporating executive function, processing speed, and attention. The PANAS was administered at Baseline, Day 2, and Week 3; the DSST was administered at Baseline, Day 2, Week 3, and Week 12; and the QIDS-SR-16 was administered at Baseline, Day 1, Day 2, and Week 3 to Week 12. All other exploratory measures were administered at Baseline, Week 3, and Week 12. For each of these efficacy measures, a total score was derived, and the exploratory efficacy endpoint for each measure was assessed as the change from Baseline (Day −1, which was the day before psilocybin administration) to Week 3 in total score.

2.3. Statistical analysis

The analysis of the primary and key secondary efficacy endpoints, along with safety endpoints, is reported elsewhere (Goodwin et al., 2022a). The design of the trial was not powered to detect statistical differences between groups for the exploratory efficacy endpoints. Each of the exploratory efficacy endpoints was evaluated with a mixed model for repeated measures (MMRM) analysis that compared the psilocybin 25 mg and 10 mg groups with the 1 mg group. The MMRM analysis included fixed effects for treatment group, visit, pooled trial site, treatment-by-visit interaction, Baseline total score as a covariate, and an unstructured correlation matrix. There was no imputation of missing total score data, and all observed total scores were used, regardless of initiations of new antidepressant treatments. For each group, the estimate of the least-squares mean (LSM) change from Baseline in total score at Week 3, LSM differences (psilocybin 25 mg and 10 mg compared with 1 mg) and associated 95 % confidence intervals (CIs) were calculated.

3. Results

The 233 participants were randomised and received psilocybin 25 mg ($n = 79$), 10 mg ($n = 75$), or 1 mg (n = 79) (safety population). All participants had at least 1 post-baseline efficacy assessment, so all randomised patients were included in the modified intention-to-treat population on which the efficacy analyses were based. Demographic and clinical characteristics were similar among the psilocybin 25 mg, 10 mg, and 1 mg groups and representative of the population of individuals with TRD (Tables 1, 2) (Yrondi et al., 2020).

At Week 3, psilocybin 25 mg and 10 mg reduced total depression scores on the QIDS-SR-16. The difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was −2.8 (95 % CI: −4.6 to −0.9), and the difference between the 10 mg group and 1 mg group was −1.6 (95 % CI: −3.5 to 0.3). Reduction in depression scores remained apparent at Week 12 (Figs. 1, 2, Tables 3,

Table 1
Baseline characteristics (safety population).

Variable	Psilocybin			
	25 mg group (n = 79)	10 mg group (n = 75)	1 mg group (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/m^2, mean (SD)	26.52 (6.134)	28.26 (8.203)	27.26 (6.025)	27.34 (6.858)
Prior psilocybin use, n (%)	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
MDD, recurrent, n (%)	75 (94.9)	74 (98.7)	73 (92.4)	222 (95.3)
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)

Abbreviations: HAM-D-17: Hamilton Depression Rating Scale-17 item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; N: number included in analysis; n: number of participants; SD: standard deviation.

Table 2
Clinical characteristics at baseline (safety population).

Measure	Psilocybin		
	25 mg group (n = 79)	10 mg group (n = 75)	1 mg group (n = 79)
Baseline total scores, mean (SD)			
QIDS-SR-16; range: 0–27	16.1 (4.14)	16.3 (4.16)	15.8 (3.96)
PANAS positive affect; range: 10–50	19.5 (5.69)	19.5 (7.19)	19.6 (6.41)
PANAS negative affect; range: 10–50	24.6 (8.37)	24.7 (8.08)	24.0 (7.54)
GAD-7; range: 0–21	11.6 (5.21)	13.2 (4.92)	12.8 (4.97)
SDS; range: 0–30	21.7 (5.21)	21.6 (4.47)	21.7 (5.44)
SDS days lost[a]	2.9 (2.79)	2.7 (2.71)	2.8 (2.77)
SDS days unproductive[a]	5.7 (1.91)	5.7 (1.59)	5.4 (2.22)
WSAS; range: 0–40	28.9 (6.83)	30.2 (5.56)	29.6 (6.21)
EQ-5D-3L; range: −0.594–1.0	0.49 (0.236)	0.46 (0.236)	0.43 (0.267)
EQ-VAS; range: 0–100	51.2 (20.50)	46.9 (20.17)	45.8 (19.09)
DSST; range: 0–100	30.8 (10.07)	32.1 (10.08)	34.1 (9.61)

Abbreviations: DSST: Digit Symbol Substitution Test; EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; EQ-VAS: EuroQol-Visual Analogue Scale; GAD-7: Generalised Anxiety Disorder-7 item; n: number of participants; PANAS: Positive and Negative Affect Schedule; QIDS-SR-16: Quick Inventory of Depressive Symptomatology-16 item; SD: standard deviation; SDS: Sheehan Disability Scale; WSAS: Work and Social Adjustment Scale.

[a] The analysis of SDS days lost and SDS days unproductive was post hoc, and not a prespecified exploratory efficacy endpoint.

S1).

The 25 mg dose was associated with an increase in the PANAS positive affect score and a decrease in the PANAS negative affect score at Week 3. For the PANAS positive affect total score, the difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was 6.2 (95 % CI: 3.5 to 8.8), and the difference between the 10 mg group and 1 mg group was 1.6 (95 % CI: −1.1 to 4.3). For the PANAS negative affect total score, the difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was −3.2 (95 % CI: −5.6 to −0.8), and the difference between the 10 mg group and 1 mg group was −1.6 (95 % CI: −4.1 to 0.8) (Table 3, Figs. 2, 3).

The GAD-7 total score, a measure of anxiety, also demonstrated that the 25 mg dose produced greater improvement compared with the 1 mg dose than the 10 mg dose at Week 3. The difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was −1.8 (95 % CI: −3.4 to −0.2), and the difference between the 10 mg group and 1 mg group was −0.5 (95 % CI: −2.1 to 1.0) (Table 3, Fig. 2).

The 25 mg and 10 mg doses also improved measures of function, including SDS total score as well as SDS lost days and unproductive days in the preceding week at Week 3 (Table 3, Fig. 2). The difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was −6.5 (95 % CI: −9.5 to −3.5), and the difference between the 10 mg group and 1 mg group was −4.0 (95 % CI: −7.0 to −1.0). A similar improvement in function was observed in the WSAS total score. The difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was −5.1 (95 % CI: −8.4 to −1.8), and the difference between the 10 mg group and 1 mg group was −3.1 (95 % CI: −6.4 to 0.2) (Table 3, Fig. 2).

Effects on quality of life (assessed by the EQ-5D-3L and EQ-VAS) and cognitive function (assessed with the DSST total score) were smaller. For the EQ-5D-3L, the difference in the LSM change from Baseline to Week 3 between the 25 mg group and 1 mg group was 0.06 (95 % CI: 0.03 to 0.15), and the difference between the 10 mg group and 1 mg group was 0 (95 % CI: −0.09 to 0.09). Corresponding values for EQ-VAS were 6.8 (95 % CI: −0.4, 13.9) and 4.3 (95 % CI: −2.9, 11.5), and for DSST total score were 1.5 (95 % CI: −0.8, 3.8) and 0.5 (95 % CI: −1.8, 2.8) (Table 3).

The treatment differences at Week 12 were less pronounced; however, the same dose-dependent trends in the LSM change from Baseline were observed (Table S1). Although it is possible that treatment with a single 25 mg dose was insufficiently durable for some participants who might have required a second dose for optimal response, this finding at Week 12 could also be due, at least in part, to the higher earlier incidence of antidepressant initiation in the 1 mg group (Table S2). Participants in the 1 mg group had more time to adjust to the newly initiated antidepressant and experience improved outcomes by the assessment at Week 12 that were closer to the experience of participants in the higher-dose groups, thus reducing the treatment differences between the groups.

4. Discussion

Psilocybin 25 mg administered alongside psychological support from trained therapists not only improved clinician-rated symptoms of depression at Week 3 in participants with TRD, but also resulted in improvement of a patient-reported measure of depression. The treatment reduced anxiety and increased positive affect while reducing negative affect. Psilocybin was also rapid-acting, with treatment differences observed as early as Day 2 on the QIDS-SR-16 and PANAS total scores after administration of a single dose. These results from patient-reported outcome measures are highly consistent with results from the clinician-rated MADRS, which was the primary efficacy measure in this study and was administered via telephone by raters who were blind as to treatment assignment and had no other contact with the participants (Goodwin et al., 2022a).

The impact of TRD typically extends beyond clinical symptoms; therefore, work, family, and social interactions; cognitive function; and

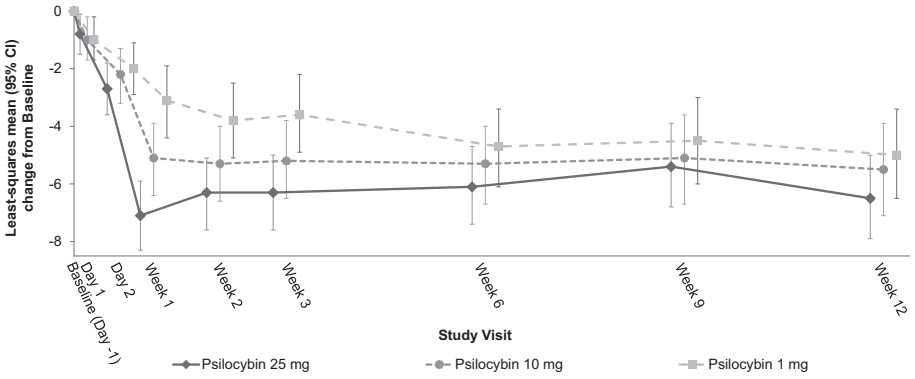

Fig. 1. Change from Baseline in QIDS-SR-16 total score over time (modified intention-to-treat population). Note: Results at Days 1 and 2 may partially reflect the effects of pre-administration due to the 1-week recall period of the measure. CI, confidence interval; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-16 item.

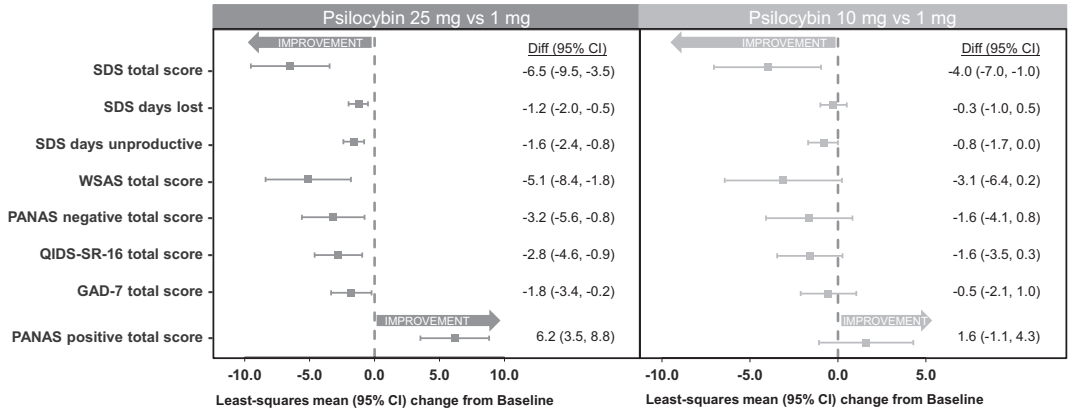

Fig. 2. Forest plot of exploratory efficacy endpoints: change from Baseline at Week 3 (modified intention-to-treat population). Improvements in functional impairment, positive and negative affect, self-rated depression symptom severity, and anxiety severity were observed in the 25 mg group compared with the 1 mg group as well as in the 10 mg group compared with the 1 mg group, albeit to a lesser degree. Note: The analysis of SDS days lost and SDS days unproductive was post hoc, and not a prespecified exploratory efficacy endpoint. CI, confidence interval; GAD-7, Generalised Anxiety Disorder-7 item; PANAS, Positive and Negative Affect Schedule; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-16 item; SDS, Sheehan Disability Scale; WSAS, Work and Social Adjustment Scale.

quality of life were also assessed. Psilocybin 25 mg improved SDS total score at Week 3, reduced the number of lost and unproductive days by Week 3, and improved function as assessed with the WSAS total score. Treatment differences in measures of quality of life and cognitive function were smaller but showed comparable trends for a greater effect of the 25 mg dose.

In nearly all the exploratory efficacy endpoint measures, a dose-response relationship was observed, with greater improvement at Week 3 seen in the 25 mg group than the 10 mg group compared with the 1 mg group. Because both the 25 mg and 10 mg doses were psychoactive, these findings suggest that the differential effect of these doses of psilocybin is unlikely to be due to simple functional unblinding or expectancy. However, a dose-response relationship was observed for the intensity of subjective experience during the psilocybin administration session, as captured by the 5-Dimensional Altered States of Consciousness questionnaire (5D-ASC) (Goodwin et al., 2022b), which supports the notion that subjective experience plays a role in therapeutic outcome.

Adverse events occurred in 66 participants (84 %) in the 25 mg group, 56 participants (75 %) in the 10 mg group, and 57 participants (72 %) in the 1 mg group. Serious adverse events occurred in 4 participants (5 %) in the 25 mg group and 4 participants (5 %) in the 10 mg group; none of these events were reported on the day of psilocybin administration. No clinically significant changes in vital signs, clinical laboratory tests, or 12-lead ECGs were observed during the trial. Details on the safety outcomes are reported elsewhere (Goodwin et al., 2022a).

The findings reported here extend the understanding of psilocybin's multifaceted effect on a comprehensive set of measures related to TRD and further support its development in treating this disease. It represents the largest dataset so far from a randomised controlled clinical trial of a serotonergic agonist producing a psychedelic experience.

4.1. Limitations

Conclusions from this trial may be limited by the absence of an active comparator and the probability of functional unblinding in participants receiving a low dose of psilocybin. The ability of the participants to identify their dose was not formally assessed because it seemed likely to shift attention away from absorbing the benefits of any immersive experience on the day of psilocybin administration. However, the finding of dose-response effects, with the 25 mg group demonstrating larger treatment differences compared with the 1 mg group than the 10 mg group, argues against simple unblinding, which was more likely with 1 mg. Additionally, 94 % of participants were psilocybin-naïve, further reducing the likelihood that participants would have been able to distinguish between the 25 mg and 10 mg doses. The study was not powered to assess the significance of the differences reported here, making these results descriptive. Larger studies will be needed to replicate the findings. Furthermore, the study population was not fully representative of real-world patient groups, as it was insufficiently ethnically diverse and excluded individuals judged to be current significant suicide risks. Finally, it is unknown whether other preparations of psilocybin will demonstrate the same effects.

5. Conclusions

This report of exploratory efficacy endpoints from the largest randomised controlled trial of psilocybin to date extends the evidence of the rapid efficacy of a single dose of psilocybin to benefits that are of paramount importance to patients—namely, patient-rated depression severity, anxiety, affect, functioning, and quality of life, and further support development of this compound in the treatment of patients with TRD.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CRediT authorship contribution statement

Guy M. Goodwin, Lindsey Marwood, Joyce Tsai, Matthew Young, and Ekaterina Malievskaia contributed to the conception and design of the work, acquisition of the data for the work, interpretation of the data for the work, and drafting of the work. James C. Bennett, Sunil Mistry, and Hollie J. Simmons contributed to the analysis and interpretation of the data for the work and drafting of the work. Megan Croal contributed to the interpretation of the data for the work and drafting of the work. Susan C. Stansfield, Merve Atli, Molly R. Lennard-Jones, Batya Septimus, Jessica R. Stuart, Sam Williams, and Rachel I. Winzer contributed to the conception and design of the work, and investigation and acquisition of the data for the work. Scott T. Aaronson, Oscar Alvarez, Charles

Table 3
Summary of exploratory efficacy endpoints: change from Baseline at Week 3 (modified intention-to-treat population).

Measure	Psilocybin		
	25 mg group (*n* = 79)	10 mg group (*n* = 75)	1 mg group (n = 79)
QIDS-SR-16 total score			
LSM (SE)	−6.3 (0.66)	−5.2 (0.68)	−3.6 (0.67)
95 % CI of the LSM	(−7.6, −5.0)	(−6.5, −3.8)	(−4.9, −2.2)
LSM difference vs 1 mg (SE)	−2.8 (0.93)	−1.6 (0.94)	–
95 % CI of the LSM vs 1 mg	(−4.6, −0.9)	(−3.5, 0.3)	–
PANAS positive affect total score			
LSM (SE)	5.9 (0.96)	1.3 (1.02)	−0.3 (0.99)
95 % CI of the LSM	(4.0, 7.8)	(−0.7, 3.3)	(−2.2, 1.7)
LSM difference vs 1 mg (SE)	6.2 (1.34)	1.6 (1.36)	–
95 % CI of the LSM vs 1 mg	(3.5, 8.8)	(−1.1, 4.3)	–
PANAS negative affect total score			
LSM (SE)	−6.7 (0.87)	−5.1 (0.92)	−3.5 (0.89)
95 % CI of the LSM	(−8.4, −5.0)	(−6.9, −3.3)	(−5.2, −1.7)
LSM difference vs 1 mg (SE)	−3.2 (1.22)	−1.6 (1.24)	–
95 % CI of the LSM vs 1 mg	(−5.6, −0.8)	(−4.1, 0.8)	–
GAD-7 total score			
LSM (SE)	−5.1 (0.57)	−3.8 (0.60)	−3.3 (0.59)
95 % CI of the LSM	(−6.2, −4.0)	(−5.0, −2.7)	(−4.5, −2.1)
LSM difference vs 1 mg (SE)	−1.8 (0.79)	−0.5 (0.80)	–
95 % CI of the LSM vs 1 mg	(−3.4, −0.2)	(−2.1, 1.0)	–
SDS total score			
LSM (SE)	−8.8 (1.05)	−6.3 (1.12)	−2.3 (1.19)
95 % CI of the LSM	(−10.8, −6.7)	(−8.5, −4.1)	(−4.6, 0.1)
LSM difference vs 1 mg (SE)	−6.5 (1.54)	−4.0 (1.54)	–
95 % CI of the LSM vs 1 mg	(−9.5, −3.5)	(−7.0, −1.0)	–
SDS days lost[a]			
LSM (SE)	−1.5 (0.26)	−0.5 (0.28)	−0.3 (0.27)
95 % CI of the LSM	(−2.0, −1.0)	(−1.1, 0.0)	(−0.8, 0.3)
LSM difference vs 1 mg (SE)	−1.2 (0.37)	−0.3 (0.37)	–
95 % CI of the LSM vs 1 mg	(−2.0, −0.5)	(−1.0, 0.5)	–
SDS days unproductive[a]			
LSM (SE)	−2.7 (0.30)	−1.9 (0.32)	−1.1 (0.31)
95 % CI of the LSM	(−3.3, −2.1)	(−2.5, −1.3)	(−1.7, −0.5)
LSM difference vs 1 mg (SE)	−1.6 (0.42)	−0.8 (0.42)	–
95 % CI of the LSM vs 1 mg	(−2.4, −0.8)	(−1.7, 0.0)	–
WSAS total score			
LSM (SE)	−9.2 (1.20)	−7.2 (1.28)	−4.1 (1.24)
95 % CI of the LSM	(−11.6, −6.8)	(−9.7, −4.7)	(−6.5, −1.6)
LSM difference vs 1 mg (SE)	−5.1 (1.67)	−3.1 (1.69)	–
95 % CI of the LSM vs 1 mg	(−8.4, −1.8)	(−6.4, 0.2)	–
EQ-5D-3L			
LSM (SE)	0.20 (0.033)	0.14 (0.035)	0.14 (0.034)
95 % CI of the LSM	(0.14, 0.27)	(0.07, 0.21)	(0.08, 0.21)
LSM difference vs 1 mg (SE)	0.06 (0.046)	0.00 (0.046)	–
95 % CI of the LSM vs 1 mg	(−0.03, 0.15)	(−0.09, 0.09)	–
EQ-VAS			
LSM (SE)	11.1 (2.58)	8.7 (2.74)	4.4 (2.66)
95 % CI of the LSM	(6.1, 16.2)	(3.3, 14.1)	(−0.9, 9.6)
LSM difference vs 1 mg (SE)	6.8 (3.62)	4.3 (3.66)	–
	(−0.4, 13.9)	(−2.9, 11.5)	–
95 % CI of the LSM vs 1 mg			
DSST total score			
LSM (SE)	6.4 (0.84)	5.4 (0.87)	4.8 (0.84)
95 % CI of the LSM	(4.7, 8.0)	(3.6, 7.1)	(3.2, 6.5)
LSM difference vs 1 mg (SE)	1.5 (1.17)	0.5 (1.18)	–
95 % CI of the LSM vs 1 mg	(−0.8, 3.8)	(−1.8, 2.8)	–

Abbreviations: CI: confidence interval; DSST: Digit Symbol Substitution Test; EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; EQ-VAS: EuroQol-Visual Analogue Scale; GAD-7: Generalised Anxiety Disorder-7 item; LSM: least-squares mean; n: number of participants; PANAS: Positive and Negative Affect Schedule; QIDS-SR-16: Quick Inventory of Depressive Symptomatology-16 item; SDS: Sheehan Disability Scale; SE, standard error; WSAS: Work and Social Adjustment Scale.

[a] The analysis of SDS days lost and SDS days unproductive was post hoc, and not a prespecified exploratory efficacy endpoint.

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All authors approved the final manuscript, revised it critically for important intellectual content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

GMG is emeritus NIHR Senior Investigator and has consulted for Beckley Psytech, Boehringer Ingelheim, Clerkenwell Health, EVApharm, H Lundbeck A/S, Janssen Global Services, Novartis, Ocean Neurosciences, P1vital, Sage Therapeutics, Servier, Takeda and WebMD.

STA has consulted for COMPASS Pathways, Genomind, Janssen Global Services, LivaNova, Neuronetics, and Sage Therapeutics.

CD has consulted for AbbVie and Corcept Therapeutics. CD has received grant funding from Beckley Psytech, Relmada Therapeutics, and Sage Therapeutics.

BWD has consulted for Cerebral Therapeutics, Greenwich Biosciences, Myriad Genetic Laboratories, Otsuka America Pharmaceutical, Sage Therapeutics, and Sophren Therapeutics. BWD has received grant funding from Boehringer Ingelheim, COMPASS Pathways, Otsuka America Pharmaceutical, and the Usona Institute.

DF has received grant funding from MindMed, Neurolief, Perception Neuroscience, and Relmada Therapeutics. DF holds a patent for psychedelic drug treatment of neuropsychiatric disorders and cerebral palsy.

DJH has consulted for Reset Pharmaceuticals. DJH has received grant funding from Assurex, Intra-Cellular Therapies, Marinus Pharmaceuticals, COMPASS Pathways, Relmada Pharmaceuticals, and Beckley Foundation.

MIH owns shares in Mindset Pharma. MIH has received consultancy fees from Psyched Therapeutics and the Wake Network.

JRK has consulted for Clerkenwell Health and has received grant funding from the Health Research Board (ILP-POR-2022-030).

RWL has participated in speaking engagements for H Lundbeck A/S, Janssen Global Services, and Teva Pharmaceuticals.

TP has consulted for Atai Life Sciences, CB21 Pharma, and GH Research. TP is a principal investigator at Ketabon GmbH and MAPS

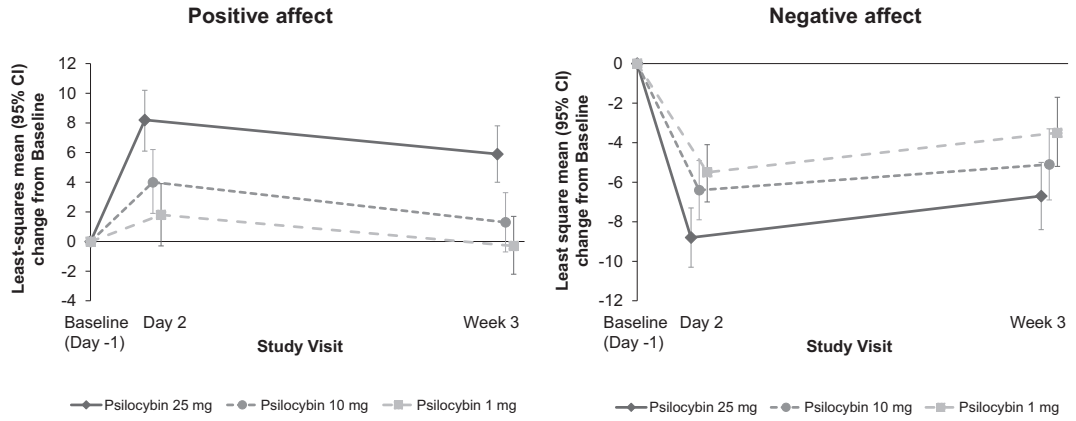

Fig. 3. Change from Baseline in PANAS total score over time (modified intention-to-treat population). CI: confidence interval; PANAS: Positive and Negative Affect Schedule.

Europe BV. TP is a fiduciary officer at the PSYRES Foundation, Psyon, and the Society for the Promotion of Neuroscience Research.

DR is honorary board chair of the nonprofit organization MAPS Deutschland.

RAS has consulted for Clexio Biosciences and GH Research and has received grant funding from Janssen Pharmaceuticals.

JCS has consulted for Alkermes, Johnson & Johnson, and Merck. JCS has received grant funding from MindMed and Relmada Therapeutics.

MW and SZ have participated in speaking engagements for COMPASS Pathways and Janssen Pharmaceuticals.

GMG, JT, LM, NKT, OR, SS, BS, HHT, SW, and EM own shares in COMPASS Pathways.

GMG, MA, JCB, MC, MRL-J, EM, LM, SM, OR, BS, HJS, JRS, HHT, NKT, JT, RIW, MBY, SCS, SW, and EM are current or past employees of COMPASS Pathways.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.01.108.

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