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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

Authors: Guy M. Goodwin, MD; Ania Nowakowska, MSc; Merve Atli, MSc; Boadie W. Dunlop, MD; David Feifel, MD, PhD; David J. Hellerstein, MD; Lindsey Marwood, PhD; Zainib Shabir; Sunil Mistry, MSc; Susan C. Stansfield, PhD; Emma Teoh, MSc; Joyce Tsai, PhD; Matthew B. Young, PhD; and Ekaterina Malievskaia, MD

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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.