Psilocybin administration to healthy participants: safety and feasibility in a placebo-controlled study

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Background

- Treatment-resistant depression remains a significant unmet medical need. From an antidepressant drug-development perspective, interest in recent years has been directed at compounds with known pharmacology
- Psilocybin belongs to a class of drugs referred to as psychedelics ('mind-manifesting'). Partial agonism of 5-HT_{2A} receptors is a key mechanism contributing to its biological effects[1,2]
- Psilocybin was used in psychiatric research and psychodynamic-orientated psychotherapy from the early 1960s, until it became a Schedule 1 substance in the US in 1970[2,3]
- More recently, several small studies have indicated efficacy of psilocybin in depressive states.[4-7] Psilocybin is now in clinical development for treatment-resistant depression in the US, Canada, and Europe
- We present safety data from an exploratory phase I study (EudraCT 2018-000978-30) that evaluated the feasibility and safety of simultaneous psilocybin administration with 1:1 psychological support in healthy participants

Methods

Study design

- This was a phase I, randomised, double-blind, placebo-controlled study to evaluate the effects of 10mg and 25mg COMP360 (psilocybin) compared with placebo in healthy participants, conducted at the Institute of Psychiatry, Psychology & Neuroscience, London, UK
- Participants, stratified by sex and age (18-35 years old; >35 years old), were randomised in a 1:1:1 ratio to placebo, 10mg psilocybin, or 25mg psilocybin, administered orally
- **Figure 1** presents an overview of the scheduled study visits
- During administration sessions, each participant received 1:1 support from a trained assisting therapist and was supervised by a study psychiatrist and a lead therapist. Each session lasted approximately 6 hours, with participants encouraged to relax and engage in introspection for the duration. After the acute effects of the study drug had subsided, participants were discharged
- The study drug was administered simultaneously to groups of up to 6 participants

Participants

- Key inclusion criteria:
  - Males or females aged between 18 and 65 years at screening
- Key exclusion criteria:
  - Current or past history of schizophrenia, psychosis, bipolar disorder, delusional disorder, paranoid personality disorder, schizoaffective disorder, borderline personality disorder, major depression, panic disorder, generalised anxiety disorder, obsessive-compulsive disorder, eating disorder, or body dysmorphic disorder
  - History of the above psychiatric conditions in a first degree relative
  - Current, or history of, substance dependency or abuse
  - Current or recent (<1 year) psychiatric medications
  - Prior psilocybin exposure within 1 year of signing of informed consent

Assessments

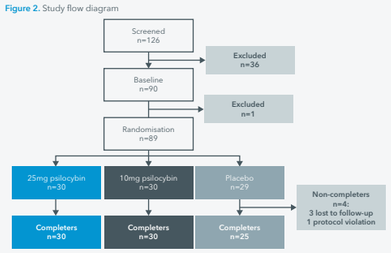
- Safety endpoints included:
  - Vital signs
  - Suicidality, measured using the Sheehan Suicidality Tracking Scale
  - Adverse events (AEs) and serious AEs (SAEs)
  - Clinical laboratory tests
- Initial screening (Visit 1) took place in the 8 weeks before study drug administration and included an evaluation of medical and psychiatric history, completion of the Mini International Neuropsychiatric Interview, assessment of prior/concomitant drug use, and a physical health check
- Baseline assessments were completed 1 day before study drug administration, including assessments of emotional processing and cognitive function. During this visit, participants took part in a 2-hour preparatory group session with the study psychiatrist, lead therapist, and assisting therapists
- On the day following drug administration, participants returned to the clinic for a safety check and to discuss their experience with a therapist
- All AEs that occurred after the signing of informed consent were recorded. All AEs occurring before the start of treatment were recorded as medical history
- The safety population consisted of all randomised participants who received study treatment
- Follow-up visits were conducted via telephone on Day 7 (± 1 day), Day 28 (± 7 days), and Day 84 (± 7 days)

Results

Participant disposition and demographics

- **Figure 2** presents participant disposition

Figure 2. Study flow diagram

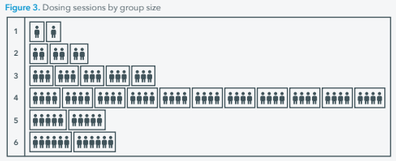


- Participant demographics are summarised in **Table 1**

Dosing sessions

- 25 dosing sessions were completed, with up to 6 participants per session (**Figure 3**)

Figure 3. Dosing sessions by group size



Effects on cognition and emotional function

- Extensive assessments of cognitive and emotional functions showed no negative impact of psilocybin. The results of these assessments will be presented in future publications

Figure 1. Schedule of visits

	Visit 1 (Day -56 to -2) Eligibility screening	Visit 2 (Day -1) Baseline assessments	Visit 3 (Day 0) Randomisation and dosing	Visit 4 (Day 1) Follow-up at clinic	Visit 5 (Day 7) Follow-up by telephone	Visit 6 (Day 28) Follow-up by telephone	Visit 7 (Day 84) Follow-up by telephone
Informed consent form	✓						
Medical and psychiatric history	✓						
Preparatory session		✓					
Dosing			✓				
Integration session				✓			
Vital signs		✓	✓	✓			
Clinical laboratory tests	✓			✓			
Recording of adverse events	✓	✓	✓	✓	✓	✓	✓
Cognitive function		✓			✓	✓	
Emotional processing		✓	✓		✓		✓

COMP360 (psilocybin) was well tolerated in healthy participants and results support further investigation of simultaneous 1:1 therapeutic administration

Table 1. Participant demographics (safety population)

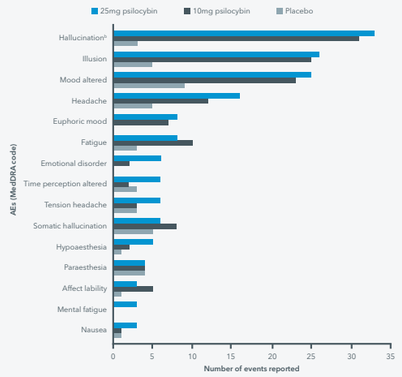
Parameter	25mg psilocybin (n=30)	10mg psilocybin (n=30)	Placebo (n=29)	Overall (n=89)
Sex, n (%)				
Male	16 (53.3)	16 (53.3)	16 (55.2)	48 (53.9)
Female	14 (46.7)	14 (46.7)	13 (44.8)	41 (46.1)
Ethnicity, n (%)				
White	25 (83.3)	27 (90.0)	20 (69.0)	72 (80.9)
Asian	2 (6.7)	1 (3.3)	3 (10.3)	6 (6.7)
Mixed	2 (6.7)	1 (3.3)	1 (3.4)	4 (4.5)
Black	-	-	1 (3.4)	1 (1.1)
Other	1 (3.3)	1 (3.3)	4 (13.8)	6 (6.7)
Age at screening, years				
Mean (SD)	36.6 (10.29)	36.1 (9.25)	35.6 (7.69)	36.1 (9.06)
BMI, kg/m^2				
Mean (SD)	23.0 (3.74)	23.0 (2.89)	23.7 (3.49)	23.2 (3.37)
Prior psilocybin experience				
Yes	11 (36.7)	15 (50.0)	7 (24.1)	33 (37.1)
No	19 (63.3)	15 (50.0)	22 (75.9)	56 (62.9)

BMI, body mass index; SD, standard deviation

Adverse events

- 511 AEs were reported throughout the 12-week duration of the study: 217 in the 25mg psilocybin arm (reported by 96.7% of participants); 203 in the 10mg psilocybin arm (reported by 96.7% of participants); and 91 in the placebo arm (reported by 89.7% of participants)
- Of these, 473 (92.6%) AEs were deemed by the investigators to potentially be related to study treatment, including 208 (95.9%) in the 25mg psilocybin arm, 188 (92.6%) in the 10mg psilocybin arm, and 77 (84.6%) in the placebo arm
- There were no SAEs, and no AEs led to withdrawal
- **Figure 4** presents the most frequently reported AEs (based on the 25mg psilocybin arm), split by treatment arm

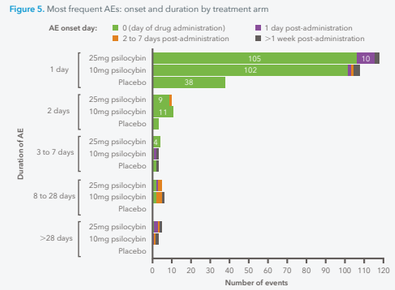
Figure 4. Most frequently reported AEs (MedDRA code)[a]



[a]Ranked by incidence in the 25mg psilocybin group
[b]Includes auditory, gustatory, olfactory, tactile, and visual hallucinations
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities

- The median duration of AEs in all treatment arms across the 12-week trial was 1 day
- Onset and duration of AEs by treatment arm are summarised in **Figure 5**
  - 67% of all AEs appeared and resolved on Day 0 (day of dosing)
  - 92% of AEs likely to be psychedelic in nature were resolved by Day 1
- Mood alteration was one of the most frequently reported AEs; 57 AEs of 'mood altered' were reported (grouped according to regulatory requirements in MedDRA terms), of which 2 were negative alterations in mood: 1 in the placebo arm ('negative mood', which started and resolved on Day 0) and 1 in the 10mg psilocybin arm ('feeling moody or sensitive', which appeared on Day 2 and lasted 8 days)
- **Table 2** shows the frequency of specific 'mood altered' AEs. Most 'mood altered' AEs were positive or neutral in nature (96%), by a post-hoc adjudication
- No clinically relevant changes in vital signs were observed

Figure 5. Most frequent AEs: onset and duration by treatment arm



The most frequent AEs were (number of events in parentheses): illusion (56); mood altered (54); hallucination, visual (44); headache (33); fatigue (21); somatic hallucinations (19); euphoric mood (14); paraesthesia (12); tension headache (12); time perception altered (11); hallucination, auditory (9); affect lability (9)
AE, adverse event

Table 2. Reported 'mood altered' AEs (ranked by incidence in the 25mg psilocybin group)

Description of 'mood altered' event	25mg psilocybin (n=30)	10mg psilocybin (n=30)	Placebo (n=29)	Overall (n=89)
Introspection	8	5	2	15
Reflections	4	3	2	9
Sense of oneness	2	4	0	6
Increased empathy	2	2	0	4
Contemplative state	1	1	0	2
Laughter	1	1	0	2
Clarity of thought	1	0	0	1
Increased compassion	1	0	0	1
Increased creativity	1	0	0	1
Increased sense of connectedness	1	0	0	1
More socially upbeat	1	0	0	1
Saw themselves from a new perspective	1	0	0	1
Being less judgemental	0	1	0	1
Feeling more moody/sensitive	0	1	0	1
Feeling rested	0	1	0	1
Increased wit	0	1	0	1
Sense of openness	0	1	0	1
Unusual appreciation of music	0	0	1	1
Calm	0	0	1	1
Feeling of adrenaline release	0	0	1	1
Negative mood	0	0	1	1

AE, adverse event

Conclusions

- Psilocybin formulation COMP360 was well tolerated; there were no SAEs, and no AEs led to withdrawal
- This study confirmed the feasibility of simultaneous psilocybin administration to healthy participants in a controlled setting with 1:1 support from trained therapists, as demonstrated by high retention rates, low levels of missing data and the willingness of participants to undergo simultaneous administration and group preparation
- Psychedelic effects associated with psilocybin administration were transient and consistent with previous studies

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Disclosures

James Rucker has received grant and congress funding from COMPASS Pathways Ltd.
Allan Young has received 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.
Catherine Bird has received research funding from COMPASS Pathways Ltd.
Aster Daniel receives salary support from COMPASS Pathways Ltd.
Molly Lennard-Jones, Lindsey Marwood, Frederick Reinholdt, Francesco Saldarini, Susan Stansfield, Sam Williams, Hans Eriksson, and Ekaterina Malievskaia are employees of COMPASS Pathways Ltd.
Kristina Grace Posadas and Neil Weston have no conflicts of interest.

Acknowledgements

Medical writing support, under the direction of the authors, was provided by Paul O'Neill, PhD, of CMC AFFINITY, a division of McCann Health Medical Communications Ltd, Glasgow, UK, in accordance with Good Publication Practice (GPP3) guidelines. This assistance was funded by COMPASS Pathways Ltd, London, UK.

Poster presented at the 58th Annual Meeting of The American College of Neuropsychopharmacology, Orlando, FL, USA, 8–11 December 2019