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Research Articles

Safety pharmacology of acute psilocybin administration in healthy participants

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ABSTRACT

Psilocybin is being studied for its therapeutic potential in various mental health disorders, such as depression, anxiety, and addiction. Initial studies suggested that psilocybin is generally safe when used under controlled conditions, but more research is needed to better understand its safety profile. We report safety pharmacology data from a pooled analysis of three randomized crossover studies that included 85 healthy participants and 113 single-dose administrations of psilocybin. Single oral doses included 15 mg, 20 mg, 25 mg, and 30 mg psilocybin dihydrate. We investigated subjective effects, blood pressure, heart rate, body temperature, acute and subacute adverse effects, reports of flashbacks, and liver and kidney function before and after the studies. The 20, 25, and 30 mg doses of psilocybin produced stronger effects than the 15 mg dose. Psilocybin at all doses induced higher "good drug effects" than "bad drug effects." Only the 25 and 30 mg doses increased anxiety. Psilocybin elevated autonomic effects only moderately. Tachycardia (>100 beats/min) was observed with 7% of all psilocybin administrations. Body temperature >38° was reached in 7%, 9%, 17%, and 32% of the participants with the 15, 20, 25, and 30 mg doses, respectively. Kidney and liver function parameters were unaltered at the end of the study. Five participants (6%) reported transient flashback phenomena. No serious adverse reactions occurred. These findings suggest that a single administration of psilocybin is safe with regard to acute psychological and physical harm in healthy participants in a controlled research setting.

1. Introduction

Psilocybin is a classic psychedelic that is used recreationally and has been investigated clinically as a medication for patients with depression (Carhart-Harris et al., 2021; Carhart-Harris et al., 2016; Davis et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Raison et al., 2023; Ross et al., 2016; von Rotz et al., 2023), anxiety (Griffiths et al., 2016; Ross et al., 2016), addiction (Bogenschutz et al., 2022; Garcia-Romeu et al., 2014; Johnson et al., 2016), cluster headache (Davenport, 2016), and migraine (Schindler et al., 2021). Additional indications are under investigation.

The future medical use of psilocybin will depend on its safety and efficacy. Initial studies suggested that psilocybin is generally safe when used under controlled conditions. Although various recent Phase 2 clinical trials showed mostly mild and transient adverse effects, more information on clinical safety is needed (Dodd et al., 2022; Rossi et al., 2022). Safety concerns include challenging experiences (i.e., "bad trips"), acute anxiety, flashbacks, and hallucinogen perception disorder (HPPD). Cardiovascular stimulation has been reported in both healthy participants and patients (Davis et al., 2021; Griffiths et al., 2016; Griffiths et al., 2011; Griffiths et al., 2006; Hasler et al., 2004; Ross et al., 2016; von Rotz et al., 2023), but studies in patients do not typically allow frequent and well-standardized assessments of vital signs. The present analysis provided additional highly controlled data on the safety pharmacology of single-dose administrations of psilocybin.

The aim of the present study was to describe acute subjective, autonomic, and adverse effects during the acute and subacute psilocybin response and blood laboratory markers of kidney and liver function at both the start and end of the study. These data were collected from a series of clinical Phase 1 trials in healthy participants that were conducted in the same laboratory and used the same highly standardized data recording methods (Becker et al., 2022; Holze et al., 2022b; Ley

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et al., 2023). The studies used a representative dose range of psilocybin from moderate-low (15 mg) to moderate (20 mg) to moderate-high (25 mg) to high (30 mg) experiential doses as used in psilocybin-assisted psychotherapy (Bogenschutz et al., 2022; Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022) and in people with no or minimal prior psilocybin use, which is also likely the case when psilocybin is used in patients.

2. Experimental procedures

2.1. Study design

This was a pooled analysis of three double-blind, placebo-controlled, random-order, crossover studies in healthy participants. All trials were previously published in detail (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023). All studies were conducted at the University Hospital Basel and included a total of 85 participants who were all psychiatrically and physically screened and healthy. The aim of the present analysis was to assess the safety pharmacology of single-dose administrations of psilocybin in healthy participants with no regular psychedelic use and no or minimal prior use. The first study (Study 1) (Becker et al., 2022) included 24 healthy participants who received two single administrations of 25 mg psilocybin with placebo or escitalopram pretreatment. Only the administration of placebo as a pretreatment was used in the present analysis. The second study (Study 2) (Holze et al., 2022b) included 28 healthy participants who received two administrations of psilocybin (15 and 30 mg), two administrations of LSD, and placebo. Study 3 (Ley et al., 2023) included 33 healthy participants who received a single dose each of LSD, mescaline, 20 mg psilocybin, and placebo. Only the psilocybin alone and placebo conditions were used for the present analysis. Overall, all three studies encompassed a total of 113 psilocybin administrations. In all studies, the washout periods between single-dose administrations were at least 10 days to reduce possible carryover effects. The studies were all registered at ClinicalTrials.gov (Study 1: NCT03912974; Study 2: NCT03604744; Study 3: NCT04227756) and approved by the local ethics committee. The studies were conducted in accordance with the Declaration of Helsinki. Psilocybin administration in healthy participants was authorized by the Swiss Federal Office for Public Health (BAG), Bern, Switzerland. Informed consent was obtained from all participants who were included in the studies. All participants were paid for their participation.

2.2. Participants

The characteristics of the study participants are shown in Table 1. A total of 85 healthy participants (43 men, 42 women), 25–55 years old (mean ± SD = 32 ± 8 years; range: 25–55 years), were mostly recruited from the University of Basel campus and included in the studies. The mean ± SD (range) ages were 34 ± 10 (25–55) years, 35 ± 9 (25–52) years, and 29 ± 4 (25–44) years for Study 1, Study 2, and Study 3, respectively. The mean ± SD body weight was 71 ± 11 kg (range: 50–112 kg). Thirty-three participants received a single dose of psilocybin only, and 52 participants received two single-dose administrations of psilocybin (28 at two different doses, 15 and 30 mg; 24 at the same dose, 25 mg; only the session with placebo as the pretreatment was used). Exclusion criteria were reported in detail elsewhere (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023) and included a history of psychiatric disorders, physical illness, a lifetime history of using illicit drugs more than 10 times (with the exception of past cannabis use) for Studies 1 and 2, a lifetime history of using psychedelic drugs more than 20 times for Study 3, illicit drug use within the last 2 months, and illicit drug use during the study, determined by urine tests that were conducted before the test sessions. Fifty-four participants (64%) had prior drug experience (1–100 times), of which 41 participants (48%) had previously used a psychedelic (1–10 times). Further substance experiences included methylenedioxymethamphetamine (MDMA; 42 participants [49%], 1–30 times), amphetamine (23 participants [27%], 1–50 times), cocaine (18 participants [21%], 1–100 times), methylphenidate (four participants [5%], 1–2 times), 4-Bromo-2,5-dimethoxyphenethylamine (2C–B; three participants [4%], 1–2 times), ketamine (five participants [6%], 1–5 times), and nitrous oxide (11 participants [13%], 1–20 times).

Table 1
Demographics of study participants.

Condition		2. And 3. Study	1. Study	2. Study	3. Study
		Placebo	Psilocybin	Psilocybin	Psilocybin
Dose	mg	0	25	15 and 30	20
Administrations	N	60	24	28	33
Body weight	kg	71 ± 11	70 ± 13	72 ± 12	71 ± 9.7
Range body weight	kg	52–104	50–112	55–104	52–90
BMI	kg/m2	23 ± 2	24 ± 2	23 ± 3	23 ± 2
Participant age	years	32 ± 8	34 ± 10	35 ± 9	29 ± 4
Range participant age	years	25–52	25–55	25–52	25–44
Previous psychedelic use	N (%)	34 (57)	7 (29)	14 (50)	20 (61)
Range previous psychedelic use		1–10	1–5	1–6	1–10

N, number of subjects; data are mean ± SD unless indicated otherwise.

2.3. Study drug

Psilocybin (99.7% purity, determined by high-performance liquid chromatography; ReseaChem GmbH, Burgdorf, Switzerland) was administered as opaque capsules that contained 5 mg psilocybin dihydrate and an exact analytically confirmed psilocybin content of 4.61 ± 0.09 mg (mean ± SD, n = 10 samples). Placebo consisted of identical opaque capsules that were filled with mannitol. All drug products were produced according to good manufacturing practice (GMP) by a licensed GMP facility (Apotheke Dr. Hysek, Biel, Switzerland). Stability of the psilocybin formulation was confirmed for the study durations. In Study 1, the participants knew they would receive psilocybin. Studies 2 and 3 were double-blind and included inactive placebo and other psychoactive substances. At the end of the study, blinding was assessed.

2.4. Study procedures

All studies included a screening visit, two to five test sessions (each separated by at least 10 days), and an end-of-study visit. The sessions were conducted in a calm standard hospital room that was equipped with a hospital bed for the participant and a desk and chair for the investigator. The room had an adjoining balcony that participants were allowed to access after peak effects had subsided in company of the investigator. Only one research participant and one or two investigators were present during each test session. Participants were allowed to bring their own music and occupy their time for when effects had subsided or for days in which placebo was administered (e.g., book, laptop, games, etc.). Blindfolds were provided upon request. The test sessions began at approximately 8:00 a.m. Individual emotional states were assessed before drug administration to exclude risk factors for emotional disturbances. This procedure consisted of several questions, including "Did anything unusual happen lately?," "Do you feel stressed for any reason (personal or professional)?," "Did you have any sleep disturbances lately?," "Do you have any expectations or fear regarding today's session?," and "Are you feeling ready to participate today?" If any of these questions were answered with "yes" (or "no" for the last question), then the reason was discussed. If the investigator had any doubt, then the session was rescheduled to ensure that none of the participants were in an unfavorable state of mind when taking psilocybin. The participants then underwent baseline measurements, including vital signs.

Psilocybin or placebo was administered at approximately 9:00 a.m. The participants were never alone during the next 7–12 h after drug administration, and an investigator was in a room next to the participant for up to 24 h (except for Study 1, in which participants were sent home after 7 h, accompanied by a friend or family member).

2.5. Pharmacodynamic measures

Visual Analog Scales (VASs) were repeatedly used to assess subjective effects over time (Hysek et al., 2014). The VASs included "any drug effect," "good drug effect," "bad drug effect," "anxiety," and "ego dissolution". The VASs were presented as 100-mm horizontal lines (0–100%), marked from "not at all" on the left to "extremely" on the right. The VASs were applied before and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 h after psilocybin or placebo administration. In Study 1, the 3.5 h time point and all time points after 7 h were not assessed. Severe anxiety was defined as > 75% on the "anxiety" VAS. The 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (Dittrich, 1998; Studerus et al., 2010) was administered 24 h (or 7 h in Study 1) after drug administration to retrospectively rate peak drug effects. The "Oceanic Boundlessness" (OB) and "Anxious Ego-Dissolution" (AED) dimensions are reported herein and serve to describe overall rather positive and negative alterations of mind, respectively (Becker et al., 2022; Holze et al., 2022b; Ley et al., 2023).

Blood pressure, heart rate, and body temperature were assessed repeatedly at the same time points when the VASs were administered. Systolic and diastolic blood pressure and heart rate were measured using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands). The measurements were performed in duplicate at an interval of 1 min and after a resting time of at least 10 min. Averages were used for further analysis. Core (tympanic) temperature was measured using a Braun ThermoScan ear thermometer (Welch Allyn, Skaneateles Falls, NY, USA). Criteria for grouping participants into proportions with a certain degree of autonomic stimulation were diastolic blood pressure > 90 and > 100 mmHg and systolic blood pressure > 140, > 160, and > 180 mmHg. Tachycardia was defined as > 100 beats/min. Hyperthermia and hyperpyrexia were defined as tympanic body temperature > 38°C and 40°C, respectively.

Acute and subacute adverse effects were assessed using the List of Complaints (Hysek et al., 2012a, 2012b; Zerssen, 1976). The scale consists of 66 items, yielding a total adverse effects score (non-weighted sum of all items) that reliably measures physical and general discomfort. The List of Complaints was administered before and 12 h (7 h for Study 1; acute adverse effects) and 24 h (subacute adverse effects) after psilocybin or placebo administration. Subacute adverse effects were not recorded in Study 1. Additionally, participants were asked at the beginning of each study session and at the end of study visit to report any adverse events from 24 h after drug administration until the next study visit. Adverse events were evaluated with a study physician. In Study 1 (Becker et al., 2022), QT times were measured, and QTc times were calculated and compared 1 h before and 2.5 h after the administration of 25 mg psilocybin.

2.6. Blood sampling and end-of-study visit

Blood chemistry and blood cell count tests were performed at the screening visit at the start of the study and at the end-of-study visit, which were separated by 161 ± 85 days (mean ± SD). The end-of-study visit, including blood sampling, occurred at variable time intervals (28 ± 18 days) after the last substance administration. The analyses were performed using standard assays according to Good Laboratory Practice by the Laboratory Medicine Department of the hospital. The glomerular filtration rate was determined by the Cockcroft-Gault Equation using plasma creatinine concentrations, age, and sex of the participant. At the end-of-study visit, the participants were asked to retrospectively rate whether the experience was positive or negative, whether earlier experiences with substances had an influence on the psilocybin experience, and whether they considered taking psilocybin again and in what setting. The participants were also asked whether they experienced "flashbacks" or any other change in perception (e.g., alterations of spatial perception, color vision, or patterns) and how long they lasted. "Flashbacks" were defined as temporary reoccurrence of the altered state of consciousness. Persistent changes in perception would have led to further assessments of possible hallucinogen perception disorder. This was assessed in a structured manner only at the end-of-study visit; therefore, we only report "flashback" phenomena that occurred until the end-of-study visit. "Flashbacks" that occurred outside this time period were not assessed.

2.7. Statistical analyses

The statistical analyses were performed using R 4.2.1 software (RStudio, PBC, Boston, MA, USA) and Statistica 12 software (StatSoft, Tulsa, OK, USA). We conducted analyses of variance (ANOVAs) with dose as a factor, followed by Tukey *post hoc* tests. Fisher's exact tests were used to compare proportions. To assess order effects of the substance administration, order (psilocybin-first vs. psilocybin-second) was incorporated as an additional factor in the ANOVAs. Differences in kidney and liver function and blood cell counts between the screening and end-of-study visit measures were analyzed using paired *t*-tests. The level of significance was set to $p < 0.05$.

3. Results

3.1. Acute subjective effects of psilocybin

Characteristics of the study participants are shown in Table 1.

Positive subjective effects. All doses from 15 to 30 mg psilocybin increased "any drug effect" and "good drug effect" on the VAS and OB ratings on the 5D-ASC compared with placebo (Table 2). The 20, 25, and 30 mg doses induced greater increases in "any drug effects" and "good drug effects" compared with the lower 15 mg dose (Table 2). Ratings of subjective "good drug effects" that were higher than 50% of the scale maximum occurred in 79%, 91%, 88%, and 96% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2). Mean ratings of OB were 24%, 31%, 41%, and 37% with 15, 20, 25, and 30 mg psilocybin, respectively. Ratings of OB that were higher than 50% of the scale maximum occurred in 14%, 27%, 42%, and 25% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2).

Negative subjective effects. "Bad drug effects" on the VAS and AED ratings on the 5D-ASC increased with all doses from 15 to 30 mg compared with placebo (Table 2). Subjective "bad drug effects" with a rating higher than 50% of the scale maximum were reported by 14%, 18%, 42%, and 32% of the participants at the 15, 20, 25, and 30 mg doses, respectively (Table 2). Ratings of "anxiety" on the VAS moderately increased at the 25 and 30 mg doses but not at 15 or 20 mg dose compared with placebo (Table 2). Ratings of "anxiety" that were higher than 50% of the scale maximum were reached in 7%, 6%, 17%, and 11% of the participants at the 15, 20, 25, and 30 mg doses, respectively (Table 2). Mean AED ratings were 9%, 10%, 25%, and 17% at the 15, 20, 25, and 30 mg doses, respectively. Ratings of AED that were higher than 50% of the scale maximum occurred in 4%, 0%, 13%, and 7% of the participants at the 15, 20, 25, and 30 mg doses of psilocybin, respectively (Table 2).

Mean ratings of "ego dissolution" on the VAS increased dose-dependently with higher doses (Table 2). Ratings of more than 50% of the scale maximum for the VAS "ego dissolution" were reached in 46%, 67%, 75%, and 89% of the participants at 15, 20, 25, and 30 mg psilocybin, respectively (Table 2). Effect onset and time to maximal effect of the subjective "any drug effect" (mean ± SD) were 0.6 ± 0.4 h and 2.1

Table 2
Subjective and adverse effects of psilocybin in healthy subjects.

Psilocybin Dose	Placebo (N = 60)	15 mg (N = 28)	20 mg (N = 33)	25 mg (N = 24)	30 mg (N = 28)	*F4,168*	*P* =
Visual Analog Scale (VAS)							
Any drug effect	2.4 ± 5.5	68 ± 26***	86 ± 17***###	86 ± 26***##	88 ± 17***###	205.35	<0.001***
>25, N (%)	1 (2)	26 (93)***	33 (100)***	22 (92)***	28 (100)***		
>50, N (%)	0 (0)	20 (71)***	31 (94)***#	22 (92)***	27 (96)***#		
>75, N (%)	0 (0)	10 (36)***	26 (79)***###	21 (88)***###	21 (75)***##		
100, N (%)	0 (0)	6 (21)***	13 (39)***	10 (42)***	16 (57)***#		
Good drug effect	1.4 ± 3.9	68 ± 25***	86 ± 18***##	80 ± 30***	84 ± 18***#	177.31	<0.001***
>25, N (%)	1 (2)	26 (93)***	33 (100)***	21 (88)***	28 (100)***		
>50, N (%)	0 (0)	22 (79)***	30 (91)***	21 (88)***	27 (96)***		
>75, N (%)	0 (0)	10 (36)***	26 (79)***###	18 (75)***##	19 (68)***#		
Bad drug effect	0.0 ± 0.2	16 ± 27*	22 ± 30***	37 ± 35***#	27 ± 32***	12.37	<0.001***
>25, N (%)	0 (0)	4 (14)**	10 (30)***	14 (58)***##	10 (36)***		
>50, N (%)	0 (0)	4 (14)**	6 (18)**	10 (42)***#	9 (32)***		
>75, N (%)	0 (0)	3 (11)*	2 (6)	4 (17)**	2 (7)		
Anxiety	0.0 ± 0.0	6.4 ± 17	6.1 ± 16	19 ± 29***	17 ± 27***	6.94	<0.001***
>25, N (%)	0 (0)	2 (7)	4 (12)*	5 (21)**	6 (21)***		
>50, N (%)	0 (0)	2 (7)	2 (6)	4 (17)**	3 (11)*		
>75, N (%)	0 (0)	1 (4)	0 (0)	2 (8)	2 (7)		
Ego Dissolution	0.3 ± 1.4	47 ± 37***	59 ± 35***	65 ± 38***	78 ± 30***###	50.25	<0.001***
>25, N (%)	0 (0)	17 (61)***	27 (82)***	19 (79)***	26 (93)***##		
>50, N (%)	0 (0)	13 (46)***	22 (67)***	18 (75)***#	25 (89)***##		
>75, N (%)	0 (0)	8 (29)***	14 (42)***	15 (63)***#	17 (61)***#		
5-Dimensions of Altered States of Consciousness (5D-ASC) scale							
Oceanic Boundlessness (OB)(%)	0.6 ± 2.4	24 ± 21***	31 ± 23***	41 ± 29***#	37 ± 20***	32.58	<0.001***
>25, N (%)	0 (0)	10 (36)***	18 (55)***	14 (58)***	19 (68)***#		
>50, N (%)	0 (0)	4 (14)**	9 (27)***	10 (42)***#	7 (25)***		
>75, N (%)	0 (0)	1 (4)	1 (3)	3 (13)*	2 (7)		
Anxious Ego-Dissolution (AED)(%)	0.0 ± 0.0	9.3 ± 15**	10 ± 11***	25 ± 20***###+++	17 ± 15***	21.29	<0.001***
>25, N (%)	0 (0)	2 (7)	4 (12)*	12 (50)***##++	7 (25)***		
>50, N (%)	0 (0)	1 (4)	0 (0)	3 (13)*	2 (7)		
>75, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
List of Complaints (LC) total score							
Before, N	0.8 ± 1.3	1.0 ± 1.7	1.1 ± 2.1	1.5 ± 2.2	0.5 ± 1.2	1.29	NS
Acute adverse effects, up to 12 h, N	1.8 ± 2.5	8.9 ± 7.6***	11 ± 8.2***	13 ± 10***	13 ± 8.6***	19.05	<0.001***
Subacute adverse effects, up to 24 h, N	1.7 ± 3.1	2.4 ± 2.6	4.0 ± 5.3*		4.1 ± 4.2*	3.96α	0.010*
Parameters describing the effect over time curve (VAS any drug effect)							
time to effect onset	mean + SD	0.8 ± 0.3+††	0.5 ± 0.3#	0.4 ± 0.3##	0.7 ± 0.4+††	7.27β	<0.001***
time to maximal effect	mean + SD	2.1 ± 0.5	2.1 ± 1.0	1.9 ± 0.8	2.1 ± 0.8	2.54β	0.064
time to effect offset	mean + SD	6.3 ± 2.1	5.3 ± 1.7	5.0 ± 1.5	7.2 ± 2.2	0.52β	0.672
effect duration	mean + SD	5.6 ± 2.2	4.9 ± 1.7	5.1 ± 1.8	6.4 ± 2.3	1.34β	0.269
range duration	hours	2.5–10	2.6–10	2.4–8.0	3.7–12		
<6h	N (%)	20 (71)	28 (88)	15 (65)	16 (57)		
6–7h	N (%)	0 (0)	1 (3)	4 (17)	2 (7)		
7–8h	N (%)	3 (11)	1 (3)	4 (17)	3 (11)		
>8h	N (%)	5 (18)	2 (6)	0 (0)	7 (25)		
Psilocin plasma concentration							
Cmax ng/mL		14 ± 3.4	18 ± 5.4#	20 ± 5.4###	25 ± 8.1###+++†	21.5γ	<0.001***
AUC∞ ng*h/mL		61 ± 15	88 ± 22###	90 ± 37###	121 ± 30###+++†††	35.2γ	<0.001***

Values are Emax (maximal effects) shown as mean ± SD or N, number of subjects (%) or count of adverse events; SD, standart deviation; *P < 0.05, **P < 0.01, ***P < 0.001 compared to placebo, #P < 0.05, ##P < 0.01, ###P < 0.001 compared to 15 mg; +P < 0.05, ++P < 0.01, +++P < 0.001 compared to 20 mg; †P < 0.05, ††P < 0.01, †††P < 0.001 compared to 25 mg; α, F(3,145); β, F(3,66); γ, F(3,108).

± 0.8 h for all doses, respectively. The effect duration was 5.5 ± 2.1 h for all doses. Respective values for each dose are shown in Table 2. Values did not differ relevantly across the dose range tested. Subjective effects of psilocybin did not differ if psilocybin was administered first or after another treatment.

3.2. Acute effects of psilocybin on vital signs

Psilocybin produced significant acute and transient increases in blood pressure and body temperature. Clear dose dependence was not observed. Systolic blood pressure values > 140, > 160, and > 180 mmHg were observed in 50%, 6%, and 0% of all psilocybin administrations, respectively (Table 3). No severe hypertension (systolic blood pressure > 180 mmHg) was observed. Maximal diastolic and systolic blood pressure values among the 113 psilocybin administrations were 115 and 180 mmHg, respectively. A peak heart rate > 100 beats/min was reached in 7%, 3%, 4%, and 11% of the administrations of 15, 20, 25, and 30 mg psilocybin, respectively. Over all 113 psilocybin administrations, tachycardia (> 100 beats/min) was observed in 7%. The highest heart rate of any participant was 140 beats/min. Body temperature increased dose-dependently with values > 38 °C reached in 7%, 9%, 17%, and 32% of administrations of 15, 20, 25, and 30 mg psilocybin. Overall, psilocybin increased body temperature to > 38°C in 16% of all psilocybin administrations. The highest body temperature was 39.0°C. No hyperpyrexia (> 40°C) occurred (Table 3). Vital sign changes did not differ if psilocybin was administered first or after another treatment. Over all participants in Study 1 (Becker et al., 2022), psilocybin did not increase the QTc time 2.5 h after administration compared with the QTc time that was measured 1 h prior. The longest QTc interval that was observed in any participant was 481 ms 2.5 h after psilocybin administration.

3.3. Adverse effects of psilocybin

Psilocybin produced significant acute and subacute adverse effects on the List of Complaints compared with placebo (Table 2). Adverse

Table 3
Maximal effects of psilocybin on vital signs.

Psilocybin dose	Placebo (N = 60)	15 mg (N = 28)	20 mg (N = 33)	25 mg (N = 24)	30 mg (N = 28)	*F4,168*	*P* =
Diastolic blood pressure (mean ± SD, mmHg)	81 ± 7	89 ± 8***	89 ± 7 ***	88 ± 7***	93 ± 8***	16.296	<0.001***
>90, N (%)	4 (7)	10 (36)**	11 (33)**	8 (33)**	13 (46)***		
>100, N (%)	0 (0)	4 (14)**	3 (9)*	0 (0)	5 (18)**		
Max, mmHg	95	111	104	100	115		
Systolic blood pressure (mean ± SD, mmHg)	131 ± 10	140 ± 11**	141 ± 13***	136 ± 11	146 ± 14***$	9.405	<0.001***
>140, N (%)	8 (13)	13 (46)**	17 (52)***	8 (33)	19 (68)***$		
>160, N (%)	0 (0)	1 (4)	2 (6)	1 (4)	3 (11)*		
>180, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Max, mmHg	156	163	170	161	180		
Heart rate (mean ± SD, beats/min)	74 ± 10	78 ± 11	79 ± 10	78 ± 12	82 ± 17	2.387	NS
>80, N (%)	15 (25)	12 (43)	14 (42)	10 (42)	12 (43)		
>100, N (%)	1 (2)	2 (7)	1 (3)	1 (4)	3 (11)		
>120, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)		
Max, beats/min	108	104	114	108	140		
Body temperature (mean ± SD, °C)	37.1 ± 0.3	37.6 ± 0.4***	37.6 ± 0.4***	37.6 ± 0.4***	37.9 ± 0.5***#	24.253	<0.001***
>38, N (%)	0 (0)	2 (7)	3 (9)*	4 (17)**	9 (32)***#+		
Max, °C	37.8	38.7	39.0	38.5	38.8		

Values are mean ± SD or N, number of subjects (%); SD, standard deviation; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with placebo, #$P < 0.05$ compared with 15 mg, +$P < 0.05$ compared with 20 mg, $P $< 0.05 compared with 25 mg. Proportions were compared using Fisher's exact test.

effects were comparable at the 15, 20, 25, and 30 mg doses and greater than with placebo (Table 2). Specific acute and subacute complaints are listed in Table 4. The most frequent acute adverse effects included fatigue, lack of concentration, headache, lethargy, vertigo, feeling of physical or emotional weakness, decreased appetite, nausea, feeling dull, and being easily exhausted (Table 4). The most frequent subacute adverse effects included tiredness, headache, lack of energy, neck pain, and feeling dull (Table 4). Acute anxiety on the List of Complaints was reported by 7%, 6%, 38%, and 21% of the participants at 15, 20, 25, and 30 mg psilocybin, respectively, and in one participant after placebo administration (Table 4). The number of adverse effects was unchanged if psilocybin was administered first or after another treatment. Five participants (6%) reported flashbacks after psilocybin. In four of the participants, flashbacks reportedly occurred once 30 ± 29 h (mean ± SD; range: 10–72 h) after psilocybin administration. One participant reported reoccurring visual flashbacks that were not disruptive or

Table 4
Acute and subacute advere effects of psilocybin on the List of Complaints.

Psilocybin Dose	Acute adverse effects (up to 12 h)					Subacute adverse effects (up to 24 h)			
	Placebo (N = 60)	15 mg (N = 28)	20 mg (N = 33)	25 mg (N = 24)	30 mg (N = 28)	Placebo (N = 60)	15 mg (N = 28)	20 mg (N = 33)	30 mg (N = 28)
N (%)									
Fatigue	37 (62)	23 (82)	28 (85)*	18 (75)	25 (89)*	31 (52)	18 (64)	28 (85)**	17 (61)+
Lack of concentration	0 (0)	17 (61)***	19 (58)***	13 (54)***	15 (54)***	1 (2)	1 (4)	4 (12)	3 (11)
Headache	18 (30)	14 (50)	17 (52)*	13 (54)*	18 (64)**	15 (25)	10 (36)	13 (39)	14 (50)*
Lethargy	4 (7)	11 (39)***	13 (39)***	11 (46)***	16 (57)***	4 (7)	3 (11)	8 (24)*	10 (36)**
Vertigo	0 (0)	9 (32)***	13 (39)***	9 (38)***	16 (57)***	0 (0)	0 (0)	0 (0)	1 (4)
Feeling of weakness	3 (5)	10 (36)***	13 (39)***	10 (42)***	14 (50)***	1 (2)	2 (7)	2 (6)	6 (21)**
Decreased appetite	1 (2)	7 (25)**	11 (33)***	9 (38)***	18 (64) ***##+	1 (2)	0 (0)	1 (3)	4 (14)*
Nausea	1 (2)	7 (25)**	17 (52)***#	11 (46)***	9 (32)***	1 (2)	0 (0)	2 (6)	2 (7)
Feeling dull	6 (10)	12 (43)**	13 (39)**	4 (17)	12 (43)**	2 (3)	2 (7)	7 (21)**	7 (25)**
Easily exhausted	1 (2)	8 (29)***	7 (21)**	9 (38)***	15 (54)***+	1 (2)	0 (0)	1 (3)	5 (18)*
Crying	0 (0)	4 (14)**	8 (24)***	10 (42)***#	11 (39)***	0 (0)	0 (0)	1 (3)	0 (0)
Dry mouth	1 (2)	9 (32)***	8 (24)***	6 (25)**	9 (32)***	1 (2)	1 (4)	0 (0)	3 (11)
Chills	2 (3)	7 (25)**	12 (36)***	5 (21)*	7 (25)**	1 (2)	0 (0)	2 (6)	0 (0)
Dizziness	0 (0)	7 (25)***	8 (24)***	7 (29)***	9 (32)***	0 (0)	0 (0)	0 (0)	0 (0)
Tension	1 (2)	8 (29)***	11 (33)***	4 (17)*	8 (29)***	1 (2)	1 (4)	1 (3)	1 (4)
Uneasiness	1 (2)	4 (14)*	7 (21)**	9 (38)***	9 (32)***	2 (3)	0 (0)	2 (6)	1 (4)
Hypersomnia	3 (5)	8 (29)**	7 (21)*	6 (25)*	7 (25)*	2 (3)	5 (18)*	5 (15)	5 (18)*
Memory impairment	0 (0)	5 (18)**	8 (24)***	6 (25)***	8 (29)***	0 (0)	0 (0)	1 (3)	0 (0)
Micturition urgency	1 (2)	6 (21)**	6 (18)**	8 (33)***	6 (21)**	4 (7)	4 (14)	2 (6)	1 (4)
Obsessive rumination	1 (2)	6 (21)**	5 (15)*	5 (21)**	9 (32)***	2 (3)	1 (4)	4 (12)	2 (7)
Sensory processing sensitivity	0 (0)	5 (18)**	9 (27)***	2 (8)	8 (29)***	0 (0)	0 (0)	0 (0)	2 (7)
Restlessness	0 (0)	5 (18)**	7 (21)***	8 (33)***	4 (14)**	0 (0)	1 (4)	1 (3)	1 (4)
Neck pain	6 (10)	3 (11)	6 (18)	5 (21)	8 (29)	6 (10)	4 (14)	8 (24)	6 (21)
Discomfort	0 (0)	4 (14)**	4 (12)*	6 (25)***	6 (21)***	0 (0)	2 (7)	1 (3)	1 (4)
Hyperhidrosis	0 (0)	4 (14)**	3 (9)*	6 (25)***	7 (25)***	0 (0)	2 (7)	3 (9)*	2 (7)
Throat tightness	2 (3)	4 (14)	5 (15)	4 (17)	6 (21)*	1 (2)	1 (4)	0 (0)	3 (11)
Anxiety	1 (2)	2 (7)	2 (6)	9 (38) ***#++	6 (21)**	0 (0)	1 (4)	0 (0)	1 (4)
Hot flush	1 (2)	3 (11)	4 (12)	4 (17)*	6 (21)**	2 (3)	0 (0)	1 (3)	3 (11)
Negative thoughts	0 (0)	3 (11)*	4 (21)*	5 (21)**	5 (18)**	1 (2)	0 (0)	1 (3)	0 (0)
Back pain	5 (8)	3 (11)	2 (6)	4 (17)	5 (18)	5 (8)	2 (7)	5 (15)	3 (11)

N, number of subjects (%); *P < 0.05, **P < 0.01, ***P < 0.001 compared with placebo, #P < 0.05, ##P < 0.01 compared with 15 mg, +P < 0.05, ++P < 0.01, +++P < 0.001 compared with 20 mg (Fisher's exact test).

frightening but were occurring over several months. Flashbacks of Study 1 and Study 2 are also described in detail elsewhere (Muller et al., 2022). No serious adverse reactions occurred. Additional possibly treatment-related adverse events that were spontaneously reported within the first 48 h after discharge from the study visits included headache (10% after psilocybin, 7% after placebo), depressive mood (4% after psilocybin, 0% after placebo), nausea (3% after psilocybin, 0% after placebo), restlessness (2% after psilocybin, 0% after placebo), insomnia/nightmares (2% after psilocybin, 0% after placebo), circulatory collapse (1% after psilocybin, 0% after placebo), paranoid thoughts (1% after psilocybin, 0% after placebo), tendency to cry (1% after psilocybin, 0% after placebo), nosebleed (1% after psilocybin, 0% after placebo), and muscle twitches (1% after psilocybin, 0% after placebo).

3.4. Plasma psilocin concentrations

Peak plasma psilocin (active metabolite of psilocybin) concentrations and areas under the plasma concentration curve for all dose groups are shown in Table 2. The full pharmacokinetics of psilocybin of the studies are reported in detail elsewhere (Holze et al., 2023a; Ley et al., 2023).

3.5. Effects of psilocybin on kidney and liver function and changes in blood cell counts

At the end of the study, 28 ± 18 days (mean ± SD) after the last substance administration, plasma creatinine levels and the estimated glomerular filtration rate were unchanged compared with the start of the study (Table 5). Similarly, plasma levels of alanine aminotransferase and γ-glutamyl transpeptidase were similar at the screening visit and end-of-study visit. Hemoglobin levels decreased during the study because of the blood sampling. Red and white blood cell counts remained unchanged.

Table 5
Kidney and liver function parameters and blood cell counts before and at study end.

Screening		End of Study	*t*-test	
Kidney and liver function	N = 85		t	P =
Creatinine (normal: <97 μM)				
mean ± SD, μM (range)	71 ± 13 (48–107)	71 ± 14 (42–100)	0.25	NS
Glomerular filtration rate CCR (normal: >90 ml/min)				
mean ± SD, ml/min (range)	109 ± 12 (79–129)	109 ± 13 (80–134)	0.08	NS
Alanine aminotransferase (normal: <59 U/l)				
mean ± SD, U/l (range)	23 ± 10 (7–64)	22 ± 13 (6–99)	0.24	NS
Blood cell counts	**N = 85**			
White blood cells (normal: 3.5–10.0 x109/l)				
mean ± SD, x109/l (range)	6.1 ± 1.5 (2.3–10)	6.2 ± 1.6 (2.5–11)	−0.60	NS
Red blood cells (normal: 4.2–6.3 x1012/l)				
mean ± SD, x1012/l (range)	4.6 ± 0.4 (3.8–5.6)	4.6 ± 0.4 (3.7–5.8)	1.79	NS
Hemoglobin (normal: 120–180 g/l)				
mean ± SD, g/l (range)	140 ± 13 (117–180)	137 ± 14 (104–167)	4.08	<0.001***
Thrombocytes (normal: 150-450 x109/l)				
mean ± SD, x109/l (range)	248 ± 51 (160–376)	251 ± 56 (147–431)	−0.79	NS

Values are mean ± SD: standard deviation (range); N: number of subjects.

3.6. Participants' interest in using psilocybin again

Seventy-two percent of the participants were psilocybin-naive at the start of the study, and the other 28% had limited experience with psilocybin (i.e., maximum ≤5 exposures). Eighty-five participants were asked at the end of the study whether they would consider taking psilocybin again. Two participants (2%) reported that they would probably not take psilocybin again under any circumstances. Seventy participants (82%) reported that they would consider taking psilocybin again. Thirteen participants (15%) reported that they might consider taking psilocybin again. Thirty-eight participants (45%) would only take psilocybin in another clinical study or safe environment. Fifty-two participants (61%) indicated that they would take psilocybin together with friends in a recreational setting. Twenty-six participants (31%) indicated that they would take psilocybin in nature rather than in a hospital setting. Seventy-four participants (87%; 34 women, 41 men) reported a positive overall psilocybin experience, nine participants (11%; seven women, one man) reported a neutral experience, and two participants (2%; one woman and one man) reported a disappointing or bad experience. Forty-two participants (49%) reported that a past drug experience with a psychedelic compound had an influence on their experience during the study, whereas 24 participants (28%) reported that their earlier experiences did not have an impact.

4. Discussion

The present study analyzed pooled data from three randomized controlled Phase 1 studies of psilocybin and characterized acute subjective, autonomic, and adverse effects of different doses in healthy participants. In contrast to the primary reports of each study, the present pooled analysis focused on reporting proportions of participants who exhibited extreme values rather than population means.

Overall, positive subjective effects, including "good drug effect" and OB, were reached already at the lower doses and to a higher extent than negative subjective drug effects, including "bad drug effect," "anxiety," and AED. These data may help identify a therapeutic dose to be used in psilocybin-assisted psychotherapy that induces strong and primarily positive acute effects and no or only minimal negative subjective effects. Several clinical studies have shown that a positive acute psychedelic experience predicted long-term therapeutic outcomes in patients with depression, anxiety, or tobacco dependence (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Holze et al., 2023b; Roseman et al., 2017; Ross et al., 2016) and long-term positive mood effects in healthy participants (McCulloch et al., 2022; Schmid and Liechti, 2018). Therefore, inducing mostly positive effects is desirable, although challenging experiences may also have therapeutic potential (Barrett et al., 2016; Carbonaro et al., 2016; Gashi et al., 2021). The 20, 25, and 30 mg doses of psilocybin appear to be comparable when considering the magnitude of their positive subjective effects and stronger than the 15 mg dose. All four doses induced greater negative subjective effects ("bad drug effect") compared with placebo, but significant "anxiety" occurred only with the 25 and 30 mg doses. The subjective "bad drug effect" was not defined exclusively as a psychological effect but could also mean that the participants were feeling physical discomfort, such as nausea or headache. "Oceanic Boundlessness" and AED ratings were comparable over all doses of psilocybin. "Ego dissolution" assessed over time increased with the dose and exhibited a stronger association with "good drug effect" than with "bad drug effect", suggesting a rather positive than negative valence.

The average onset time, time to peak effect, and effect duration (mean ± SD) over all doses of psilocybin were 0.6 ± 0.4 h, 2.1 ± 0.8 h, and 5.5 ± 2.1 h, respectively. Previously, the onset time of psilocybin was reported to be 20–40 min, and the duration was reported to be shorter than 6 h (Hasler et al., 2004), which was confirmed by our analysis. However, the time to peak effects in the present analysis was 2 h and longer than the previously reported 60–90 min (Hasler et al.,

2004).

With regard to cardiovascular risks, psilocybin induced mild sympathomimetic activation in most participants. Tachycardia (> 100 beats/min) was observed in 7% of psilocybin administrations, and hypertension (systolic blood pressure > 140 mmHg) was observed in 50% of psilocybin administrations. Tachycardia occurred in 3% and 20% of the participants, and hypertension occurred in 52% and 53% after the administration of equivalent doses of 20 mg psilocybin and 0.1 mg LSD, respectively (Holze et al., 2022a). In contrast, MDMA, which is also used in substance-assisted therapy, induced tachycardia in 33% of the participants and hypertension in 90% of the participants in a similar analysis of pooled studies (Vizeli and Liechti, 2017). Thus, MDMA produces overall clearly greater cardiovascular stimulation than the psychedelics psilocybin and LSD at commonly used doses. Psilocybin may thus be an alternative to MDMA in patients with cardiovascular risk factors.

The data confirmed the overall comparable cardiovascular stimulation of psilocybin and LSD at equivalent psychoactive doses (Holze et al., 2022b). In another previous study, psilocybin also produced comparable sympathomimetic activation at doses of 10, 20, and 30 mg/70 kg body weight (Carbonaro et al., 2018) as reported in the present study. The present analysis also showed that psilocybin increased body temperature dose-dependently. Psilocybin increased body temperature to > 38°C in 16% of all psilocybin administrations and comparably to LSD (Holze et al., 2022a). Only in one participant did body temperature increase above 38.8°C (to 39.0°C), which was presumably because of a beginning COVID-19 infection. No hyperpyrexia (> 40°C) occurred. We did not find significant QTc interval prolongation during the peak response to psilocybin compared with the QTc interval before psilocybin administration in Study 1 (Becker et al., 2022).

Acute negative psychological effects are considered the main risk of psychedelic substance use in humans (Holze et al., 2022a; Johnson et al., 2008). However, psilocybin also induces physical discomfort. Frequent acute adverse events were general exhaustion, including fatigue, lack of concentration, lethargy, vertigo, feeling of weakness, and decreased appetite. The reported subacute adverse effects up to 24 h suggest a state of "exhaustion" akin to fatigue that is experienced after intense mental or physical activity. In contrast, between-session adverse events were equally frequent after psilocybin and placebo administration, indicating no prolonged after-effects of psilocybin beyond 24 h. Notably, adverse effects, such as fatigue and headache, could also be seen in participants after placebo administration, so lying in a hospital bed for most of the day and not being able to consume caffeine could have exacerbated these symptoms.

Headache and nausea are two adverse events that have been typically described in other clinical studies after psilocybin administration (Dodd et al., 2022; Johnson et al., 2012; Rossi et al., 2022). In the present analysis, headache up to 12 h after psilocybin administration occurred in 55% of the participants and up to 24 h in 42% of the participants. Nausea up to 12 h after administration occurred in 39% of the participations and up to 24 h in 4% of the participations. There was no clear dose dependence for headache or nausea. Anxiety on the List of Complaints was indicated by 38% of the participants who ingested the 25 mg psilocybin. During the study sessions, anxiety could be reduced by verbal support in all participants, and benzodiazepines were not used. No cases of severe anxiety, panic attacks, or acute suicidality occurred. Overall acute adverse effects were quite common and mostly not dose-dependent within the 15–30 mg dose range. Adverse effects of psilocybin were transient and not sufficiently disabling or severe to require medical intervention. As subacute adverse events, flashbacks and hallucinogen persisting perception disorder have been previously described following the use of psychedelics. However, the frequency and nature of flashbacks and risk factors are still unidentified (Halpern et al., 2016; Martinotti et al., 2018). A pooled analysis of several studies was published in 2022 (Muller et al., 2022), which also included Studies 1 and 2 in the present pooled analysis. Together with the present analysis, the findings indicate that even in controlled studies, flashbacks are possible but mostly transient and not frightening. One participant reported reoccurring visual flashbacks after psilocybin and LSD administration, which were not disruptive or frightening but were occurring over several months as already described previously (Muller et al., 2022). Hallucinogen persisting perception disorder (Halpern et al., 2016) was not observed in the present pooled analysis. Similar to the present analysis, flashbacks were reported by 7% of the participants within 24–86 h after LSD administration (Holze et al., 2022a).

In the present study, psilocybin did not influence average levels of liver enzymes 1 month after psilocybin administration. An expected decrease in hemoglobin levels was observed at the end-of-study visit. These findings were attributable to the overall blood loss of 250–800 ml through blood sampling during the test sessions as observed previously in similar studies (Holze et al., 2022a; Vizeli and Liechti, 2017) or after blood donation.

Retrospectively, 87% of the participants in the present analysis reported an overall positive subjective experience, whereas only 2% reported a disappointing or bad psilocybin experience. The results of this study indicate that psilocybin appears to be safe in a controlled setting with transient adverse effects. The safety data can partially be applied to the use of psilocybin in patients. The study participants typically had no or very little previous psilocybin experience, similar to most patients. Furthermore, psilocybin-assisted therapy is typically used sporadically 2–3 times and spaced several weeks apart in addition to conventional non-substance-assisted psychotherapy (Schmid et al., 2021). Consistent with the present data, there are no reports of acute serious adverse reactions to psilocybin or other serotonergic psychedelics in modern clinical studies (Andersen et al., 2021; Breeksema et al., 2022). However, these data were collected from mostly young and physically and psychiatrically healthy people. The results may also differ in patients with psychiatric or cardiovascular disorders.

The present study has several strengths. We used data from three randomized controlled trials that were conducted within the same highly controlled laboratory setting. All studies included similar numbers of male and female participants and used psilocybin capsules from the same batch that was well-characterized pharmaceutically with a known exact drug content. The doses in this pooled analysis were in the typical range that is used in clinical research with psilocybin in patients. Additionally, the doses of psilocybin were well defined. Drug dose is the most important known predictor of the psilocybin experience (Studerus et al., 2012).

The present study also has limitations. We pooled three studies that included different people. Only the 15 and 30 mg doses in Study 2 were administered in the same participants. Study 1 that included the 25 mg dose was not a placebo-controlled study, and measures were only assessed up to 7 h after psilocybin administration. In Studies 2 and 3, participants also ingested other substances (LSD and mescaline), which might have partially affected the psilocybin experience or changed expectations when administered before psilocybin. However, no significant main effect of order of the substance sessions was detected, and there was no interaction with dose when order was incorporated as an additional factor in the ANOVAs. Additionally, previous substance use has not been shown to affect the acute subjective effects of LSD in a previous smaller study (Holze et al., 2021). Another important caveat poses that although the unpleasant effects in our study were modest and transient, we only included psychiatrically healthy participants. Therefore, the risks of psilocybin use might be different in a more heterogeneous population and in patients in a therapeutic setting and need to be further investigated. Moreover, the participants were mostly young and physically healthy, but older patients or patients with cardiovascular risk factors may also be treated with psilocybin. Furthermore, we included 85 participants who received psilocybin a total of 113 times. This sample size is too small to detect infrequent (0.1–1%) or rare (<0.1%) adverse events. Additionally, there was no long-term follow-up. Although doses of psilocybin were well defined, individual differences in the bioavailability or metabolism of psilocybin were not

included in this study. In this analysis we have outlined acute safety concerns related to psilocybin administration but have not examined potential risk factors for adverse events. Previous analyses indicated that "emotional excitability" prior to drug intake predicts unpleasant or anxious reactions to psilocybin, whereas factors such as drug use, sex, and body weight do not relevantly alter acute effects or safety of psilocybin (Holze et al., 2023a; Studerus et al., 2012).

5. Conclusion

Single-dose administrations of psilocybin up to 30 mg were safe with regard to acute psychological and physical harm in healthy participants in a controlled clinical setting. Psilocybin induced mild cardiovascular stimulation. Acute subjective effects were predominantly positive, but transient anxiety and "bad drug effects" occurred. These safety data do not raise any concerns about single-dose, infrequent psilocybin administration in a controlled clinical setting. However, risks and benefits of using psilocybin in patients need further study.

Author contributions

IS analyzed the data. IS and FH wrote the manuscript. FH, AMB, LL, and NH conducted the research. MEL conceived the study, obtained funding, analyzed the data, and wrote the manuscript.

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Declaration of competing interest

MEL is a consultant for Mind Medicine, Inc. The other authors declare no conflicts of interests. Knowhow and data associated with this work and owned by the University Hospital Basel were licensed by Mind Medicine, Inc. Mind Medicine, Inc., had no role in financing, planning, or conducting the present study or the present publication.

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