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Single Intranasal Administration of the Psychedelic Mebufotenin for Treatment-Resistant Depression
A Randomized Clinical Trial

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IMPORTANCE Psychedelics represent a potential breakthrough for treatment-resistant depression; however, the prolonged in-clinic monitoring required for compounds such as psilocybin and lysergic acid diethylamide is a logistical hurdle to widespread use. Intranasal mebufotenin (5-methoxy-*N*,*N*-dimethyltryptamine), a 5-hydroxytryptamine 1A (5-HT_{1A}) and 5-HT_{2A} agonist associated with brief psychedelic experiences, may address this limitation.

OBJECTIVE To evaluate the safety, efficacy, and time to discharge readiness following a single dose of intranasal mebufotenin benzoate in adults with treatment-resistant depression.

DESIGN, SETTING, AND PARTICIPANTS Phase 2b, randomized, double-blind trial with an 8-week blinded follow-up conducted between September 2023 and April 2025 at 38 sites in Australia, Europe, and the US. Participants were aged 18 to 75 years with moderate to severe major depressive disorder nonresponsive to 2 to 5 antidepressant trials in the current episode. The last date of follow-up was April 28, 2025.

INTERVENTIONS After antidepressant washout as needed, participants were randomly assigned to receive a single dose of intranasal mebufotenin benzoate, 8 mg (n = 46), 12 mg (n = 73), or 0.3 mg (a low-dose comparator; n = 74), alongside psychological support.

MAIN OUTCOMES AND MEASURES The primary end point was total score change on the Montgomery-Åsberg Depression Rating Scale (MADRS; score range, 0-60; higher scores indicate more severe depression) from baseline to day 29 in the 12-mg vs 0.3-mg dose groups. Eighteen secondary end points were assessed for the 12-mg and 8-mg vs 0.3-mg doses. Discharge readiness was assessed starting 90 minutes after dosing.

RESULTS Among the 193 included participants, the mean age was 41 (SD, 11.1) years and 59.1% were female. From baseline to day 29, treatment with 12-mg intranasal mebufotenin benzoate vs the 0.3-mg dose (the primary end point) was associated with significantly reduced MADRS scores (mean score change, −11.1 [SD, 11.6] vs −5.5 [SD, 9.9], respectively; mean difference, −5.3 [95% CI, −8.9 to −1.8]; *P* = .003). The 8-mg dose also led to reduced scores from baseline to day 29 (mean score change, −12.5 [SD, 12.7]) vs the 0.3-mg dose (mean difference, −6.2 [95% CI, −10.2 to −2.1]; *P* = .003). MADRS reductions with the 8-mg and 12-mg doses were similar and significantly greater at all other time points from 2 to 57 days post dose vs the 0.3-mg dose. Day 29 response rates were 35%, 34%, and 12% and remission rates were 26%, 18%, and 8% in the 8-mg, 12-mg, and 0.3-mg dose groups, respectively. Treatment-emergent adverse events were reported in 76%, 85%, and 73% of participants in the 8-mg, 12-mg, and 0.3-mg dose groups, respectively; most events (99.7%) were mild or moderate. Overall, most participants were deemed ready for discharge within 2 hours post dose (85% for 8 mg and 78% for 12 mg).

CONCLUSIONS AND RELEVANCE In adults with treatment-resistant depression, single doses of intranasal mebufotenin benzoate were well tolerated and produced rapid, robust, and durable reductions in depressive symptoms. Intranasal mebufotenin benzoate may improve treatment access and convenience, requiring a shorter monitoring period and fewer clinic visits compared with psilocybin and esketamine, respectively.

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Research Summary
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Major depressive disorder is a debilitating psychiatric disorder affecting approximately 290 million people worldwide.[1] About one-third of patients with major depressive disorder have treatment-resistant depression, having had inadequate response to 2 or more trials with antidepressants,[2,3] and experience lower quality of life, greater emotional distress, increased risk of mortality by suicide, and higher health care costs compared with people with major depressive disorder that responds to treatment.[4-7]

Recent advances in treatment options for treatment-resistant depression include *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists (ketamine/esketamine) and transcranial magnetic stimulation, but these require frequent administration by qualified health care professionals, representing a significant logistical barrier for many patients.[8-10] Emerging research indicates that psychedelic treatments, mediated primarily through 5-hydroxytryptamine 2A receptor (5-HT_{2A}) agonism, offer potential advantages over current options due to their rapid onset of symptom improvement and sustained benefits after a single administration.[11-17] However, there are concerns about the feasibility and practicality of compounds such as psilocybin and lysergic acid diethylamide (LSD), which require 4 to 12 hours of in-clinic observation.[16-18] This underscores a clear unmet need for effective treatment-resistant depression therapies with a lower logistical burden.[19]

Mebufotenin benzoate nasal spray (BPL-003) is a novel, synthetic formulation of the psychedelic mebufotenin (5-methoxy-*N*,*N*-dimethyltryptamine [5-MeO-DMT]), a potent agonist of the 5-HT_{1A} and 5-HT_{2A} receptors associated with relatively short psychedelic experiences.[20,21] Intranasal mebufotenin benzoate is rapidly absorbed and eliminated,[21] with subjective acute psychedelic effects following a time course similar to systemic exposure (peak intensity, 8-15 minutes; return to baseline, 45-60 minutes).[20] In an open-label study in treatment-resistant depression, a single 10-mg dose of intranasal mebufotenin benzoate had acceptable safety and tolerability, with a rapid antidepressant effect that was sustained over 3 months.[22] The current phase 2b trial evaluated the efficacy, safety, and tolerability of single 8-mg and 12-mg doses of intranasal mebufotenin benzoate compared with a low-dose comparator in adults with treatment-resistant depression.

Key Points

Question Is mebufotenin benzoate nasal spray, a 5-hydroxytryptamine 1A (5-HT_{1A}) and 5-HT_{2A} agonist with a short psychedelic duration, effective, safe, and well tolerated in patients with treatment-resistant depression?

Findings In this randomized, double-blind, phase 2b trial of single doses of 8-mg or 12-mg mebufotenin benzoate nasal spray in 193 adults with treatment-resistant depression, the primary outcome of change from baseline in the Montgomery-Åsberg Depression Rating Scale total score at day 29 between the 12-mg dose and a subperceptual low-dose comparator (0.3 mg) was statistically significant (mean difference, −5.3 points).

Meaning Mebufotenin benzoate nasal spray demonstrates potential as an effective, well-tolerated therapy for treatment-resistant depression with a rapid recovery time.

Methods

Study Design and Participants

This double-blind, low-dose comparator–controlled, randomized, phase 2b trial was conducted from September 2023 to April 2025 at 38 sites across Australia, Germany, Poland, Spain, the UK, and the US (eAppendix 1 in Supplement 3). The trial consisted of a screening period followed by an 8-week blinded core study (eAppendix 2 in Supplement 3). Participants could enroll in an optional open-label extension study, with an additional 12-mg dose in some territories (to be reported separately).

Eligible participants were aged 18 to 75 years, diagnosed with single-episode (≥3 months and ≤2 years) or recurrent major depressive disorder (confirmed by Mini International Neuropsychiatric Interview), had at least moderate severity of depression (defined by a Hamilton Depression Rating Scale score ≥19 and a Clinical Global Impression–Severity [CGI-S] score ≥4 at screening and baseline), and were nonresponsive to 2 to 5 antidepressants after 8 weeks or longer in the current episode. Full eligibility criteria are described in eAppendix 3 in Supplement 3.

The trial was conducted in accordance with the Declaration of Helsinki[23] and the International Council for Harmonization Good Clinical Practice guidelines, and the trial protocol (Supplement 1) was approved by the required institutional review boards/independent ethics committees (eAppendix 4 in Supplement 3). All participants provided written informed consent. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Procedures

Eligible participants were initially randomized 1:1:1 to receive a single intranasal dose of mebufotenin benzoate, 8 mg, 12 mg, or 0.3 mg (subperceptual low-dose comparator). The planned randomization ratio was modified to 3:1:3 approximately midway through recruitment for operational reasons, and recruitment efforts were focused into the 2 groups used in the primary end point analysis (12 mg and 0.3 mg), resulting in a net randomization of approximately 3:2:3. Randomization was stratified by region (US or rest of world). A block size of 6 was used in the original randomization scheme and was changed to 7 under the amended scheme. Further randomization details are described in eAppendix 5 in Supplement 3.

Participants, investigators, independent Montgomery-Åsberg Depression Rating Scale (MADRS) raters, and all other site personnel, including the sponsor and clinical research organization teams, were blinded. To preserve blinding, site personnel present in the dosing room during the acute psychedelic effects were not permitted to conduct outcome measures.

To assess intranasal mebufotenin benzoate as a monotherapy, participants who were taking antidepressants at screening underwent a supervised washout following local treatment guidelines, which was completed at least 2 weeks prior to dosing. Participants received manualized, psychological support from qualified facilitators before, during, and after dosing (eAppendix 6 in Supplement 3).

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On day 1, a single dose of mebufotenin benzoate, 8 mg, 12 mg, or 0.3 mg, was delivered as a single spray into 1 nostril by a trained clinician using a preloaded Aptar Unidose dry powder intranasal spray device. The dosing session was held in a private, comfortable, and aesthetically pleasant room, with a physician in close proximity. Study procedures during and after dosing are detailed in eAppendix 5 in Supplement 3. Participants were assessed for discharge readiness using prespecified criteria (eAppendix 7 in Supplement 3) every 30 minutes starting 90 minutes after dosing. The earliest participants could be discharged was 4 hours after dosing. Follow-up visits to assess efficacy and safety were conducted every 2 weeks from day 2 (the day after dosing) to day 57.

Efficacy Assessments

Trained, certified raters assessed all outcome measures. All MADRS assessments were conducted remotely by independent, centralized, qualified, blinded raters via video call using the Structured Interview Guide for MADRS[24]; all MADRS end points were based on the total score. The primary end point was the difference in mean change from baseline to day 29 in MADRS total score (range, 0-60; higher scores indicate more severe depression) between the 12-mg and 0.3-mg doses of intranasal mebufotenin benzoate. Key secondary end points (in hierarchical testing order following the primary end point) were change from baseline in MADRS score (1) to day 8 between the 12-mg and 0.3-mg dose groups; (2) to day 29 between the 8-mg and 0.3-mg dose groups; and (3) to day 8 between the 8-mg and 0.3-mg dose groups. Additional end points included change from baseline in MADRS score for all remaining time points; percentage of responders (≥50% reduction in MADRS score), percentage of remitters (MADRS score ≤10); change from baseline in CGI-S, Quality of Life in Depression Scale (QLDS), and 16-Item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) scores; subjective experience and its relationship to outcomes; expectancy and its relationship to outcomes; and adequacy of blinding (eAppendix 8 in Supplement 3).

Safety Assessments

Adverse event data were collected from the time of consent to the last visit and graded by investigators for severity, seriousness, and relationship to the study drug. Adverse events occurring after dosing were deemed treatment-emergent adverse events (TEAEs) and classified as drug related if there was a reasonable possibility in the investigator's opinion that the study drug or procedure caused the event. Suicidality was assessed using the Columbia-Suicide Severity Rating Scale at every visit. Laboratory assessments, physical examinations (including nasal site assessment), 12-lead electrocardiogram, and vital sign measurement were performed throughout the study (see schedule of assessments in Section 7.1 of the trial protocol [Supplement 1]).

Statistical Analysis

The statistical analysis plan is available in Supplement 2. The study was designed with 80% power to detect a treatment difference of 6 points on the MADRS, with a common SD of 12 points, between the 12-mg and 0.3-mg dose groups,[25] using a 2-group *t* test with an $\alpha = .05$ and accounting for a dropout rate of 15% or less. Efficacy analyses were performed on the primary analysis set; safety analyses were performed on the safety analysis set (defined in eAppendix 9 in Supplement 3).

Primary, key secondary, and select secondary end points were analyzed using a mixed-effects model for repeated measures (eAppendix 9 in Supplement 3). A prespecified sensitivity analysis by randomization scheme was performed to assess the impact of the change in randomization on the primary end point. The correlation between predose treatment expectancy and MADRS score change from baseline to day 29 was analyzed using Pearson correlation coefficients. Percentage of responders and remitters, adequacy of blinding, and safety outcomes were summarized using descriptive statistics.

To account for type I error, a hierarchical testing procedure was applied for the primary and key secondary end points and continued until the first nonsignificant test was observed, with all testing performed at a 2-sided $\alpha = .05$ level. Analyses for other secondary end points were not adjusted for multiple comparisons.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Participants

Of the 443 participants enrolled, 247 had screening failures and 193 were randomized and included in the primary analysis and safety analysis sets (intranasal mebufotenin benzoate dose groups: 8 mg, n = 46; 12 mg, n = 73; 0.3 mg, n = 74) (**Figure 1**). The dropout rate was low (19/193 [9.8%]); the most common reason was participant withdrawal (8 mg, n = 2 [40.0%]; 12 mg, n = 3 [75.0%]; 0.3 mg, n = 10 [100.0%]). No participants withdrew due to adverse events.

Demographics and baseline clinical characteristics were generally well balanced across groups (**Table 1**). Mean baseline measures were, for MADRS total score, 31.8 (SD, 5.8), time since major depressive disorder diagnosis, 13.4 (SD, 9.9) years, duration of current depressive episode, 2.6 (SD, 2.7) years, and number of failed antidepressants in the current episode, 2.3 (SD, 0.6). Twelve participants started antidepressants during the study (8 mg, n = 3; 12 mg, n = 6; 0.3 mg, n = 3). Six participants (3.1%) reported previous exposure to psychedelic drugs as part of their medical history.

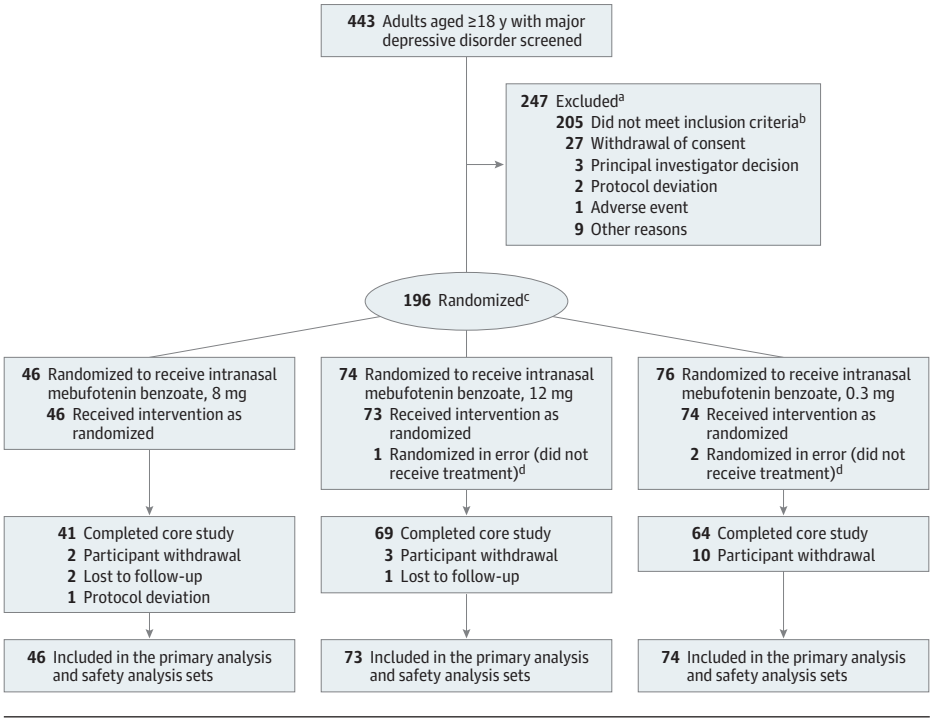
Efficacy

All primary and key secondary end points were met. There was a statistically significant and clinically relevant difference in change from baseline in MADRS scores between the 12-mg and 0.3-mg dose groups and between the 8-mg and 0.3-mg dose groups, from the first (day 2) to last (day 57) assessment, including day 29. The least-squares mean difference in the MADRS score change from baseline to day 29 between the 12-mg dose and the 0.3-mg dose (the primary end point) was −5.3 (95% CI, −8.9 to −1.8; $P = .003$); the least-squares mean difference in the MADRS score change from baseline to day 29 between the 8-mg dose and the 0.3-mg dose was −6.2

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Figure 1. Flow Diagram of Participants in a Trial of Single Administration of Intranasal Mebufotenin Benzoate for Treatment-Resistant Depression



[a]Seven participants were initially excluded and were enrolled after rescreening (participants were permitted to repeat the full screening process only once).

[b]Detailed reasons for exclusion were not maintained.

[c]Randomization was stratified by region (US or rest of world).

[d]Two participants randomized in error did not meet predose blood pressure requirements; 1 participant was lost to follow-up after predose illness.

(95% CI, −10.2 to −2.1; P = .003) (**Figure 2A-**D and **Table 2**). Figure 2E shows observed MADRS change scores at day 29 and eFigure 1 in Supplement 3 shows observed MADRS scores at each time point. Sensitivity analysis of the MADRS day 29 data showed no appreciable outcome differences between randomization schema (eFigure 2 in Supplement 3). When antidepressant washout status was included as a covariate in the analysis, washout status was not associated with the primary efficacy outcome (P > .99).

Responder rates at each time point were similar for both active doses and were numerically greater than the 0.3-mg dose group; at day 29, the remitter rate was numerically greater in the 8-mg dose group (26%) vs the 12-mg (18%) and 0.3-mg (8%) dose groups (**Table 3**). Significant improvements in symptoms of depression assessed by the CGI-S, QLDS, and QIDS-SR-16 were observed for the 8-mg and 12-mg dose groups vs the 0.3-mg dose group at all time points, except the QIDS-SR-16 at days 29 and 57 for the 8-mg vs 0.3-mg dose comparison (Figure 2 and Table 2).

After dosing on day 1, the mean total Mystical Experience Questionnaire (MEQ-30) score was higher with the 8-mg and 12-mg doses (2.4 [SD, 1.4] and 2.6 [SD, 1.3], respectively) vs the 0.3-mg dose (0.4 [SD, 0.6]) (eFigure 3 in Supplement 3). There was no evidence of a correlation between MEQ-30 total score on day 1 and change from baseline in MADRS score at day 29 (eFigure 4 in Supplement 3), nor was there a correlation between positive or negative expectancy and change from baseline in MADRS score at day 29 (eTable 1 in Supplement 3). Results from the Bang Blinding Index indicated significant degrees of functional unblinding of clinicians and participants; however, blinding was more preserved for the independent external MADRS raters (eFigure 5 in Supplement 3).

Safety

Treatment-emergent adverse events were reported by 76.1% of participants in the 8-mg, 84.9% in the 12-mg, and 73.0% in the 0.3-mg dose groups (**Table 4**). Across all groups, most TEAEs were mild or moderate (739/741 events [99.7%]). Two severe TEAEs of panic attack were reported by 1 participant in the 12-mg dose group, which were deemed related to the study treatment. Most TEAEs in the 8-mg (72%) and 12-mg (78%) dose groups occurred on the day of dosing (Table 4) and resolved within 24 hours (74% and 78%, respectively). Overall, the most common TEAEs were headache (29.5%), nausea (23.8%), and administration site pain (15.5%) (eTable 2 in Supplement 3). Drug-related TEAEs were more common in the 12-mg (82.2%) than the 8-mg (69.6%) and 0.3-mg (33.8%) dose groups (eTable 2 in Supplement 3). Two serious TEAEs (deemed not related to study treatment) were reported by 1 participant each in the 8-mg and 0.3-mg dose groups (eTable 2 in Supplement 3). No suicidal behavior occurred during the trial and all TEAEs of suicidal ideation in the 8-mg and 12-mg dose groups were without intent and reported in participants with a history of suicidal ideation (eTable 3 in Supplement 3). Of the 8 drug-related TEAEs of suicidal ideation without intent, 1 occurred in the 8-mg dose group, 4 (2 events in 2 participants) occurred in the 12-mg dose group, and 3 occurred in the 0.3-mg dose group; all were mild or moderate.

No clinically significant changes in laboratory test findings were observed. Transient postdose increases in heart

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Table 1. Baseline Participant Characteristics

Characteristics	Intranasal mebufotenin benzoate dose		
	8 mg (n = 46)	12 mg (n = 73)	0.3 mg (n = 74)
Sex, No. (%)			
Female	27 (58.7)	43 (58.9)	44 (59.5)
Male	19 (41.3)	30 (41.1)	30 (40.5)
Age, mean (SD), y	40.6 (12.1)	41.2 (10.6)	41.0 (11.2)
No. (%)			
18-64	44 (95.7)	72 (98.6)	73 (98.6)
65-84	2 (4.3)	1 (1.4)	1 (1.4)
Country/region, No. (%)			
Poland	13 (28.3)	18 (24.7)	18 (24.3)
US	11 (23.9)	22 (30.1)	22 (29.7)
Germany	10 (21.7)	14 (19.2)	14 (18.9)
Australia	7 (15.2)	8 (11.0)	6 (8.1)
UK	4 (8.7)	7 (9.6)	6 (8.1)
Spain	1 (2.2)	4 (5.5)	8 (10.8)
Ethnicity, No. (%)[a]			
Hispanic or Latino	3 (6.5)	3 (4.1)	6 (8.1)
Not Hispanic or Latino	43 (93.5)	70 (95.9)	68 (91.9)
Race, No. (%)[a]			
Asian	3 (6.5)	5 (6.8)	3 (4.1)
Black or African American	5 (10.9)	1 (1.4)	4 (5.4)
White	38 (82.6)	66 (90.4)	67 (90.5)
Multiple	0	1 (1.4)	0
Clinical history of depression and baseline severity			
Severity of depression, No. (%)[b]			
Moderate (MADRS score 20-34)	32 (69.6)	47 (64.4)	52 (70.3)
Severe (MADRS score ≥35)	11 (23.9)	26 (35.6)	22 (29.7)
Time since diagnosis, median (IQR), y	10.2 (5.1-17.0)	12.0 (6.4-20.0)	9.8 (6.2-20.0)
No. of lifetime episodes, median (IQR)	4.0 (3.0-5.0)	3.0 (3.0-5.0)	3.0 (2.0-5.0)
Duration of current episode, median (IQR), y	1.7 (0.6-3.0)	1.4 (0.6-3.3)	2.0 (1.0-4.2)
MADRS total score, mean (SD)[b]	31.1 (6.7)	32.5 (5.1)	31.7 (5.9)
QIDS-SR-16 score, mean (SD)[c]	15.9 (3.7)	16.7 (3.3)	17.2 (3.2)
QLDS score, mean (SD)[c]	19.8 (4.2)	19.7 (4.0)	20.0 (4.2)
CGI-S score, mean (SD)[d]	4.5 (0.5)	4.6 (0.6)	4.8 (0.6)
Comorbid psychiatric disorders (>10% in any group), No. (%)			
Insomnia[e]	6 (13.0)	11 (15.1)	9 (12.2)
Attention-deficit/hyperactivity disorder	4 (8.7)	7 (9.6)	10 (13.5)
Anxiety[e]	5 (10.9)	8 (11.0)	5 (6.8)
Drug exposure			
Previous exposure to psychedelic drugs, No. (%)[e,f]	2 (4.3)	7 (9.7)	1 (1.4)
No. of failed antidepressant drugs in current episode, median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-2.0)	2.0 (2.0-3.0)
Antidepressant drug washout during screening, No. (%)	31 (67.4)	49 (67.1)	46 (62.2)

Abbreviations: CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16, 16-Item Quick Inventory of Depressive Symptomatology–Self-Report; QLDS, Quality of Life in Depression Scale.

[a] To ascertain sample representation of the treatment-resistant depression population, race and ethnicity were investigator observed using fixed categories; multiple race selections were possible. There were no participants observed to have American Indian or Alaska Native race or Native Hawaiian or Other Pacific Islander race.

[b] The MADRS, a diagnostic depression severity score, was assessed by an independent central rater. The total score range is 0-60; higher scores indicate more severe depression.

[c] The QIDS-SR-16 and QLDS are self-rated assessments of depression symptom severity and impact, respectively. The QIDS-SR-16 total score range is 0-27 and the QLDS total score range is 0-34; higher scores indicate more severe depression and worse quality of life, respectively.

[d] The CGI-S is an investigator-assessed measure of overall illness severity, calculated by comparing the current condition with that at screening. The CGI-S total score range is 0-7; higher scores indicate more severe illness.

[e] Reported in participants' medical history.

[f] Psychedelic drugs included lysergic acid diethylamide, psilocybin, dimethyltryptamine, mescaline, and other therapeutic products.

rate and blood pressure occurred, but levels returned to the reference range within 1 hour of dosing (eFigure 6 in Supplement 3). Most participants (85% in the 8-mg dose group and 78% in the 12-mg dose group) were deemed ready for discharge no more than 2 hours after dosing (eTable 4 in Supplement 3).

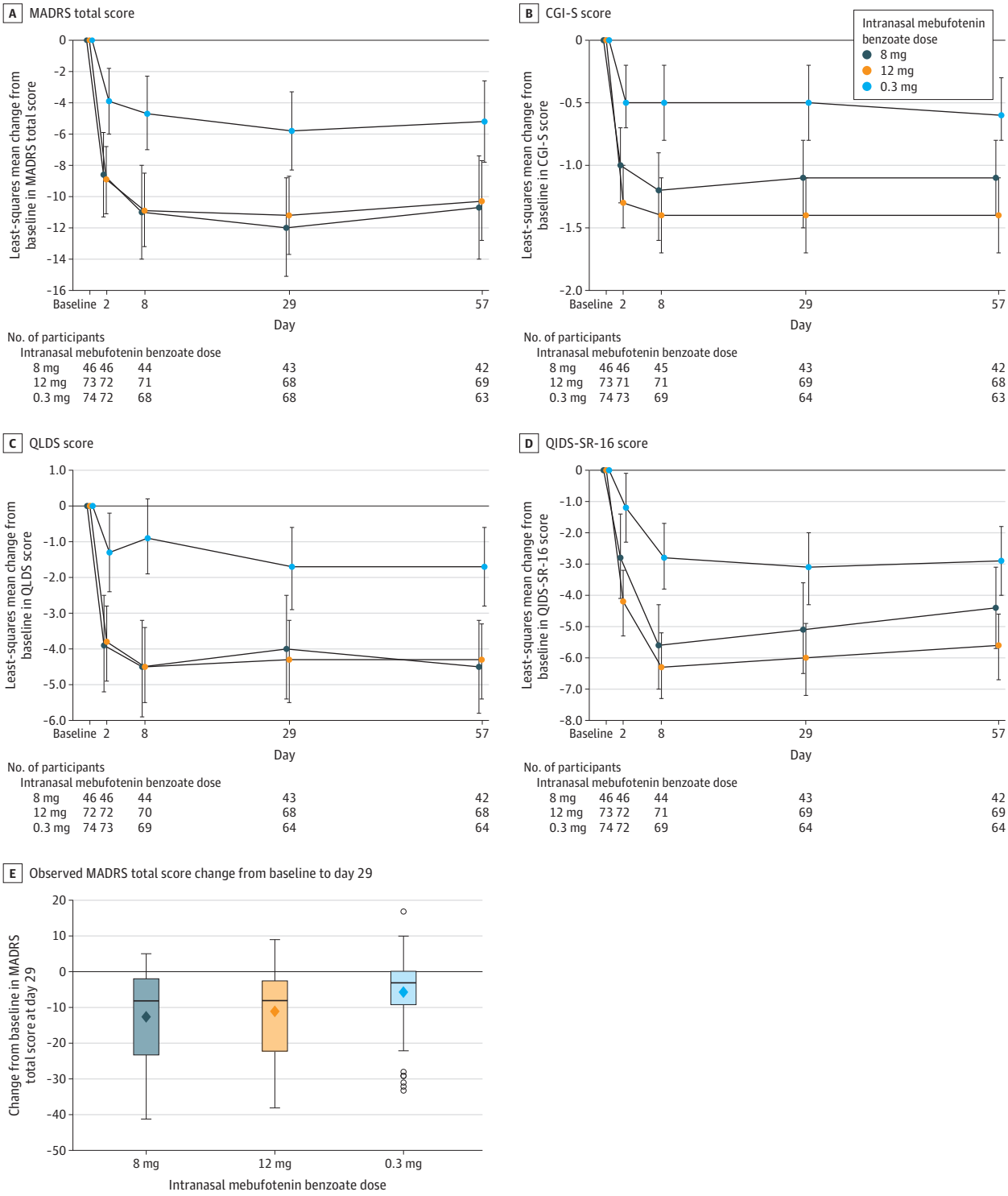
Discussion

To our knowledge, this trial is the largest and most robust study of mebufotenin in adults with treatment-resistant depression to date. A single intranasal administration of mebufotenin

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Figure 2. Line Graphs and Box-and-Whisker Plot for Change From Baseline in MADRS, CGI-S, QLDS, and QIDS-SR-16 Assessments



CGI-S indicates Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16, 16-Item Quick Inventory of Depressive Symptomatology–Self-Report; and QLDS, Quality of Life in Depression Scale. Results are from mixed model for repeated measures analysis including treatment, time, region, randomization schedule, and treatment × time interaction as fixed effects, participant as a random effect, and baseline MADRS total score (panel A), CGI-S score (panel B), QLDS score (panel C), and QIDS-SR-16 score (panel D) as covariates. Whiskers represent 95% CIs. Panel E shows the observed MADRS total score change from baseline to day 29. Means are indicated by diamonds; medians, bars inside boxes; and IQRs, box tops and bottoms. Whiskers indicate the most extreme point that is less than or equal to 1.5 times the IQR, and circles indicate outliers. For detailed description of the MADRS, CGI-S, QLDS, and QIDS-SR-16 assessments, see Table 1 footnotes.

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Table 2. Primary, Key Secondary, and Additional Secondary Efficacy Outcomes

Outcomes	Observed mean (SD) by intranasal mebufotenin benzoate dose[a]								8 mg vs 0.3 mg		12 mg vs 0.3 mg	
	8 mg			12 mg		0.3 mg						
	Baseline	End point	Difference	Baseline	End point	Difference	Baseline	End point	Difference	Least-squares mean difference (95% CI)[b]	*P* value	Least-squares mean difference (95% CI)[b]	*P* value
Primary outcome[c]													
MADRS total score change from baseline to day 29[d]				32.5 (5.1) [n = 73]	21.2 (11.5) [n = 68]	−11.1 (11.6) [n = 68]	31.7 (5.9) [n = 74]	26.1 (9.9) [n = 68]	−5.5 (9.9) [n = 68]			−5.3 (−8.9 to −1.8)	.003
Key secondary outcomes[e]													
MADRS total score[d]													
Day 8	31.1 (6.7) [n = 46]	19.9 (10.9) [n = 44]	−11.1 (12.7) [n = 44]	32.5 (5.1) [n = 73]	21.4 (10.3) [n = 71]	−11.1 (10.4) [n = 71]	31.7 (5.9) [n = 74]	27.1 (10.3) [n = 68]	−4.4 (10.1) [n = 68]	−6.3 (−10.1 to −2.5)	.001	−6.2 (−9.5 to −2.8)	<.001
Day 29	31.1 (6.7) [n = 46]	19.1 (11.5) [n = 43]	−12.5 (12.7) [n = 43]				31.7 (5.9) [n = 74]	26.1 (9.9) [n = 68]	−5.5 (9.9) [n = 68]	−6.2 (−10.2 to −2.1)	.003		
Additional secondary outcomes													
MADRS total score[d]													
Day 2	31.1 (6.7) [n = 46]	22.5 (10.6) [n = 46]	−8.6 (9.4) [n = 46]	32.5 (5.1) [n = 73]	23.4 (10.3) [n = 72]	−9.1 (10.3) [n = 72]	31.7 (5.9) [n = 74]	27.9 (8.7) [n = 72]	−3.8 (8.3) [n = 72]	−4.7 (−8.2 to −1.3)	.007	−5.0 (−8.0 to −2.1)	.001
Day 57	31.1 (6.7) [n = 46]	20.5 (11.7) [n = 42]	−10.9 (11.7) [n = 42]	32.5 (5.1) [n = 73]	21.9 (12.3) [n = 69]	−10.7 (11.9) [n = 69]	31.7 (5.9) [n = 74]	26.7 (10.1) [n = 63]	−5.2 (10.7) [n = 63]	−5.5 (−9.7 to −1.3)	.01	−5.0 (−8.7 to −1.4)	.008
CGI-S[f]													
Day 2	4.5 (0.5) [n = 46]	3.5 (1.1) [n = 46]	−1.0 (1.2) [n = 46]	4.6 (0.6) [n = 73]	3.4 (1.2) [n = 71]	−1.2 (1.3) [n = 71]	4.8 (0.6) [n = 74]	4.2 (0.9) [n = 73]	−0.6 (0.8) [n = 73]	−0.6 (−1.0 to −0.2)	.004	−0.8 (−1.1 to −0.5)	<.001
Day 8	4.5 (0.5) [n = 46]	3.4 (1.4) [n = 45]	−1.2 (1.5) [n = 45]	4.6 (0.6) [n = 73]	3.2 (1.3) [n = 71]	−1.4 (1.5) [n = 71]	4.8 (0.6) [n = 74]	4.1 (1.0) [n = 69]	−0.6 (1.0) [n = 69]	−0.7 (−1.2 to −0.3)	.003	−0.9 (−1.3 to −0.5)	<.001
Day 29	4.5 (0.5) [n = 46]	3.5 (1.3) [n = 43]	−1.1 (1.4) [n = 43]	4.6 (0.6) [n = 73]	3.2 (1.2) [n = 69]	−1.4 (1.4) [n = 69]	4.8 (0.6) [n = 74]	4.1 (1.1) [n = 64]	−0.6 (1.1) [n = 64]	−0.6 (−1.0 to −0.1)	.01	−0.9 (−1.3 to −0.5)	<.001
Day 57	4.5 (0.5) [n = 46]	3.5 (1.2) [n = 42]	−1.0 (1.2) [n = 42]	4.6 (0.6) [n = 73]	3.2 (1.2) [n = 68]	−1.4 (1.4) [n = 68]	4.8 (0.6) [n = 74]	4.1 (0.9) [n = 63]	−0.7 (0.9) [n = 63]	−0.5 (−1.0 to −0.1)	.01	−0.8 (−1.2 to −0.5)	<.001
QLDS[g]													
Day 2	19.8 (4.2) [n = 46]	15.8 (5.1) [n = 46]	−4.0 (5.2) [n = 46]	19.7 (4.0) [n = 72]	16.0 (5.6) [n = 73]	−3.8 (5.4) [n = 72]	20.0 (4.2) [n = 74]	18.7 (5.7) [n = 73]	−1.3 (4.0) [n = 73]	−2.6 (−4.3 to −0.8)	.004	−2.5 (−4.1 to −1.0)	.001
Day 8	19.8 (4.2) [n = 46]	15.1 (5.5) [n = 44]	−4.6 (5.7) [n = 44]	19.7 (4.0) [n = 72]	15.3 (5.3) [n = 71]	−4.4 (5.0) [n = 70]	20.0 (4.2) [n = 74]	19.2 (5.3) [n = 69]	−0.9 (3.7) [n = 69]	−3.7 (−5.4 to −1.9)	<.001	−3.6 (−5.1 to −2.1)	<.001
Day 29	19.8 (4.2) [n = 46]	15.6 (5.8) [n = 43]	−4.2 (5.5) [n = 43]	19.7 (4.0) [n = 72]	15.6 (5.7) [n = 69]	−4.2 (5.4) [n = 68]	20.0 (4.2) [n = 74]	18.4 (5.4) [n = 64]	−1.7 (4.2) [n = 64]	−2.2 (−4.1 to −0.4)	.02	−2.6 (−4.2 to −0.9)	.002
Day 57	19.8 (4.2) [n = 46]	15.0 (4.5) [n = 42]	−4.8 (4.1) [n = 42]	19.7 (4.0) [n = 72]	15.4 (5.6) [n = 69]	−4.2 (4.9) [n = 68]	20.0 (4.2) [n = 74]	18.4 (5.5) [n = 64]	−1.7 (4.2) [n = 64]	−2.8 (−4.5 to −1.1)	.001	−2.6 (−4.1 to −1.1)	<.001

(continued)

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Table 2. Primary, Key Secondary, and Additional Secondary Efficacy Outcomes (continued)

Outcomes	Observed mean (SD) by intranasal mebufotenin benzoate dose[a]									8 mg vs 0.3 mg		12 mg vs 0.3 mg	
	8 mg			12 mg			0.3 mg			Least-squares mean difference (95% CI)[b]	*P* value	Least-squares mean difference (95% CI)[b]	*P* value
	Baseline	End point	Difference	Baseline	End point	Difference	Baseline	End point	Difference				
QIDS-SR-16[g]													
Day 2	15.9 (3.7) [n = 46]	13.0 (4.3) [n = 46]	−2.8 (4.2) [n = 46]	16.7 (3.3) [n = 73]	12.6 (5.1) [n = 73]	−4.0 (5.2) [n = 73]	17.2 (3.2) [n = 74]	15.9 (3.9) [n = 72]	−1.2 (3.4) [n = 72]	−1.6 (−3.1 to −0.1)	.04	−3.0 (−4.3 to −1.7)	<.001
Day 8	15.9 (3.7) [n = 46]	10.0 (6.0) [n = 44]	−5.9 (6.3) [n = 44]	16.7 (3.3) [n = 73]	10.5 (5.7) [n = 71]	−6.1 (5.8) [n = 71]	17.2 (3.2) [n = 74]	14.3 (5.5) [n = 69]	−2.8 (5.0) [n = 69]	−2.8 (−4.9 to −0.8)	.006	−3.5 (−5.3 to −1.8)	<.001
Day 29	15.9 (3.7) [n = 46]	10.7 (5.6) [n = 43]	−5.3 (5.9) [n = 43]	16.7 (3.3) [n = 73]	10.9 (6.3) [n = 69]	−5.9 (5.8) [n = 69]	17.2 (3.2) [n = 74]	14.2 (5.7) [n = 64]	−3.1 (5.2) [n = 64]	−2.0 (−4.1 to −0.1)	.06	−2.9 (−4.7 to −1.1)	.002
Day 57	15.9 (3.7) [n = 46]	11.3 (5.7) [n = 42]	−4.6 (5.0) [n = 42]	16.7 (3.3) [n = 73]	11.1 (5.8) [n = 69]	−5.6 (5.4) [n = 69]	17.2 (3.2) [n = 74]	14.3 (5.8) [n = 64]	−3.0 (5.5) [n = 64]	−1.5 (−3.6 to 0.5)	.14	−2.8 (−4.5 to −1.0)	.002

Abbreviations: CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16, 16-Item Quick Inventory of Depressive Symptomatology–Self-Report; QLDS, Quality of Life in Depression Scale.

[a] Descriptive, unadjusted statistics.

[b] Between-group differences in change from baseline in MADRS, CGI-S, QLDS, and QIDS-SR-16 scores were analyzed using a mixed model for repeated measures that included treatment, time, region, randomization schema, and treatment × time interaction as fixed effects, participant as a random effect, and baseline MADRS, CGI-S, QLDS, or QIDS-SR-16 score, respectively, as covariates. Baseline was defined as the last nonmissing value prior to dosing on day 1.

[c] Primary outcome: least-squares mean difference in MADRS score change from baseline to day 29 for the 12-mg vs 0.3-mg dose.

[d] The MADRS, a diagnostic depression severity score, was assessed by an independent central rater. The total score range is 0-60; higher scores indicate more severe depression.

[e] Key secondary end points: least-squares mean difference in MADRS score change from baseline to day 8 (12-mg vs 0.3-mg dose and 8-mg vs 0.3-mg dose) and to day 29 (8-mg vs 0.3-mg dose).

[f] The CGI-S is an investigator-assessed measure of overall illness severity, calculated by comparing the current condition with that at screening. The CGI-S total score range is 0-7; higher scores indicate more severe illness.

[g] The QIDS-SR-16 and QLDS are self-rated assessments of depression symptom severity and impact, respectively. The QIDS-SR-16 total score range is 0-27 and the QLDS total score range is 0-34; higher scores indicate more severe depression and worse quality of life, respectively.

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Table 3. MADRS Responders and Remitters[a]

	Intranasal mebufotenin benzoate dose, No. (%)		
	8 mg (n = 46)	12 mg (n = 73)	0.3 mg (n = 74)
Day 2			
Responders	10 (21.7)	17 (23.3)	4 (5.4)
Remitters	7 (15.2)	8 (11.0)	3 (4.1)
Day 8			
Responders	15 (32.6)	24 (32.9)	10 (13.5)
Remitters	12 (26.1)	11 (15.1)	6 (8.1)
Day 29			
Responders	16 (34.8)	25 (34.2)	9 (12.2)
Remitters	12 (26.1)	13 (17.8)	6 (8.1)
Day 57			
Responders	13 (28.3)	23 (31.5)	8 (10.8)
Remitters	12 (26.1)	14 (19.2)	6 (8.1)

[a] Responders were defined as participants with a ≥50% reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) total score vs baseline and remitters were defined as participants with a MADRS total score ≤10. The MADRS, a diagnostic depression severity score, was assessed by an independent central rater. The total score range is 0-60; higher scores indicate more severe depression.

benzoate (8 mg or 12 mg) resulted in rapid, robust, and durable reductions in depressive symptoms compared with a low-dose comparator. Improvements in MADRS score were statistically significant at all time points from 1 day to 8 weeks post dose. Moreover, the control-adjusted reductions in MADRS score for 8 mg and 12 mg of intranasal mebufotenin benzoate at day 29 are consistent with those reported in the largest trial of psilocybin in treatment-resistant depression reported to date[26] and similar or favorable to available treatment options, including transcranial magnetic stimulation and intranasal esketamine.[27,28] Results from a recent phase 2b trial show that an inhaled mebufotenin formulation produced rapid, significant improvements in depression symptoms at day 8 relative to placebo.[29]

Control-adjusted improvement in MADRS with the 8-mg and 12-mg doses of intranasal mebufotenin benzoate continued to increase from 1 day to 4 weeks post dose, contrasting with the peak antidepressant effect observed in randomized clinical trials of psilocybin and intranasal esketamine by 24 hours post dose.[26,27] Moreover, neither active dose of intranasal mebufotenin benzoate showed noticeable attenuation in their control-adjusted difference in MADRS at 8 weeks, indicating that the duration of antidepressant efficacy may persist beyond this time frame. The durability of the response to intranasal mebufotenin benzoate will be further evaluated in phase 3 studies with a longer duration of follow-up.

Response and remission rates were higher in both active groups vs the low-dose comparator group at all time points; at day 29 in the 8-mg dose group, about a third of participants were responders and a quarter were in remission. Lower remission rates with the 12-mg dose may reflect a tolerability trade-off. Additionally, the significant improvements in outcomes assessing global severity (CGI-S) and quality of life (QLDS) across all time points for both active doses indicate benefits beyond symptom reduction, including functional recovery—a treatment goal considered important by patients with treatment-resistant depression.[30]

Intranasal mebufotenin benzoate was generally safe and well tolerated, with a safety profile in line with previous reports of mebufotenin in humans.[22,29,31] Adverse events were overwhelmingly mild to moderate, transient, and occurred on the day of dosing. Some dose-related adverse events, including nausea, anxiety, and panic attack, occurred more frequently with the 12-mg dose. Consistent with previous reports,[22] other psychedelics in the same class,[29,32] and esketamine,[33] transient increases in blood pressure and heart rate were observed and resolved within 1 hour without intervention. No suicide-related safety signals were observed in the active treatment groups. Although both active doses had comparable efficacy and durability, the 8-mg dose had a more optimal balance of efficacy and safety, supporting its selection for phase 3 evaluation.

A key distinguishing feature of intranasal mebufotenin benzoate is the brief duration of the acute psychedelic experience.[20-22] In this study, two-thirds of participants were deemed ready for discharge at the 90-minute postdose assessment, which required confirmation that any acute psychedelic effects had subsided. This rapid return of dosed participants to baseline, together with infrequent dosing indicated by the long antidepressant durability after a single dose, can offer important potential advantages for patients and clinicians compared with treatment options currently available or in advanced stages of development; esketamine and transcranial magnetic stimulation require frequent retreatment,[34,35] and psilocybin and LSD require 4 to 12 hours of monitoring due to longer acute subjective effects.[16,18,26] Mechanistically, the comparable efficacy and durability of response of intranasal mebufotenin benzoate to psychedelic compounds with longer half-lives and duration of acute psychedelic effects, despite its shorter duration of psychedelic experience, is hypothesized to be associated with its potent agonism of 5-HT_{1A} alongside 5-HT_{2A}.[36] Although there is evidence to suggest that the subjective experience is a predictor of therapeutic outcomes with other psychedelics,[37-39] we found no evidence of a correlation between the acute subjective effects of intranasal mebufotenin benzoate and change in MADRS score at day 29. This might indicate that alternative therapeutic mechanisms of action drive the observed improvements in symptoms[20,22] or that the MEQ-30 scale is not well suited for

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Table 4. Treatment-Emergent Adverse Events[a]

Treatment-emergent adverse events (≥5% of participants in any group)[b]	Intranasal mebufotenin benzoate dose, No. (%) [No. of events]											
	8 mg (n = 46)				12 mg (n = 73)				0.3 mg (n = 74)			
	Day 1	Days 2-7	Days 8-57	Total, days 1-57[c]	Day 1	Days 2-7	Days 8-57	Total, days 1-57[c]	Day 1	Days 2-7	Days 8-57	Total, days 1-57[c]
Any treatment-emergent adverse event	33 (71.7) [103]	17 (37.0) [23]	13 (28.3) [19]	35 (76.1) [145]	57 (78.1) [235]	31 (42.5) [68]	36 (49.3) [95]	62 (84.9) [401]	30 (40.5) [76]	18 (24.3) [25]	39 (52.7) [93]	54 (73.0) [195]
Nausea	13 (28.3) [13]	2 (4.3) [2]	0	15 (32.6) [15]	26 (35.6) [28]	5 (6.8) [5]	4 (5.5) [4]	29 (39.7) [37]	1 (1.4) [1]	0	1 (1.4) [1]	2 (2.7) [2]
Headache	9 (19.6) [11]	3 (6.5) [3]	2 (4.3) [2]	12 (26.1) [16]	20 (27.4) [21]	3 (4.1) [3]	6 (8.2) [10]	24 (32.9) [34]	12 (16.2) [12]	5 (6.8) [5]	10 (13.5) [14]	21 (28.4) [31]
Administration site pain	8 (17.4) [9]	0	0	8 (17.4) [9]	16 (21.9) [17]	0	0	16 (21.9) [17]	6 (8.1) [6]	0	0	6 (8.1) [6]
Anxiety	2 (4.3) [2]	0	0	2 (4.3) [2]	6 (8.2) [7]	5 (6.8) [7]	4 (5.5) [4]	12 (16.4) [18]	0	0	6 (8.1) [8]	6 (8.1) [8]
Administration site discomfort	5 (10.9) [5]	0	0	5 (10.9) [5]	11 (15.1) [11]	2 (2.7) [2]	0	12 (16.4) [13]	2 (2.7) [2]	0	0	2 (2.7) [2]
Blood pressure increased	6 (13.0) [6]	0	0	6 (13.0) [6]	12 (16.4) [12]	0	0	12 (16.4) [12]	2 (2.7) [3]	0	1 (1.4) [2]	3 (4.1) [4]
Vomiting	6 (13.0) [8]	0	0	6 (13.0) [8]	9 (12.3) [9]	0	2 (2.7) [2]	9 (12.3) [11]	0	1 (1.4) [1]	2 (2.7) [2]	3 (4.1) [3]
Insomnia	0	1 (2.2) [1]	0	1 (2.2) [1]	4 (5.5) [4]	2 (2.7) [2]	5 (6.8) [5]	9 (12.3) [11]	0	3 (4.1) [3]	4 (5.4) [5]	6 (8.1) [8]
Suicidal ideation	0	0	1 (2.2) [1]	1 (2.2) [1]	0	2 (2.7) [3]	3 (4.1) [4]	5 (6.8) [7]	1 (1.4) [1]	1 (1.4) [1]	5 (6.8) [5]	7 (9.5) [8]
Psychomotor hyperactivity	0	0	0	0	4 (5.5) [4]	0	0	4 (5.5) [4]	0	0	0	0
Upper respiratory tract infection	0	0	1 (2.2) [1]	1 (2.2) [1]	0	1 (1.4) [1]	2 (2.7) [2]	3 (4.1) [3]	0	0	6 (8.1) [7]	6 (8.1) [7]
Crying	3 (6.5) [3]	0	0	3 (6.5) [3]	2 (2.7) [2]	0	0	2 (2.7) [2]	1 (1.4) [1]	0	0	1 (1.4) [1]
Influenza	0	0	0	0	0	0	1 (1.4) [1]	1 (1.4) [1]	0	0	4 (5.4) [4]	4 (5.4) [4]
Sneezing	3 (6.5) [3]	0	0	3 (6.5) [3]	0	0	0	0	0	0	0	0

[a] Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities version 26.0.

[b] Treatment-emergent adverse events occurring between days 1 and 57 are listed in descending order of frequency in the 12-mg dose group.

[c] Participants are counted once for each category for total day 1 to day 57 treatment-emergent adverse events, regardless of the number of events. The total number of events for the 12-mg dose group includes 3 events with unknown timing of onset and for the 0.3-mg dose group includes 1 event with unknown timing of onset.

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assessing the entire spectrum of acute subjective effects of mebufotenin.

Limitations

Several limitations warrant consideration. First, functional unblinding is an inherent limitation of clinical trials involving psychedelics, wherein the psychoactive effects, although variable between participants, may be recognized.[40] Although the use of a low-dose comparator was intended to improve blinding, participants and clinicians were largely able to guess the treatment assignment; however, blinding was maintained for the centralized raters, and participants' pretreatment expectancy was not correlated with MADRS score changes. Future research will address this limitation with the inclusion of a mid-dose of intranasal mebufotenin benzoate, which was shown in a phase 1 study to be perceptible but with a less intense subjective effect than the 8-mg dose.[21] As well as helping to control functional unblinding, inclusion of this mid-dose should allow for a more robust assessment of the dose-response effect to support selection of 8 mg as the most appropriate therapeutic dose.

Second, as the randomization ratio was altered to prioritize the primary end point, the reduced sample size of the 8-mg dose group may have limited the statistical power to detect significant differences in secondary patient-reported outcomes, such as the QIDS-SR-16, at later time points. The observed divergence between the MADRS and QIDS-SR-16 results at some time points might be due to psychometric limitations.[41]

Third, as intranasal mebufotenin benzoate was developed as a monotherapy, participants taking antidepressants at screening were required to discontinue those medications, which has the potential to induce withdrawal symptoms and recurrence of depression[42] and might not reflect future clinical practice, if sufficient safety data will be available.[43] Nonetheless, results from the ad hoc analysis of the primary outcome by washout status indicated that treatment effects were consistent between those who washed out antidepressants and those who did not.

Fourth, as is common across recent trials of psychedelics,[29,44,45] there was a lack of diverse ethnic representation in this study. Additionally, the trial population may underrepresent more severely treatment-resistant patients. Fifth, prior psychedelic exposure (identified through medical history) was potentially underreported. Sixth, the potential impact of psychological support on study outcomes was not evaluated.

Conclusions

In this largest and most robust randomized clinical trial of mebufotenin to date, a single administration of intranasal mebufotenin benzoate, 8 mg or 12 mg, in adults with treatment-resistant depression was generally safe and well tolerated and produced a robust antidepressant effect that emerged 1 day after dosing and was largely maintained to 8 weeks. The rapid postdose recovery time and therapeutic efficacy and durability of intranasal mebufotenin benzoate could increase patient acceptability while reducing health care resource utilization. Moreover, these findings suggest that a prolonged psychedelic effect is not required for durable antidepressant efficacy.

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Inc, Incannex Healthcare, and the Multidisciplinary Association for Psychedelic Studies and personal fees for advisory board membership from Otsuka Pharmaceuticals, Natural Medtech, Emyria, and Toga Health. Dr Pierce reported being an employee of AtaiBeckley. Dr Repantis reported receipt of compensation for clinical trial activities from Compass Pathways, Definium, Helus Pharma, and MAPS Europe and grants from the German Federal Ministry of Research, Technology, and Space and ERA-NET Neuron. Dr Roberts reported being an employee of Beckley Psytech during the conduct of the study, being a consultant for AtaiBeckley at the time of submission, and having a patent pending for P39010:US for uses of particular doses of 5-MeO-DMT to treat depression (waived ownership and commercial rights). Dr Wiegand reported being an employee of Beckley Psytech and having a patent pending for P39010:US for uses of particular doses of 5-MeO-DMT to treat depression (waived ownership and commercial rights). Dr Conley reported being a stockholder in Eli Lilly. No other disclosures were reported.

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