ORIGINAL ARTICLE

Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression

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ABSTRACT

BACKGROUND

In treatment-resistant depression, commonly defined as a lack of response to two or more consecutive treatments during the current depressive episode, the percentage of patients with remission is low and the percentage with relapse is high. The efficacy and safety of esketamine nasal spray as compared with extended-release quetiapine augmentation therapy, both in combination with ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI), in patients with treatment-resistant depression are unknown.

METHODS

In an open-label, single-blind (with raters unaware of group assignments), multicenter, phase 3b, randomized, active-controlled trial, we assigned patients, in a 1:1 ratio, to receive flexible doses (according to the summary of product characteristics) of esketamine nasal spray (esketamine group) or extended-release quetiapine (quetiapine group), both in combination with an SSRI or SNRI. The primary end point was remission, defined as a score of 10 or less on the Montgomery–Åsberg Depression Rating Scale (MADRS), at week 8 (scores range from 0 to 60, with higher scores indicating more severe depression). The key secondary end point was no relapse through week 32 after remission at week 8. All patients were included in the analysis; patients who discontinued the trial treatment were considered as having had an unfavorable outcome (i.e., they were grouped with patients who did not have remission or who had a relapse). Analyses of the primary and key secondary end points were adjusted for age and number of treatment failures.

RESULTS

Overall, 336 patients were assigned to the esketamine group and 340 to the quetiapine group. More patients in the esketamine group than in the quetiapine group had remission at week 8 (91 of 336 patients [27.1%] vs. 60 of 340 patients [17.6%]; P=0.003) and had no relapse through week 32 after remission at week 8 (73 of 336 patients [21.7%] vs. 48 of 340 patients [14.1%]). Over 32 weeks of follow-up, the percentage of patients with remission, the percentage of patients with a treatment response, and the change in the MADRS score from baseline favored esketamine nasal spray. The adverse events were consistent with the established safety profiles of the trial treatments.

CONCLUSIONS

In patients with treatment-resistant depression, esketamine nasal spray plus an SSRI or SNRI was superior to extended-release quetiapine plus an SSRI or SNRI with respect to remission at week 8. (Funded by Janssen EMEA; ESCAPE-TRD ClinicalTrials.gov number, NCT04338321.)

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The primary goal of initial treatment for major depressive disorder is remission, with maintenance treatment aimed at preventing relapse.[1,2] In up to two thirds of patients with major depressive disorder, remission might not occur with initial antidepressant treatment; many patients who require multiple treatments have a relapse within a year after remission.[3,4] Treatment-resistant depression is commonly defined as a lack of response to two or more pharmacologic treatments that are given for an adequate duration and at an adequate dose during the same major depressive episode.[5] Treatment-resistant depression, which affects 10 to 30% of patients with major depressive disorder, is associated with increased hospitalizations and coexisting conditions, higher mortality and suicide rates, and a greater economic burden.[3,6-9]

Effective and specific treatments for treatment-resistant depression are urgently needed.[10] In clinical practice, pharmacologic treatments approved for major depressive disorder, including oral antidepressants and augmentation medications, are used in various treatment strategies.[5,10,11] Extended-release quetiapine, a guideline-supported antipsychotic augmentation agent, is commonly used for treatment-resistant depression.[12-16]

Esketamine nasal spray, administered in combination with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI), is the only treatment approved in Europe specifically for treatment-resistant depression.[17] In patients with treatment-resistant depression, reductions in depressive symptoms and in the risk of relapse were observed with esketamine nasal spray as compared with placebo nasal spray when both agents were given in combination with a newly initiated SSRI or SNRI.[18-20] Data on direct comparisons of esketamine nasal spray with an augmentation strategy in patients with treatment-resistant depression are limited.

We hypothesized that among patients with treatment-resistant depression, remission at week 8 and freedom from relapse through week 32 would occur in a higher percentage of patients treated with esketamine nasal spray and an SSRI or SNRI than with extended-release quetiapine and an SSRI or SNRI.

Methods

Oversight

This trial was conducted in accordance with the principles of the Declaration of Helsinki; country-specific ethics review boards approved the trial.[21] All patients provided written informed consent. This trial was sponsored by Janssen EMEA. Janssen EMEA and a subgroup of investigators designed and coordinated the trial. A list of the investigators, the author contributions, and the medical writers who provided writing support in accordance with Good Publication Practice guidelines is provided in the Supplementary Appendix (available with the full text of this article at NEJM.org). All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). All the authors contributed to the writing of the manuscript and to the decision to submit the manuscript for publication.

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Patients

Adult patients (18 to 74 years of age) with treatment-resistant depression were eligible for inclusion (Table S1 in the Supplementary Appendix). Patients met the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, criteria for major depressive disorder,[22] with a score of 34 or higher on the 30-item Inventory of Depressive Symptomatology–Clinician-Rated scale (scores range from 0 to 84, with higher scores indicating more severe depressive symptoms). In the current major depressive episode, two to six consecutive treatments — including the current treatment — with agents from at least two different antidepressant classes had failed (<25% reduction in symptoms). Patients were receiving an antidepressant treatment that included an SSRI or an SNRI; no patients had had a response to the treatment, but all patients had had signs of minimal clinical improvement after treatment for least 6 weeks at an adequate dose, with an increase to the maximum tolerated dose. Treatment with the current SSRI or SNRI was continued, whereas treatment with all other antidepressant drugs, including augmentation agents, was discontinued. Patients receiving 50 mg or less of quetiapine per day (extended release or immediate release) at the time of screening could participate in the trial after a washout period of at least 7 days.

DESIGN

The ESCAPE-TRD trial was an open-label, single-blind (with raters unaware of trial-group assignments), randomized, active-controlled trial that was conducted across 171 sites comprising hospitals, inpatient and outpatient clinics, and research centers in 24 countries. The goal of the trial was to evaluate the efficacy, safety, and side-effect profile of esketamine nasal spray as compared with extended-release quetiapine, both in combination with a continuing SSRI or SNRI, in patients with treatment-resistant depression.

The trial consisted of a screening phase of up to 14 days, an initial treatment phase of 8 weeks, a maintenance phase of 24 weeks, and a safety follow-up through 2 weeks after the last dose of trial treatment (Fig. S1). After the screening phase, patients were randomly assigned, in a 1:1 ratio, to receive esketamine nasal spray plus an SSRI or SNRI (esketamine group) or extended-release quetiapine plus an SSRI or SNRI (quetiapine group). Randomization was performed with the use of a computer-generated schedule prepared before the trial, in randomly permuted blocks and with stratification according to age (18 to ≤64 years vs. 65 to ≤74 years) and the total number of past treatments that failed (2 vs. ≥3). Patients who discontinued the trial treatment remained in the trial and were invited to attend all visits through week 32. The doses of esketamine nasal spray and extended-release quetiapine were flexible and accorded with the summary of product characteristics for each agent.[12,17] Details about the dosing and administration of the trial treatments are provided in the Supplementary Material S1 section in the Supplementary Appendix.

EFFICACY

The efficacy analyses included all the patients who underwent randomization (intention-to-treat approach). The primary and key secondary end points were assessed according to the score on the Montgomery–Åsberg Depression Rating Scale (MADRS; scores range from 0 to 60, with higher scores indicating more severe depression); the clinical interview to determine the score was performed on site by independent raters who were unaware of the trial-group assignments. The primary end point was remission — defined as a score of 10 or less on the MADRS[23] — at week 8 after randomization (short-term efficacy). The key secondary end point was no relapse through week 32 after remission at week 8 (long-term efficacy). Relapse was defined as a MADRS score that worsened to 22 or higher at two consecutive assessments within 5 to 15 days of each other; hospitalization for worsening depression, suicide prevention, or suicide attempt; suicide attempt; completed suicide; or any other event assessed by the investigator to be indicative of relapse.

Analyses of the rates of remission (defined as a MADRS score of ≤10) and response (defined as an improvement of ≥50% in the MADRS score from baseline or as a MADRS score of ≤10) and analysis of the change in the MADRS score from baseline over time are also reported. In addition, we analyzed remission at week 8 and freedom from relapse through week 32 after remission at week 8 using a MADRS score of 12 or less as the threshold for remission — a threshold that was used in the registrational trials of esketamine nasal spray — to facilitate the contextualization of our trial with the previous phase 3 trials in the clinical development program of esketamine nasal spray (see the Supplementary Material S2 section).[18,20,24-26]

SAFETY

The safety analysis included all the patients who received at least one dose of the trial treatment. Adverse events (classified according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, versions 23 to 25) were considered to have occurred during the treatment period if they occurred between the first dose and the safety follow-up visit (14 days after the last dose) or, in the case of serious adverse events, if they occurred between the first dose and 30 days or less after last dose. Safety evaluations were performed throughout the trial.

STATISTICAL ANALYSIS

The trial was designed to have 90% power for assessment of the primary end point and 80% power for assessment of the key secondary end point. Using the nonresponder imputation approach, we estimated that 41.25% of patients in the esketamine group and 28.88% of patients in the quetiapine group would have remission at week 8 and that 25.99% and 16.17% of patients,

respectively, would have no relapse through week 32 after remission at week 8. Therefore, we estimated that 311 patients per treatment group would be needed to detect a significant between-group difference with respect to the primary end point and that 270 patients per treatment group would be needed to detect a significant between-group difference with respect to the key secondary end point, at a two-sided significance level of 0.05 with the use of chi-square tests.

The primary and key secondary end points were analyzed with the use of the nonresponder imputation approach, whereby patients who discontinued the trial treatment were considered as having had an unfavorable outcome (i.e., they were grouped with patients who did not have remission or who had a relapse). Missing data from week 8 in patients who did not discontinue the trial treatment were imputed with the last-observation-carried-forward approach. Cochran–Mantel–Haenszel chi-square tests, adjusted for age (18 to ≤64 years vs. 65 to ≤74 years) and total number of past treatments that failed (2 vs. ≥3) were used to compare the trial treatments and to estimate adjusted odds ratios, relative risks, and risk differences. We performed a sensitivity analysis on the primary end point using an unadjusted Cochran–Mantel–Haenszel test. For patients who discontinued the trial treatment but remained in the trial, a retrieved dropout analysis (in which missing data from patients who remained in the trial despite the occurrence of intercurrent events were imputed alongside data from patients who completed the trial to derive a single estimate) was performed on the primary and key secondary end points, whereby follow-up visits (which occurred every other week after discontinuation of the trial treatment) were reintegrated into the regular visit schedule; nonresponder imputation was used to impute data from patients who withdrew from the trial.

The percentage of patients with remission over time and the percentage with a response over time were estimated on the basis of data from visits during the treatment period and with use of the nonresponder imputation method (with estimates corroborated with the use of the last-observation-carried-forward approach); unadjusted odds ratios were calculated to compare the percentages in the esketamine group with those in the quetiapine group. The change in the MADRS score from baseline at each visit during the treatment period was assessed with the use of a mixed model for repeated measures (with an unstructured covariance matrix) and was based on observed cases. The model included the baseline MADRS score as a covariate and treatment, stratification factors, time (week 1, week 2, and every 2 weeks thereafter through week 32), and time-by-treatment interaction as fixed effects. Analyses of secondary end points are reported with 95% confidence intervals, which were not adjusted for multiple comparisons and should not be used in place of hypothesis testing.

RESULTS

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

Between August 26, 2020, and November 5, 2021, we screened 811 patients, of whom 676 were randomly assigned to the esketamine group (336 patients) or to the quetiapine group (340 patients) (Fig. S2). Baseline demographic and clinical characteristics were generally similar in the two groups (Table 1). Patients in the trial were representative of the wider population of patients with treatment-resistant depression with respect to age, sex, race, and ethnic group (Table S2). The doses of continued SSRIs and SNRIs at baseline are provided in Table S3. Discontinuation of the trial treatment occurred in a greater number of patients in the quetiapine group than in the esketamine group (137 patients [40.3%] vs. 78 patients [23.2%]); more patients in the quetiapine group than in the esketamine group discontinued the trial treatment because of adverse events that occurred during the treatment period or because the trial treatment lacked efficacy (Fig. S2).

PRIMARY END POINT

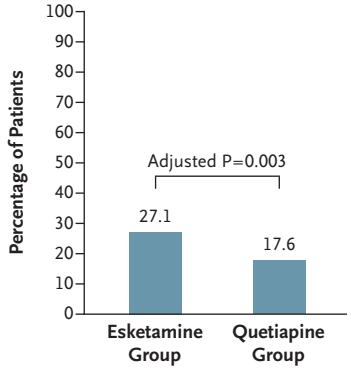
Remission, defined as a MADRS score of 10 or less, at week 8 (primary end point) occurred in significantly more patients in the esketamine group than in the quetiapine group (91 patients [27.1%] vs. 60 patients [17.6%]; adjusted $P=0.003$) (Fig. 1). The adjusted odds ratio was 1.74 (95% confidence interval [CI], 1.20 to 2.52), favoring esketamine, which was consistent with findings from the unadjusted sensitivity analysis (Table

Table 1. Demographic and Psychiatric Characteristics at Baseline.*

Characteristic	Esketamine Group (N=336)	Quetiapine Group (N=340)
Age		
Mean — yr	44.3±13.6	45.7±13.4
Median (range) — yr	45.0 (18–72)	47.0 (18–74)
Distribution — no. (%)		
18–64 yr	317 (94.3)	322 (94.7)
≥65 yr	19 (5.7)	18 (5.3)
Sex — no. (%)		
Male	111 (33.0)	118 (34.7)
Female	225 (67.0)	222 (65.3)
Body-mass index — no./total no. (%)†		
<18.5	6/282 (2.1)	5/290 (1.7)
18.5 to <25	110/282 (39.0)	90/290 (31.0)
25 to <30	100/282 (35.5)	102/290 (35.2)
≥30	66/282 (23.4)	93/290 (32.1)
Employment status — no. (%)		
Employed	179 (53.3)	178 (52.4)
Unemployed	156 (46.4)	162 (47.6)
Other	1 (0.3)	0 (0.0)
No. of past failed treatments — no. (%)		
2	204 (60.7)	211 (62.1)
≥3	132 (39.3)	129 (37.9)
Age at MDD diagnosis — yr		
Mean	33.5±11.74	34.8±11.72
Median (range)	33.0 (10–54)	35.0 (10–55)
Duration of current MDD episode — wk		
Mean	68.8±84.17	64.6±65.66
Median (range)	43.0 (12–780)	38.0 (13–449)
Total no. of depressive episodes		
Mean	3.4±2.44	3.6±4.10
Median (range)	3.0 (1–21)	3.0 (1–60)
MADRS score‡		
Mean	31.4±6.06	31.0±5.83
Median (range)	31.0 (6–52)	31.0 (12–51)
IDS-C30 score§		
Mean	44.6±6.58	45.0±6.87
Median (range)	44.0 (17–66)	45.0 (28–71)
CGI-S score¶		
Mean	4.8±0.62	4.9±0.70
Median (range)	5.0 (3–7)	5.0 (3–6)

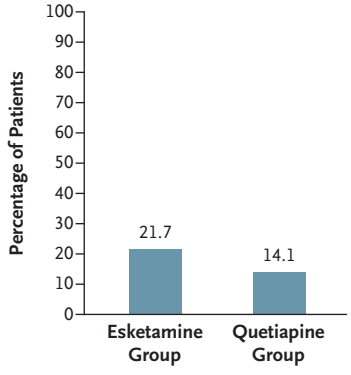
* Plus–minus values are means ±SD. Data are from the full analysis set, which includes all patients who underwent randomization. MDD denotes major depressive disorder.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. A body-mass index of less than 18.5 indicates underweight; 18.5 to less than 25, normal weight; 25 to less than 30, overweight; and greater than 30, obese.
‡ Scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating more severe depression. The baseline score was missing from one patient in the quetiapine group.
§ Scores on the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C30) scale range from 0 to 84, with higher scores indicating more severe depressive symptoms.
¶ Scores on the Clinical Global Impression–Severity (CGI-S) scale range from 1 to 7, with higher scores indicating more severe depression.

A Remission at Week 8



	Esketamine Group	Quetiapine Group
Remission at Wk 8 — no. (%)	91 (27.1)	60 (17.6)
Adjusted Percentage-Point Difference (95% CI)	9.5 (3.3–15.8)	
Adjusted OR (95% CI)	1.74 (1.20–2.52)	
Adjusted P Value	0.003	
Adjusted RR (95% CI)	1.54 (1.15–2.06)	

B No Relapse through Week 32 after Remission at Week 8



	Esketamine Group	Quetiapine Group
No Relapse through Wk 32 after Remission at Wk 8 — no. (%)	73 (21.7)	48 (14.1)
Adjusted Percentage-Point Difference (95% CI)	7.7 (2.0–13.5)	
Adjusted OR (95% CI)	1.72 (1.15–2.57)	
Adjusted RR (95% CI)	1.55 (1.12–2.16)	
Relapse — no. (%)	8 (2.4)	6 (1.8)
Hospitalized for worsening depression or for suicide attempt	2 (0.6)	3 (0.9)
MADRS score ≥22	6 (1.8)	3 (0.9)
No Relapse but Discontinued or Withdrew — no. (%)	10 (3.0)	6 (1.8)

Figure 1. Primary and Key Secondary End Points.

Panel A shows the percentage of patients with remission (primary end point) in the two trial groups; the esketamine group received esketamine nasal spray plus a selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI); the quetiapine group received extended-release quetiapine plus an SSRI or SNRI. Remission was defined as a score of 10 of less on the Montgomery–Åsberg Depression Rating Scale (MADRS; scores range from 0 to 60, with higher scores indicating more severe depression) and no treatment or study discontinuation before week 8. Panel B shows the comparison of the two trial groups with respect to freedom from relapse through week 32 after having remission at week 8, without treatment or study discontinuation (key secondary end point), as well as the number of patients who had a relapse and the number of patients who remained free from relapse through week 32 after having remission at week 8 but who discontinued treatment. The percentages were based on the number of patients in the full analysis set, which included all the patients who underwent randomization (336 in the esketamine group and 340 in the quetiapine group). Cochran–Mantel–Haenszel chi-square tests, adjusted for age group (18 to ≤64 years vs. ≥65 years) and number of past failed treatments (2 vs. ≥3), were used to estimate risk differences, odds ratios (ORs), and relative risks (RRs). Missing data for patients who did not discontinue the trial treatment or withdraw from the trial were imputed with the use of the last-observation-carried-forward approach; the data from patients who discontinued the trial treatment were imputed with use of the nonresponder imputation approach. CI denotes confidence interval.

S4). The adjusted relative risk was 1.54 (95% CI, 1.15 to 2.06). A retrieved dropout analysis showed that remission occurred in 27.7% of patients assigned to the esketamine group and in 17.9% assigned to the quetiapine group (odds ratio, 1.76 [95% CI, 1.22 to 2.54]; relative risk, 1.55 [95% CI, 1.16 to 2.07]) (Table S5). A comparison of the trial groups with respect to a MADRS score of 12 or less as the threshold for remission is provided in Table S6.

KEY SECONDARY END POINT

More patients in the esketamine group than in the quetiapine group had no relapse through week 32 after remission at week 8 (73 patients [21.7%] vs. 48 patients [14.1%]) (Fig. 1). The

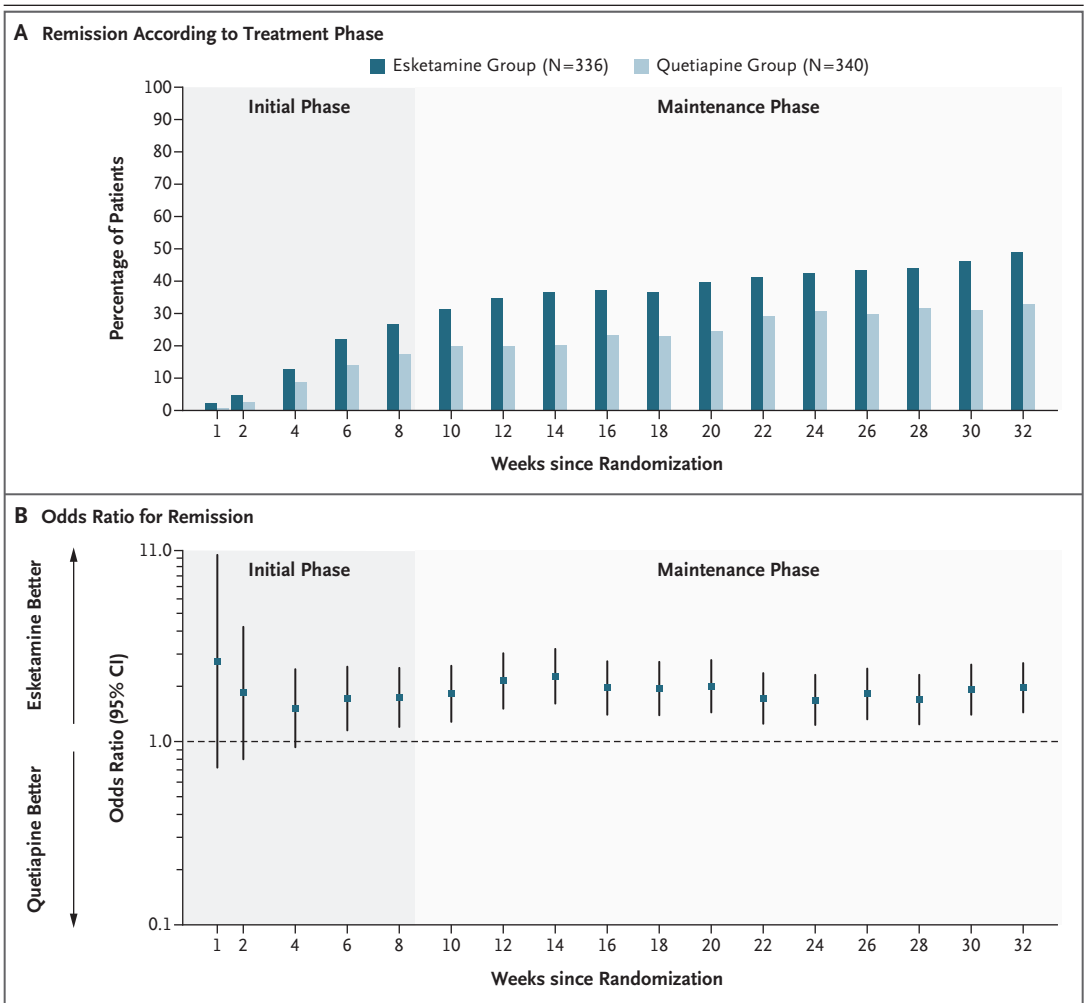


Figure 2. Remission over Time.

Panel A shows the percentage of patients in the esketamine group and in the quetiapine group who had remission (MADRS score ≤10), according to treatment phase and weeks since randomization. The nonresponder imputation approach was used to impute data for patients who discontinued the trial treatment. Panel B shows the odds of remission in the esketamine group as compared with the quetiapine group according to treatment phase and weeks since randomization. Data are from the full analysis set, which includes all patients who underwent randomization (336 in the esketamine group and 340 in the quetiapine group).

adjusted odds ratio was 1.72 (95% CI, 1.15 to 2.57), favoring esketamine; the adjusted relative risk was 1.55 (95% CI, 1.12 to 2.16). A comparison of the trial groups with respect to a MADRS score of 12 or less as the threshold for remission is provided in Table S6.

OTHER SECONDARY END POINTS

The percentage of patients with remission increased over time in both treatment groups (Fig. 2). Using the nonresponder imputation method, we found that the odds ratio for remission at week 32 was 1.96 (95% CI, 1.44 to 2.68), favoring esketamine (last-observation-carried-forward odds ratio, 2.09; 95% CI, 1.53 to 2.85) (Fig. S3). Remission at week 32 occurred in 49.1% of patients in the esketamine group and in 32.9% of patients in the quetiapine group (55.0% and 37.0% of patients, respectively, with the use of the last-observation-carried-forward method).

We observed a similar pattern in the percentage of patients with a treatment response over time (Fig. S4). Use of the nonresponder imputa-

tion method showed that a response at week 32 occurred in 65.5% of patients in the esketamine group as compared with 47.1% of patients in the quetiapine group; the odds ratio was 2.13 (95% CI, 1.57 to 2.91), favoring esketamine. Using the last-observation-carried-forward method, we found that a treatment response at week 32 occurred in 75.5% of patients in the esketamine group and in 55.5% in the quetiapine group (odds ratio, 2.48; 95% CI, 1.78 to 3.46) (Fig. S5).

The MADRS score decreased over time in both treatment groups, with a greater reduction in depressive symptoms (indicated by a greater decrease in MADRS score) from baseline at each time point in the esketamine group than in the quetiapine group (Fig. 3). At week 32, the estimated difference between the two treatment groups in the least-squares mean change from baseline in the MADRS score was –2.2 (95% CI, –3.6 to –0.8), favoring esketamine.

Table 2. Adverse Events during the Treatment Period.*

Adverse Event	Esketamine Group (N=334)	Quetiapine Group (N=336)
	no. of patients (%)	
At least 1 adverse event	307 (91.9)	262 (78.0)
Adverse event possibly related to treatment	283 (84.7)	208 (61.9)
Adverse event leading to death	1 (0.3)	1 (0.3)
At least 1 serious adverse event	19 (5.7)	17 (5.1)
Adverse event leading to treatment discontinuation	14 (4.2)	37 (11.0)
Adverse event leading to dose interruption, dose reduction, or both	35 (10.5)	43 (12.8)

* Data are from the safety analysis set, which includes all patients who underwent randomization and received at least one dose of any trial treatment. An adverse event was considered to have occurred during the treatment period if the event started between the first dose and 14 days after last dose of trial treatment (safety follow-up visit) or, in the case of serious adverse events, if it occurred between the first dose and 30 days or less after last dose.

SAFETY AND ADVERSE EVENTS

Adverse events occurred during the treatment period in 307 patients (91.9%) in the esketamine group and in 262 patients (78.0%) in the quetiapine group (Table 2 and Table S7). Serious adverse events during the treatment period occurred in 19 patients (5.7%) in the esketamine group and in 17 patients (5.1%) in the quetiapine group (Table S8). Two patients who were being

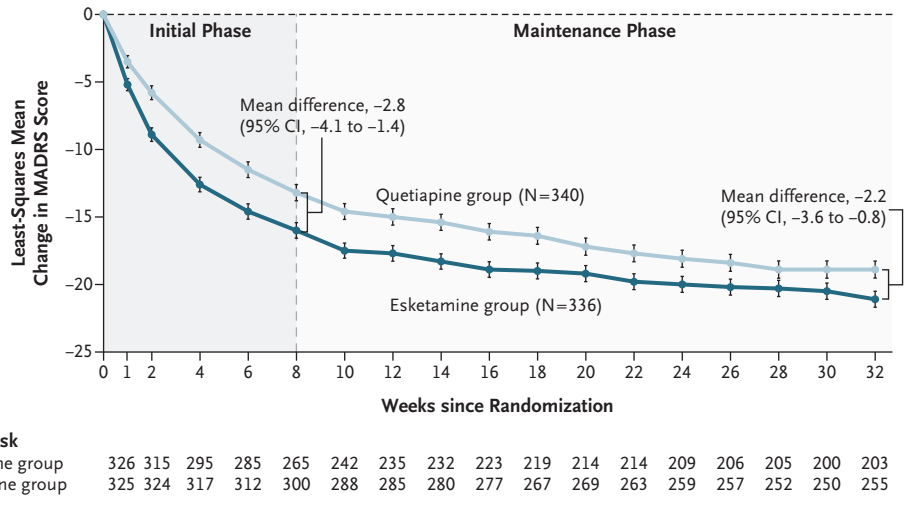


Figure 3. Change in MADRS Score from Baseline over Time.

The least-squares mean change from baseline in the MADRS score in the esketamine group and the quetiapine group is shown according to treatment phase and weeks since randomization. I bars indicate standard errors. Data are from the full analysis set, which includes all patients who underwent randomization. The analyses were performed with the use of a mixed model for repeated measures with an unstructured covariance matrix, with treatment, age group, number of past failed treatments, time, time-by-treatment interaction, and MADRS score at baseline as covariates.

treated with esketamine had a serious adverse event during the treatment period that was considered by the investigator to be related to the trial treatment: acute coronary syndrome (after 21 weeks of treatment) in one patient and dizziness (after 2 weeks of treatment) in the other. No quetiapine-treated patients had a serious adverse event during the treatment period that was considered to be related to the trial treatment.

Adverse events that led to discontinuation of the trial treatment occurred in 14 patients (4.2%) in the esketamine group and in 37 patients (11.0%) in the quetiapine group (Table 2 and Table S9). Suicide attempts occurred in two esketamine-treated patients and in one quetiapine-treated patient; none of the attempts were considered by the investigator to be related to the trial treatment. Two deaths were reported during the trial: one death occurred during week 9 in an esketamine-treated patient and had an undetermined cause, and one death occurred during week 17 in a quetiapine-treated patient and was due to a cerebrovascular accident (Table 2); neither death was considered by the investigator to be related to the trial treatment.

DISCUSSION

Although remission is the primary goal of initial treatment of depression, remission occurs in a markedly low percentage of patients who have required three or more consecutive treatments.[1,3,27] Thus, an unmet need exists for effective treatment options specifically for treatment-resistant depression.[10] This trial compared esketamine nasal spray with extended-release quetiapine, a commonly used, guideline-recommended antipsychotic augmentation agent, both in combination with a continuing SSRI or SNRI, during the initial and maintenance phases of treatment in patients with treatment-resistant depression.[14,15] The primary and key secondary end points were clinically relevant and aligned with treatment goals (remission and prevention of relapse).

Previously, esketamine nasal spray plus newly initiated treatment with an SSRI or SNRI was compared with newly initiated treatment with an oral antidepressant plus placebo nasal spray.[18-20,24-26] In those trials, a flexible dose of esketamine nasal spray plus an SSRI or SNRI was superior to placebo nasal spray plus an SSRI or SNRI in reducing the MADRS score over 4 weeks in patients with a history of nonresponse to at least two antidepressant agents[18] and in preventing relapse in patients with stable remission and patients with a stable response.[20]

In the present trial, patients receiving esketamine nasal spray were 1.54 times as likely as patients receiving extended-release quetiapine to have remission at week 8 (27.1% vs. 17.6%; risk difference, 9.5 percentage points). These results show the superiority of esketamine nasal spray to extended-release quetiapine with respect to the primary goal of antidepressant treatment in patients with a poor prognosis, in whom treatment goals are rarely met.[15] In addition, patients in the esketamine group were 1.55 times as likely as patients in the quetiapine group to have no relapse through week 32 after remission at week 8 (secondary end point).

The percentage of patients with remission and the percentage with a treatment response increased over the 32-week treatment period in both treatment groups, with odds ratios consistently favoring esketamine. Concordant with these findings, the MADRS score continued to decrease from baseline throughout the trial, with a greater decrease at all time points in the esketamine group than in the quetiapine group. More patients receiving esketamine nasal spray had an early response than those receiving extended-release quetiapine. Pertinent to this finding, early reduction in depressive symptoms during antidepressant treatment is a strong predictor of subsequent remission.[28,29] Indeed, by week 32 in the esketamine group, approximately half the patients were in remission, and two thirds of the patients had a response to treatment; these findings emphasize the importance of continuing treatment with esketamine nasal spray in patients who do not have remission during the initial phase of treatment.

As a 32-week head-to-head comparison of esketamine nasal spray with an active control, our trial appears to be an important addition to the phase 3 clinical program of esketamine nasal spray. In the previous phase 3 trials, another commonly used remission threshold — a MADRS score of 12 or less — was used.[18-20,24-26,30,31] Thus, to facilitate the contextualization of our trial with the previous trials, additional analyses were performed with a MADRS score of 12 or less as the threshold for remission. With the use of this alternative threshold, the percentage of patients

with remission increased to within the range of values reported in previous studies.[18,20,25] With remission defined as a MADRS score of 12 or less, more patients in the esketamine group than in the quetiapine group had remission at week 8 (38.7% vs. 22.9%) and had no relapse through week 32 after remission at week 8 (32.1% vs. 17.6%), which appears to reinforce the superiority of esketamine nasal spray to extended-release quetiapine. Existing guidelines for the treatment of patients with treatment-resistant depression lack uniformity; collectively, these data provide support for the use of esketamine nasal spray in treatment-resistant depression and may be of value for informing future guidelines.

In both trial groups, the adverse events that occurred during the treatment period and the percentage of patients who discontinued the trial treatment were consistent with the established safety profiles of esketamine nasal spray and extended-release quetiapine, with no new safety signals identified.[16-18,24,26,30,32,33] Although adverse events occurring during the treatment period were more common in the esketamine group than in the quetiapine group, the events in the esketamine group generally appeared to be transient and mild in severity and occurred on the day of dosing.[17,34] For example, whereas dizziness was more common in the esketamine group, discontinuation of the trial treatment because of dizziness was more common in the quetiapine group. In conjunction with the lower overall incidence of discontinuation due to adverse events during the treatment period in the esketamine group than in the quetiapine group, adverse events associated with esketamine nasal spray may have been less burdensome than those associated with extended-release quetiapine.

The present trial had certain limitations as an open-label trial. The open-label design was selected to minimize the burden on patients by eliminating the need for placebo, since the routes of trial-drug administration were different in the two treatment groups. Because a double-dummy design would have been required to enable masking of the trial-group assignments, the open-label design reduced the frequency of patient visits and trial procedures. In addition, given the distinct safety profile of each trial treatment, functional unmasking of the trial-group assignments could have nevertheless occurred. Although the open-label design introduced some risk of early discontinuation of the trial treatment because of the patient's knowledge of the treatment they were receiving, we felt that the design better reflected real-world practice because it permitted administration of the treatments according to their label instructions. Retrieved dropout analysis showed that the difference between the groups in the number of patients who discontinued the trial treatment had a minimal effect on the primary and key secondary end-point results.

To minimize bias, the MADRS score was assessed by an independent rater who was unaware of the trial-group assignments and was not otherwise involved in the trial. Furthermore, the MADRS score was not among the trial inclusion and exclusion criteria, nor was it used for decisions about continuation of treatment. In the esketamine group, the awareness of the group assignment and the greater frequency of clinical interactions may have influenced patient perceptions about efficacy; however, the frequency of clinical interactions during the trial reflected the frequency during treatment with esketamine nasal spray in clinical practice. Conversely, the frequency of clinical interactions in the quetiapine group in the trial was greater than the typical frequency in clinical practice.[8]

Extended-release quetiapine was chosen as an active comparator because it is approved for and frequently used as an augmentation treatment in patients with previous failed treatments.[12,15] However, because real-world treatment is heterogeneous and lacks consensus, with patients receiving multiple antidepressant treatments during a major depressive episode, the generalizability of our findings is limited.[10,15,35]

In this trial involving patients with treatment-resistant depression, esketamine nasal spray was superior to the comparator, extended-release quetiapine, a commonly used antipsychotic augmentation agent, when both were used in combination with an SSRI or SNRI.

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APPENDIX

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REFERENCES

1. Mendlewicz J. Towards achieving remission in the treatment of depression. Dialogues Clin Neurosci 2008;10:371-5.
2. Preventing recurrent depression: long-term treatment for major depressive disorder. Prim Care Companion J Clin Psychiatry 2007;9:214-23.
3. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
4. Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J Affect Disord 2009;116:4-11.
5. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of depression. May 30, 2013 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression_en.pdf).
6. Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. BMC Psychiatry 2019;19:247.
7. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence 2012;6:369-88.
8. Heerlein K, De Giorgi S, Degraeve G, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: healthcare resource utilization. J Affect Disord 2022;298:442-50.
9. Lundberg J, Cars T, Lööv S-Å, et al. Association of treatment-resistant depression with patient outcomes and health care resource utilization in a population-wide study. JAMA Psychiatry 2023;80:167-75.
10. Heerlein K, Perugi G, Otte C, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: treatment patterns and clinical outcomes. J Affect Disord 2021;290:334-44.
11. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. Dialogues Clin Neurosci 2015;17:111-26.
12. European Medicines Agency. Seroquel: summary of product characteristics, labelling and package leaflet (https://www.ema.europa.eu/en/documents/referral/seroquel-seroquel-xr-associated-names-article-30-referral-annex-iii_en.pdf).
13. European Medicines Agency. Questions and answers on Seroquel, Seroquel XR and associated names (quetiapine). August 6, 2014 (https://www.ema.europa.eu/en/documents/referral/questions-answers-seroquel-seroquel-xr-associated-names-quetiapine_en.pdf).
14. Nationale Versorgungs Leitlinien. Nationale Versorgungs Leitlinie: Unipolare depression. 2022 (https://www.leitlinien.de/themen/depression/version-3/kapitel-7#mehr-zum-thema).
15. Heerlein K, Godinov Y, Kambarov Y, Mulhern-Haughey S, Ito T, von Holt C. HSD28 most common treatments in patients with treatment resistant depression based on European cohort study real-world evidence. Value Health 2022;25:S278-S279. abstract.
16. Food and Drug Administration. Seroquel XR prescribing information. March 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022047Orig1s042lbl.pdf).
17. European Medicines Agency. Spravato: summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf).
18. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry 2019;176:428-38.
19. Daly EJ, Turkoz I, Salvadore G, et al. The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder. Depress Anxiety 2021;38:1120-30.
20. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2019;76:893-903.
21. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association, 2013.
23. Hawley CJ, Gale TM, Sivakumaran T, Hertfordshire Neuroscience Research group. Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord 2002;72:177-84.
24. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry 2020;81(3):19m12891.
25. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). Int J Neuropsychopharmacol 2019;22:616-30.
26. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in el-

derly patients with treatment-resistant depression-TRANSFORM-3. Am J Geriatr Psychiatry 2020;28:121-41.
27. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31:1841-53.
28. van Calker D, Zobel I, Dykierek P, et al. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. J Affect Disord 2009;114:243-53.
29. Henkel V, Seemüller F, Obermeier M, et al. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord 2009; 115:439-49.
30. Bauer M, Dell'osso L, Kasper S, et al. Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder. J Affect Disord 2013;151:209-19.
31. Jha MK, Williamson DJ, Mgharehabed G, Turkoz I, Daly EJ, Trivedi MH. Intranasal esketamine effectively treats treatment-resistant depression in adults regardless of baseline irritability. J Affect Disord 2023;321:153-60.
32. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2018;75:139-48.
33. El-Khalili N, Joyce M, Atkinson S, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol 2010;13:917-32.
34. Nikayin S, Murphy E, Krystal JH, Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. Expert Opin Drug Saf 2022; 21:777-87.
35. Heerlein K, Young AH, Otte C, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: baseline patient characteristics. J Affect Disord 2021;283: 115-22.

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