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Treatment response to esketamine nasal spray in patients with major depressive disorder and acute suicidal ideation or behavior without evidence of early response: a pooled post hoc analysis of ASPIRE

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Abstract

Objective. To assess the likelihood of attaining response/remission of depressive symptoms with esketamine nasal spray (ESK) plus standard of care (SoC) vs placebo nasal spray (PBO) plus SoC at 4 weeks in patients with major depressive disorder and active suicidal ideation with intent (MDSI) without early response.

Methods. A post hoc analysis of pooled data from ASPIRE I and ASPIRE II evaluated ESK plus SoC vs PBO plus SoC in adults with MDSI without response (≥50% improvement from baseline in Montgomery-Åsberg Depression Rating Scale [MADRS] score) at 24 hours after the first dose or at week 1 after the first two doses (ie, 24-hour and week 1 nonresponders). Response and remission (MADRS score ≤ 12) rates were assessed on day 25.

Results. The analysis included 362 patients (n = 182, ESK plus SoC; n = 180, PBO plus SoC). Among 24-hour nonresponders, more patients receiving ESK plus SoC vs PBO plus SoC achieved response (63.9% vs 48.0%, $P = .010$) and remission (35.1% vs 24.4%, $P = .074$) at day 25. Odds of response/remission were higher with ESK plus SoC vs PBO plus SoC (response: 1.89, 95% CI, 1.17-3.05; remission: 1.48, 95% CI, 0.93-2.35). Similar findings were observed among week 1 nonresponders for response (48.4% vs 34.5%, $P = .075$), remission (25.0% vs 13.1%, $P = .060$), and odds of response/remission (response: 2.03, 95% CI, 1.22-3.40; remission: 1.63, 95% CI, 1.01-2.62).

Conclusions. Patients with MDSI not responding within the first week of treatment with ESK plus SoC may still benefit from a full 4-week treatment course.

Introduction

In adults with major depressive disorder (MDD), suicidal ideation and planning are common,[1,2] with a pooled lifetime prevalence of suicide attempt of 31%, based on a meta-analysis of 65 observational studies of patients with MDD.[3] Depression with suicidal ideation is a particularly serious form of MDD that is characterized by more significant depressive symptoms and poorer response to treatment and remission compared with those with MDD but without suicidal ideation.[4-6] Patients with MDD with suicidal ideation are likely to have greater psychiatric and medical comorbidity, a greater experience of loss, and shorter life expectancy.[7-9] Suicidal ideation or behavior is a psychiatric emergency that requires immediate intervention.[10] Current standard of care (SoC) includes initiation or optimization of oral antidepressants (ADs) and hospitalization; however, oral medications can take 4 or more weeks for optimal effect, and benefits of hospitalization are often short-lived.[11]

Esketamine nasal spray (ESK) is a noncompetitive N-methyl-D-aspartate receptor antagonist indicated, in conjunction with an oral AD, for the treatment of adults with treatment-resistant depression (TRD) and for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior.[12] In studies of patients with TRD, ESK in conjunction with an oral AD was shown to provide a clinically meaningful improvement in depressive symptoms.[13-16] In those who attained response or remission based on Montgomery-Åsberg Depression Rating Scale (MADRS) score, continuation of ESK plus AD resulted in a statistically significant delay in time to relapse compared to those who switched to AD plus placebo nasal spray (PBO).[17]

Two phase-3, double-blind, multicenter studies (ASPIRE I and ASPIRE II) examined the efficacy and safety of ESK in reducing MDD symptoms, including suicidal ideation, in patients with major depressive disorder and active suicidal ideation with intent (MDSI).[18,19] In both studies, ESK plus comprehensive SoC (SoC, initial hospitalization, and initiation or optimization of AD therapy) significantly reduced depressive symptoms compared with PBO plus SoC 24 hours after ESK dosing. Severity of suicidality was also reduced; however, the difference between treatment groups was not statistically significant.[18,19] Not all patients with MDD in these studies experienced an early response to ESK treatment. This observation is noteworthy given that results of TRD studies have shown that a lack of response within the first week of ESK treatment is not necessarily predictive of future nonresponse.[20] Among a pooled dataset of patients without a response within the first week of treatment from the TRANSFORM-1 and TRANSFORM-2 trials of ESK in TRD, significantly more patients treated with ESK plus AD achieved response after 4 weeks of treatment compared with patients treated with AD plus PBO. We hypothesized that a similar pattern would be evident in patients with MDSI.

This post hoc analysis of the ASPIRE I and ASPIRE II studies assessed the likelihood of patients with MDSI achieving response/remission in depressive symptoms with ESK plus SoC compared with that of PBO plus SoC at 4 weeks if they did not meet response criteria within the first week of treatment.

Methods

Study design and treatment

This was a post hoc analysis of a pooled dataset from the ASPIRE I (NCT03039192)[18] and ASPIRE II (NCT03097133)[19] trials. ASPIRE I and ASPIRE II were two identically designed, double-blind, placebo-controlled, randomized studies conducted to evaluate the efficacy and safety of ESK compared with those of PBO in the context of comprehensive SoC in adults with MDD who had active suicidal ideation with intent (Supplementary Figure 1). The study designs were previously reported in detail.[18,19] The ASPIRE I study was conducted between June 2017 and December 2018, and the ASPIRE II study was conducted between June 2017 and April 2019.[18,19] The studies consisted of 3 phases, including a 24- to 48-hour screening period to assess patients' eligibility for study enrollment, a 4-week double-blind treatment phase (days 1-25), and a 9-week follow-up phase (days 26-90). All patients were screened after presenting to an emergency department or an inpatient psychiatric unit; study patients were to remain hospitalized for a recommended 5 days or 14 days for some countries in the ASPIRE II study, with shorter or longer hospitalizations permitted if clinically warranted per local SoC.

At the start of the 4-week double-blind phase, eligible patients were randomly assigned (1:1) to receive ESK (84 mg) or PBO. Patients self-administered the intranasal study drug under direct supervision twice weekly throughout the double-blind phase. SoC AD(s) treatment (ie, AD monotherapy or AD plus augmentation therapy) was based on the investigator's clinical judgment and was initiated or optimized on day 1 at the start of randomization. Augmentation therapy could include a second AD, an atypical antipsychotic, or a mood stabilizer (such as lithium, lamotrigine, or valproic acid). Dose titration/adjustment of SoC treatment occurred during the first 2 weeks of double-blind treatment (ie, by day 15), after which the doses remained consistent until the end of the double-blind phase (day 25).

Patient population

Adult patients aged 18 to 64 years with a diagnosis of MDD per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition,[21] criteria and confirmed by the Mini-International Neuropsychiatric Interview (MINI)[22] were eligible for enrollment in the ASPIRE trials. Patients were required to have moderate to severe MDD (MADRS score > 28),[23] active suicidal ideation with intent confirmed by an affirmative response to MINI questions ("Think [even momentarily] about harming or of hurting or of injuring yourself, with at least some intent or awareness that you might die as a result, or think about suicide [ie, about killing yourself]?" and "Intend to act on thoughts of killing yourself?") within 24 hours of randomization, and a clinical need for psychiatric hospitalization. Full inclusion and exclusion criteria have been previously published.[18,19,24]

Ethical practices

The ASPIRE study protocols and amendments were reviewed by an independent ethics committee/institutional review board. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. Possible side effects of treatment were fully explained to participants. All patients provided written informed consent before participation.

Definitions

For depressive symptoms, response was defined as ≥50% improvement (ie, reduction of scores) from baseline in MADRS total score, and remission was defined as MADRS total score ≤ 12. Early response was defined as ≥50% improvement from baseline in MADRS total score at 24 hours (4 hours and 24 hours after the first dose) and within week 1 (4 hours and 24 hours after the first dose and day 8 after 2 doses). Two cohorts without evidence of early response were defined for this post hoc analysis: (1) 24-hour nonresponders: patients who did not meet MADRS response criteria at 4 hours and 24 hours after the first dose, and (2) week 1 nonresponders: patients who did not meet MADRS response criteria at 4 hours and 24 hours after the first dose and at day 8 after 2 doses.

Analyses and statistics

The full analysis set included all randomly assigned patients who received at least 1 dose of double-blind study medication and had both a baseline and a postdose evaluation for the MADRS total score. For this post hoc analysis, randomly assigned patients who had day 25 MADRS data were included in the dataset.

In both ASPIRE studies, the primary efficacy endpoint was changed in the MADRS total score from baseline (day 1, before dosing) to 24 hours after the first dose (day 2). Based on MADRS total scores, response and remission rates on day 25 were determined for patients who did not meet response criteria (nonresponders) at 24 hours or within the first week of treatment. Predose assessments on day 25 are reported for consistency with the endpoint of the double-blind treatment phase described in the U.S. package information (day 25 predose MADRS assessment). Observed response and remission rates on day 25 were compared between ESK plus SoC and PBO plus SoC groups using Cochran-Mantel-Haenszel tests. Multiple logistic regression models were performed to estimate the probability of patients achieving

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Table 1. Baseline Demographics and Disease Characteristics

	MADRS nonresponders at 24 hours[a] (N = 284)		MADRS nonresponders at week 1[b] (N = 184)	
Characteristic	ESK (n = 126)	PBO (n = 158)	ESK (n = 80)	PBO (n = 104)
Mean age, years (SD)	39.3 (12.9)	39.3 (12.9)	40.4 (13.1)	38.4 (13.2)
Female, n (%)	74 (58.7)	92 (58.2)	45 (56.3)	63 (60.6)
Race				
N	123	150	79	100
White, n (%)	90 (73.2)	110 (73.3)	62 (78.5)	72 (72.0)
Black/African American, n (%)	2 (1.6)	11 (7.3)	1 (1.3)	5 (5.0)
Others, n (%)	31 (25.2)	29 (19.3)	16 (20.3)	23 (23.0)
MADRS total score,[c] mean (SD)	40.5 (5.10)	40.6 (5.65)	40.5 (5.31)	40.5 (5.64)
CGI-SS-r[d]				
1 = Questionably suicidal	3 (2.4)	6 (3.8)	2 (2.5)	3 (2.9)
2 = Mildly suicidal	5 (4.0)	11 (7.0)	3 (3.8)	7 (6.7)
3 = Moderately suicidal	31 (24.6)	40 (25.3)	18 (22.5)	26 (25.0)

Abbreviations: CGI-SS-r, Clinical Global Impression-Severity of Suicidality Scale-revised; MADRS, Montgomery-Åsberg Depression Rating Scale.
[a]Patients who did not meet response criteria at day 1 (day 1; 4 hours and 24 hours after the first dose).
[b]Patients who did not meet response criteria at day 1 (day 1; 4 hours and 24 hours after the first dose) and day 8 (after 2 doses).
[c]Range: 0-60 points (higher scores indicate more severe depression).
[d]Range 0-6 (higher score indicates a more severe condition); captures response to "Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?"

response or remission on day 25 if early response criteria were not met; odds ratios (ORs), 95% CIs, and number needed to treat (NNT) were computed. No adjustments for multiple comparisons were made.

Results

Patients

Of 451 patients in the full efficacy analysis set (n = 226, ESK plus SOC; n = 225, PBO plus SOC), 362 had MADRS total score data on day 25 (n = 182, ESK plus SoC; n = 180, PBO plus SoC) and were included in this post hoc analysis. Detailed information on the disposition of the ASPIRE studies has been published previously.[18,19,24] Baseline demographics and disease characteristics were similar among the ESK plus SoC and PBO plus SoC populations in MADRS nonresponders at 24 hours and at week 1 (Table 1).

Response and remission rates

Overall, response was attained by a greater proportion of patients in the ESK plus SoC group compared with the PBO plus SoC group at each visit for the full efficacy analysis set (Figure 1a). At 4 hours after the first dose, 26.6% of patients in the ESK plus SoC group and 14.7% in the PBO plus SoC group attained a response ($P < .002$). At 24 hours after the first dose, 35.3% of patients in the ESK plus SoC group and 25.7% in the PBO plus SoC group attained response ($P < .030$). At day 25, 74.6% of patients in the ESK plus SoC group and 58.3% in the PBO plus SoC group attained response ($P < .001$). In patients without evidence of an early response at 24 hours, significantly more patients in the ESK plus SoC group compared with the PBO plus SoC group achieved response on day 25 (Figure 1b). A nonstatistically significant difference was observed in patients without evidence of an early response at week 1.

Similar results favoring ESK plus SoC were observed for overall rates of remission at each visit for the full efficacy analysis set (Figure 2a). A statistically significant difference in remission was attained by 20.7% (ESK plus SoC) and 9.9% (PBO plus SoC) of patients at 24 hours after the first dose, ($P = .002$). Similarly, remission was attained by 52.2% (ESK plus SoC) and 38.3% (PBO plus SoC) of patients on day 25 ($P = .007$). Although adjustments for multiple comparisons were not made for the time course of response assessments, 4 of the 9 visits assessed demonstrated significant differences in patient response rates between treatment groups. In patients not meeting criteria for early response, more patients in the ESK plus SoC group compared with the PBO plus SoC group achieved remission on day 25 (Figure 2b); however, the observed differences in remission rates between treatment groups were not statistically significant.

Multiple logistic regression models

Based on multiple logistic models of MADRS response and remission, the ORs for a response on day 25 with ESK plus SoC compared with PBO plus SoC among patients without evidence of response at 24 hours and at the end of week 1 are shown in Figure 3a. Patients in the ESK plus SoC group had an 89% increased odds of response on day 25 compared with patients in the PBO plus SoC group after adjusting for 24-hour nonresponder status (OR, 1.89; 95% CI, 1.17-3.05; $P = .009$; probability of response [PR]: ESK plus SoC, 64.0%; PBO plus SoC, 48.0%), with an NNT of 7. Patients in the ESK plus SoC group were twice as likely as patients in the PBO plus SoC group to attain response on day 25 after adjusting for week 1 nonresponder status (OR, 2.03; 95% CI, 1.22-3.40; $P = .007$; PR: ESK plus SoC, 50.0%; PBO plus SoC, 33.0%), with an NNT of 6. The ORs for remission on day 25 with ESK plus SoC compared with PBO plus SoC among patients without evidence of response at 24 hours and at the end of week 1 are shown in Figure 3b. Odds of remission were 48% and 63% higher in the ESK plus SoC vs PBO plus SoC group on day 25 (after adjusting for 24-hour

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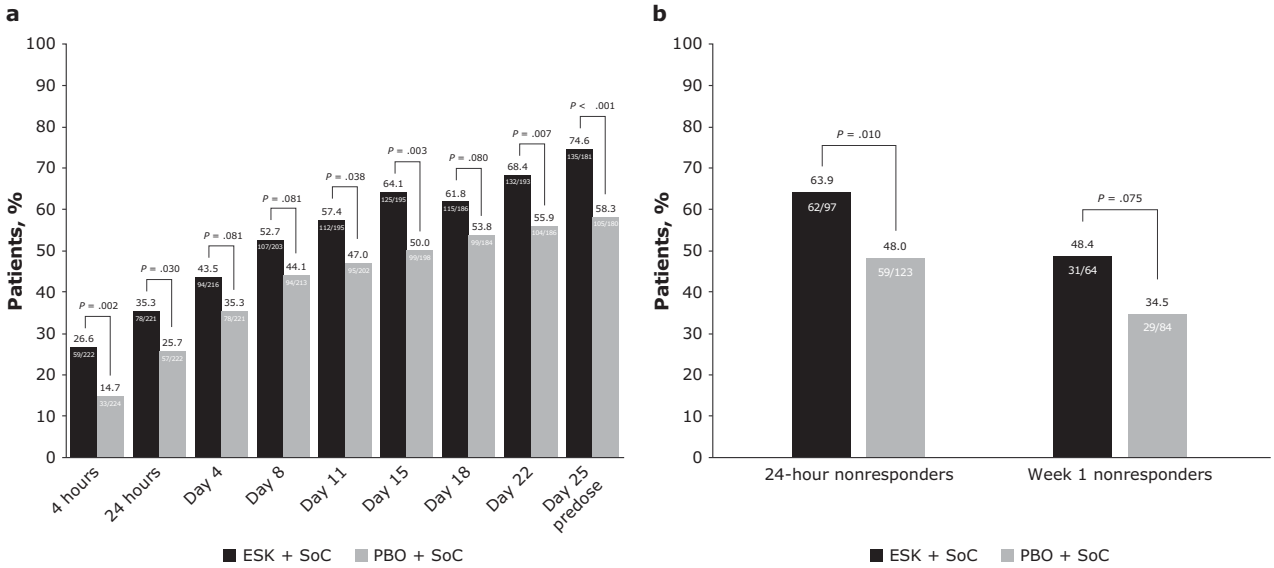

Figure 1. Observed MADRS response rates. (a) All patients by study visit; (b) a subset of patients not meeting study-defined criteria for early response to treatment (nonresponders) who subsequently attained a response on day 25. Response is defined as having improvement from baseline (double-blind) in total MADRS score ≥ 50%. The values inside bars represent patients in each group/total number of patients. Abbreviations: ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo nasal spray; SoC, standard of care.

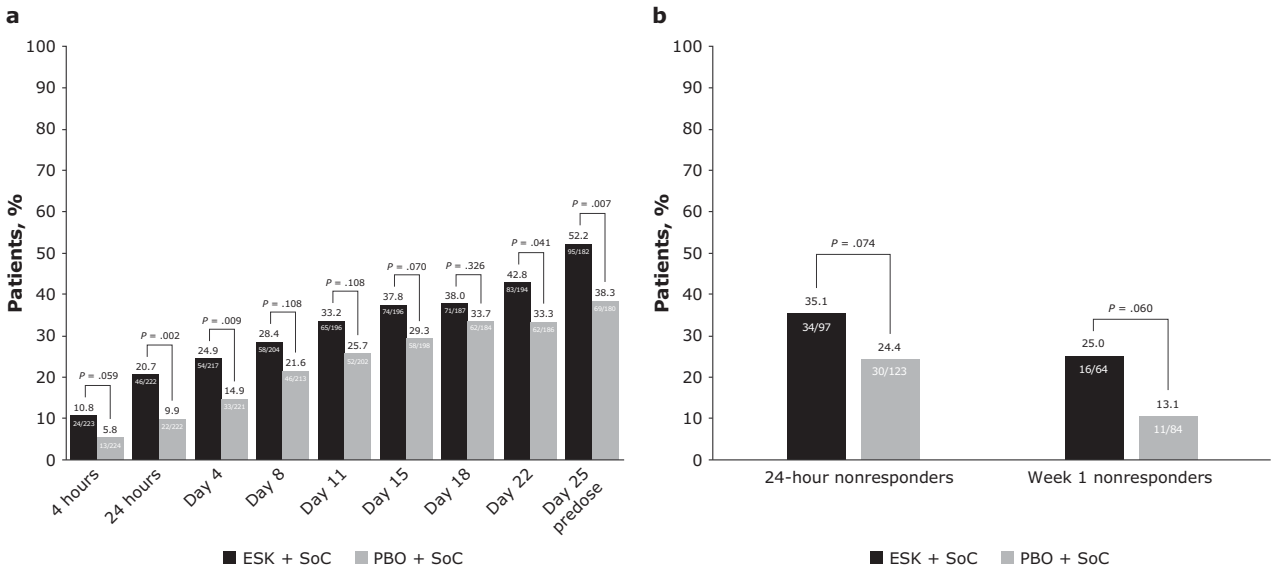

Figure 2. Observed MADRS remission rates. (a) All patients by study visit; (b) a subset of patients not meeting study-defined criteria for early response to treatment (nonresponders) who subsequently attained remission on day 25. Remission is defined as having a MADRS total score of ≤12. The values inside bars represent patients in each group/total number of patients. Abbreviations: ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo nasal spray; SoC, standard of care.

nonresponders: OR, 1.48; 95% CI, 0.93-2.35; $P = .095$; probability of remission: ESK plus SoC, 34.0%; PBO plus SoC, 25.0%), with an NNT of 12; after adjusting for week 1 nonresponders: OR, 1.63; 95% CI, 1.01-2.62; $P = .043$; probability of remission: ESK plus SoC, 22.0%; PBO plus SoC, 15.0%), with an NNT of 15.

Discussion

Among patients with MDD and active suicidal ideation with intent who did not meet criteria for MADRS response within 24 hours after the first dose or within the first week of treatment in the ASPIRE I and ASPIRE II studies, those who received ESK plus SoC had a higher likelihood of achieving response or remission of depressive symptoms on day 25 compared with those who received PBO plus SoC. It is important to note, however, that the differences in observed remission rates were somewhat smaller and did not meet statistical significance parameters.

The results of this analysis align with prior findings with ESK in patients with TRD and further strengthen the evidence that patients who do not attain an early response are still likely to receive benefit from the full 4-week treatment cycle. In a prior post hoc analysis in patients with TRD, among patients who did not respond by days 2 and 8, a significantly higher proportion of

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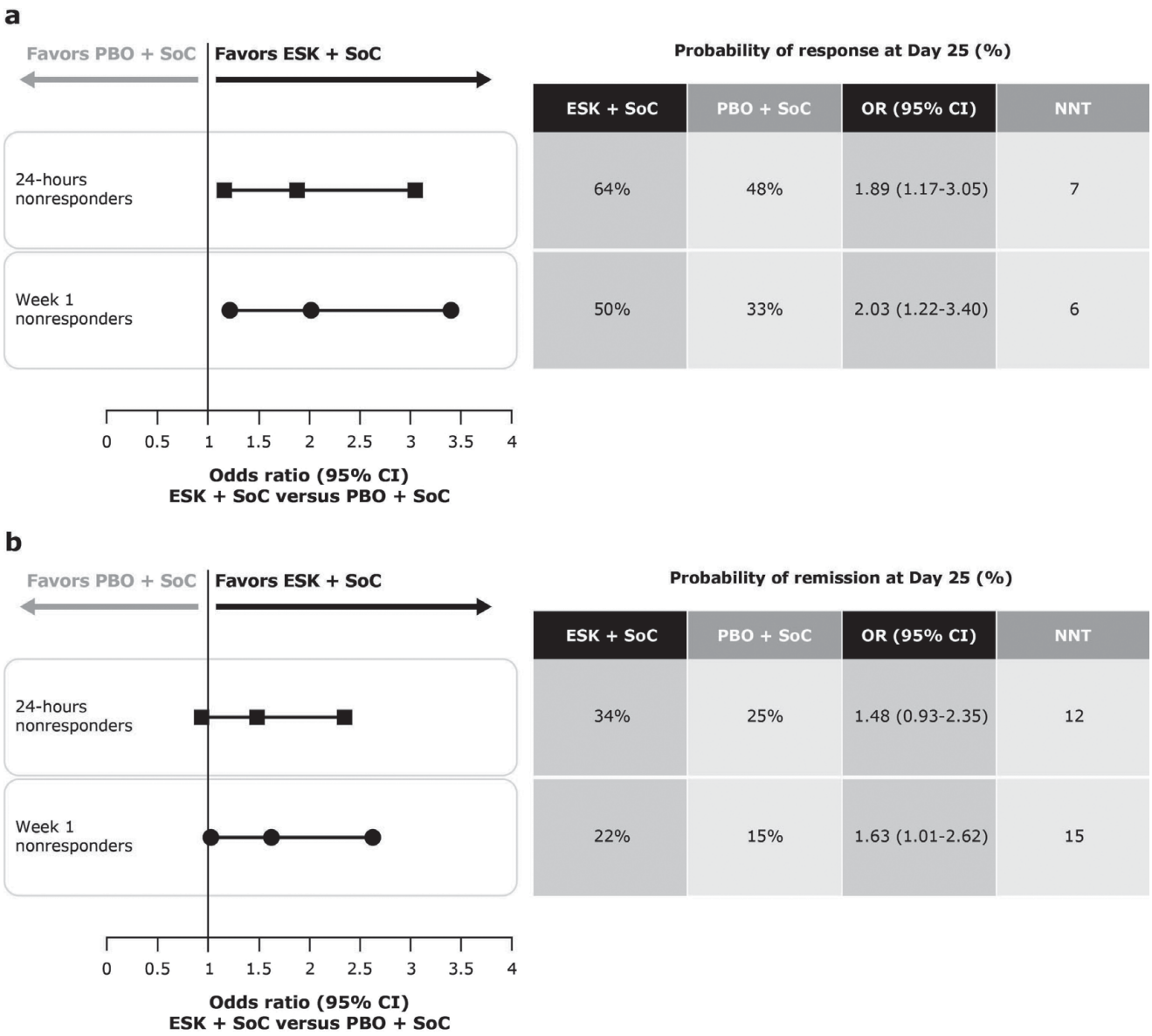

Figure 3. Multiple logistic models of MADRS (b) response and (a) remission at day 25 in patients not meeting criteria for early MADRS response. Multiple logistic regression models included nonresponders' status in addition to factors for treatment, study ID, and SoC antidepressant (AD) treatment as randomized (AD monotherapy or AD plus augmentation therapy). Abbreviations: ESK, esketamine nasal spray; MADRS, Montgomery-Åsberg Depression Rating Scale; NNT, number needed to treat; PBO, placebo nasal spray; SoC, standard of care.

patients treated with ESK plus a newly initiated AD vs AD plus PBO attained response after 4 weeks of treatment (52.1% vs 42.4%, $P = .01$; OR [95% CI], 1.56 [1.04-2.35]; PR: ESK plus AD, 0.52; AD plus PBO, 0.41). [20] The two analyses together provide evidence supporting continued treatment with ESK for a full 4-week period, regardless of early response, in patients with TRD or MDD with active suicidal ideation with intent.

In the ASPIRE studies, patients in both treatment groups experienced a rapid reduction in severity of suicidality as measured by the Clinical Global Impression-Severity of Suicidality Scale-revised (CGI-SS-r) scale at 24 hours after the first dose, and a significant difference between treatment groups was not observed. Therefore, CGI-SS-r outcomes at 4 weeks in patients with early nonresponse were not explored in the current analysis.

We recognize that other methods have been utilized to predict the likelihood of response or nonresponse of ADs and may have yielded different results. The rapid effects of ESK are evident within 1 week of initiating treatment,[25] which supports the assessment of early responders on days 1 and 7 of treatment in this analysis. Similarly, assessing AD response at day 14 could also have been employed in assessing response or lack of response to treatment, which has served as an important prognostic indicator for other ADs.[26] However, the 20% partial response criterion for MADRS total score[26] probably would not be suitable because a rapid reduction in MADRS total scores was observed at 24 hours after the first dose in this severely depressed patient population (mean MADRS score of approximately 40); thus, most patients would already be considered partial responders after 1 and 7 days of treatment. This analysis sought to assess the rate of response among later responders by extending the net of response through day 25 of treatment.

Several limitations of this analysis should be noted. First, notable response and remission rates were observed in both the ESK

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plus SoC and the PBO plus SoC groups in this severely ill and vulnerable patient population. A robust placebo effect may have limited the effect size of ESK treatment. This finding could be attributed to the nonspecific effects associated with frequent, intensive treatment visits as well as the comprehensive SoC received by all patients in the ASPIRE studies. All patients were initially hospitalized in a psychiatric unit for a recommended duration of 5 days or 14 days for some countries (with shorter or longer hospitalizations permitted if considered clinically warranted by the investigator), and patients were provided with optimized SoC AD therapy with possible augmentation therapy. Because the ASPIRE studies were multinational, regional differences in SoC treatment may have also impacted the results. Furthermore, this was a post hoc analysis of studies that were not powered to specifically address this research question, and all reported *P*-values are nominal.

Because patients with MDD and active suicidal ideation with intent are an understudied, vulnerable patient population, findings from the ASPIRE studies are valuable additions to the therapeutic knowledge base. Prior to the approval of ESK, no rapid-acting, approved pharmacological treatment existed for this patient population.[18,19] The current findings expand our understanding of the therapeutic utility of ESK in patients with MDD and acute suicidal ideation or behavior (MDSI) by showing that, even in patients without an early response, ESK treatment may still result in clinically meaningful benefit following a full 4-week treatment period. Additional studies are needed to further translate these findings into routine clinical practice.

Conclusions

In conclusion, the results of this post hoc analysis demonstrate that, although many patients may experience clinically meaningful improvement within a short time frame, some patients may require a full course of treatment (4 weeks) to achieve optimal results. Patients with MDSI who do not attain a response within the first week of treatment with ESK may still benefit from a full 4-week cycle of treatment.

Prior presentation. Data reported in this manuscript were previously presented (poster presentation) at the 2021 American Psychiatric Association Annual Meeting (Virtual), May 1-3, 2021.

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Author contributions. The sponsor was involved in the design and conduct of the study; management, analysis, and interpretation of data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication. All authors had major roles in the conceptualization and oversight of the current post hoc analysis. D.-J.F. was also directly involved in the design and oversight of the original phase-3 trials in patients with MDD and active suicidal ideation with intent. G. Sanacora and R.S. were site investigators who provided direct patient care to clinical trial participants. In accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines, all authors contributed to the development of the manuscript, approved the final version of the manuscript before submission, and were involved in the decision to submit the manuscript for publication.

Disclosures. I.T., D.-J.F., and O.L. are employees of Janssen and stockholders of Johnson & Johnson, Inc.

G. Salvadore is currently an employee and stockholder of Acadia Pharmaceuticals Inc. At the time that this work was conducted, G. Salvadore was an employee of Janssen and a stockholder of Johnson & Johnson, Inc.

G. Sanacora has served as a consultant for Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Engrail Therapeutics, Clexio, Denovo Biopharma, F. Hoffmann-La Roche, Gilgamesh, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Naurex, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Labs; has received research contracts from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, F. Hoffmann-La Roche, Merck, Naurex, Servier, and Usona; holds equity in BioHaven Pharmaceuticals; and is a co-inventor on a U.S. patent (no. 8778979) held by Yale University and on U.S. Provisional Patent Application no. 047162-7177P1 (00754) filed on August 20, 2018, by the Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

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Supplementary Materials. To view supplementary material for this article, please visit http://doi.org/10.1017/S1092852922000931.

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