Esketamine
Clinical Trials in Major Depressive Disorder and Active Suicidal Ideation with Intent

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Background

- ESK has been evaluated in two subpopulations of MDD in adults in clinical trials - 1) approved in combination with a SSRI or SNRI, for the treatment of major depressive disorder in adults have not responded adequately to at least two separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate to severe depressive episode 2) investigational for the rapid reduction of depressive symptoms in patients (<65 years of age) with MDD and active suicidal ideation and intent.
- **ESK nasal spray has not been proven to be effective in preventing suicide or in reducing suicidal ideation or behavior.**
- For information on ongoing clinical trials for ESK nasal spray, please access the following link on www.clinicaltrials.gov: http://jan4.me/17RroVK.

Phase 3 Studies in Adults: ASPIRE-1 and ASPIRE-2

- Two double-blind, randomized, PBO-controlled studies (ASPIRE-1 [NCT03039192] and ASPIRE-2 [NCT03097133]) evaluated the efficacy and safety of ESK in addition to comprehensive SOC for the rapid reduction of depressive symptoms in those who have MDD and active suicidal ideation with intent.[1-4]
  - Primary endpoint: Both studies found that ESK+SOC statistically significantly improved depressive symptoms based on the MADRS total score at 24 hours post first dose compared with PBO+SOC (ASPIRE-1 study: LSMD, -3.8; ASPIRE-2 study: LSMD, -3.9; *P*=0.006 in both studies).
  - A pooled analysis of the two studies showed a LS mean change in MADRS total score of -16 vs -12.1 (LSMD: -3.8; 95% CI: -5.75, -1.89) for the ESK+SOC vs PBO+SOC groups.[5]
  - The most common TEAEs (≥20% in any arm) were dizziness, dissociation, and nausea in ASPIRE-1 and dizziness, dissociation, nausea, dysgeusia, somnolence, headache, and paresthesia in ASPIRE-2.
- A post hoc analysis of North American patients (n=122) in ASPIRE-1 and ASPIRE-2 revealed that, at baseline, these patients tended to be younger, had a longer duration of the current episode, a greater number of depressive episodes, and reported more frequent and severe suicidal thoughts than patients enrolled in the trials in the rest of the world (n=328).[6]
  - Patients in the ESK+SOC arm showed a statistically significant improvement in the MADRS total score at 24 hours post first dose compared with patients in the PBO+SOC arm (-21.3 vs -14.8; LSMD: -6.6; 95% CI: -10.6, -2.7). TEAEs were consistent with the overall clinical trials.

Phase 2 Study in Adolescents

- A double-blind, randomized, double-dummy, psychoactive PBO-controlled study is currently ongoing in adolescents to assess the efficacy of ESK versus oral midazolam in rapidly reducing depressive symptoms in adolescents with MDD who have active suicidal ideation with intent (NCT03185819).[7,8]

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ASPIRE-1 and ASPIRE-2[1-4]

Identically Designed, Phase 3, Randomized, Double-blind, Placebo-controlled Studies

Rapid reduction of depressive symptoms in adults with MDD with active suicidal ideation and intent

Inclusion Criteria[3,4]

- Age 18-64 years
- DSM-5 diagnosis of MDD
- Suicidal ideation with intent
- MADRS total score of >28 on day 1, predose
- Require acute psychiatric hospitalization due to imminent risk of suicide

Exclusion Criteria[3,4]

- Current DSM-5 diagnosis of bipolar (or related) disorder, OCD, antisocial personality disorder, or borderline personality disorder
- Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis
- History of moderate or severe substance or alcohol use within 6 months before screening
- SBP >140 mm Hg or DBP >90 mm Hg
- Positive urine test result(s) for phencyclidine, cocaine, or amphetamines

Study Design[1-4]

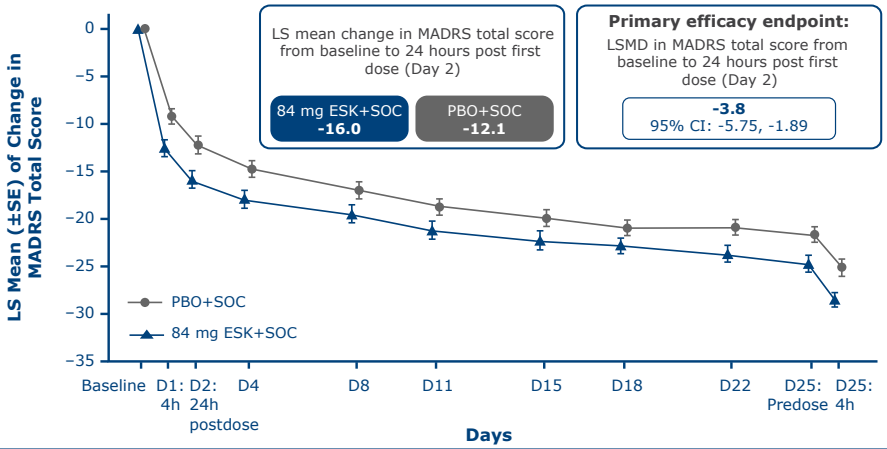
Adults with MDD who have active suicidal ideation with intent
ASPIRE-1
N=224
→ **84 mg ESK+SOC (n=112)**
→ **PBO+SOC (n=112)**

Adults with MDD who have active suicidal ideation with intent
ASPIRE-2
N=227
→ **84 mg ESK+SOC (n=114)**
→ **PBO+SOC (n=113)**

SOC: Hospitalization with optimized antidepressant and psychotherapy, enhanced by twice weekly visits during the double-blind phase.

Pooled Primary Endpoint Results[5]

Statistically significant improvement in depressive symptoms in patients treated with ESK+SOC vs those treated with PBO+SOC



LS mean change in MADRS total score from baseline to 24 hours post first dose (Day 2)

84 mg ESK+SOC	PBO+SOC
-16.0	**-12.1**

Primary efficacy endpoint:
LSMD in MADRS total score from baseline to 24 hours post first dose (Day 2)

-3.8
95% CI: -5.75, -1.89

Safety Results[3,4]

Most common TEAEs (≥20% in either arm)

ASPIRE-1:
- Dizziness
- Dissociation
- Nausea

ASPIRE-2:
- Dizziness
- Dissociation
- Nausea
- Dysgeusia
- Somnolence
- Headache
- Paresthesia

- 1 death in follow-up phase in ASPIRE-1

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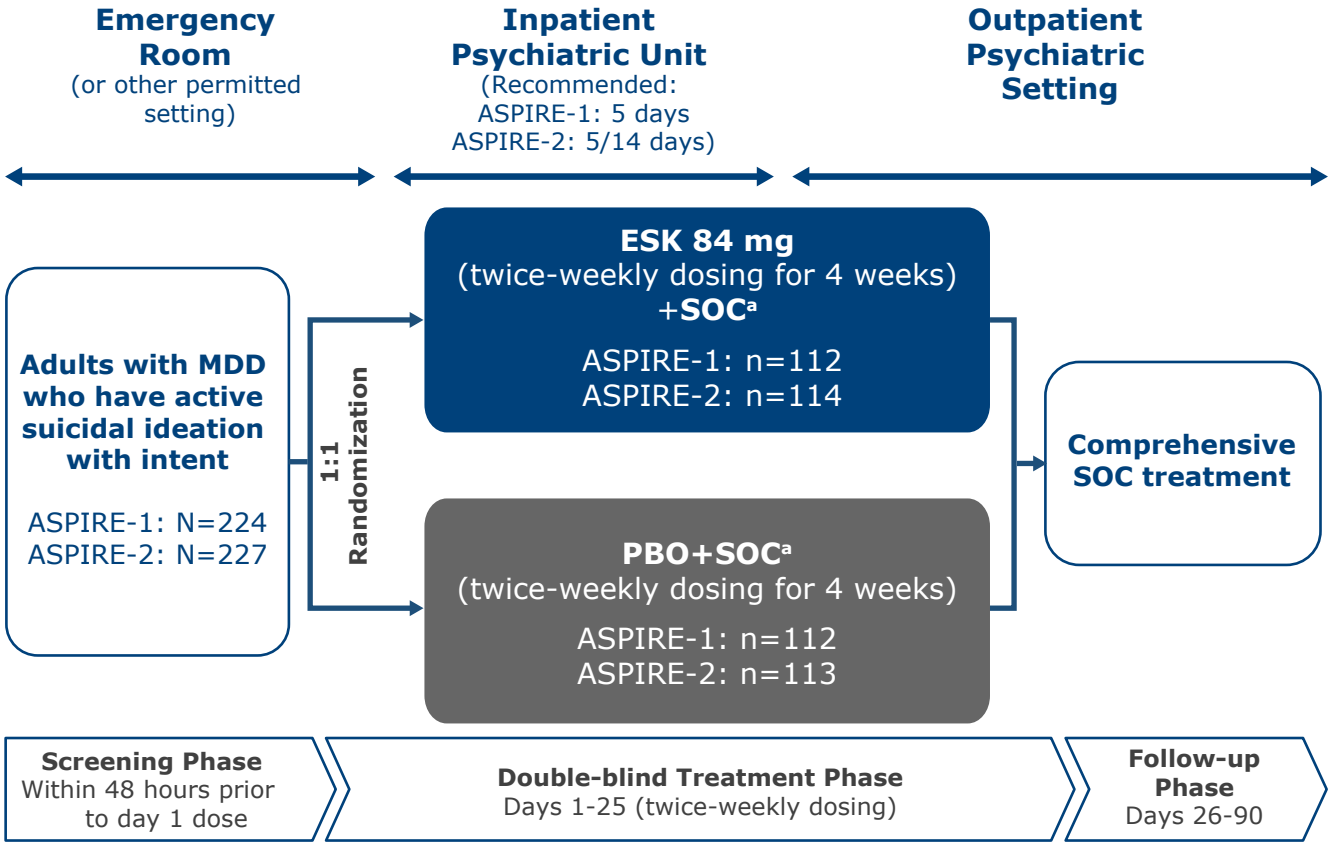
- ASPIRE-1 (NCT03039192) and ASPIRE-2 (NCT03097133) were 2 identically designed phase 3, multicenter, 1:1 randomized, double-blind, PBO-controlled studies that evaluated rapidly reducing depressive symptoms adults with MDD who have active suicidal ideation with intent.[1-4]



[a]Includes the initial inpatient hospitalization with newly initiated or optimized antidepressant therapy and psychotherapy, enhanced by twice-weekly intensive visits during the double-blind phase.

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Inclusion Criteria[3,4]	**Exclusion Criteria**[3,4]

• Age 18-64 years
• DSM-5 diagnosis of MDD
• Suicidal ideation with intent within 24 hours of randomization, confirmed by a positive response when asked:
  ○ "Think about suicide (killing yourself)?"
  ○ "Intend to act on thoughts of killing yourself?"
• MADRS total score of >28 on day 1, predose
• Require acute psychiatric hospitalization due to imminent risk of suicide, and admitted voluntarily
	• Current DSM-5 diagnosis of bipolar (or related) disorder, OCD, antisocial personality disorder, or borderline personality disorder
	• Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis
	• History of moderate or severe substance or alcohol use disorder per DSM-5 criteria within 6 months before screening
	• SBP >140 mm Hg or DBP >90 mm Hg
	• Positive urine test result(s) for phencyclidine, cocaine, or amphetamines

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Primary Efficacy Endpoint[3,4]

- Change from baseline in MADRS total score at 24 hours after first dose.

Key Secondary Efficacy Endpoint[3,4]

- Change from baseline in severity of suicidality (CGI-SS-r from SIBAT) score at 24 hours after first dose.

Other Secondary Efficacy Endpoints[3,4]

Measured at 4 hours and 24 hours after first dose, and through day 25:

- Percentage of participants with remission of MDD (MADRS total score ≤12).
- Reduction in CGI-SR-I and changes in FoST, clinician-rated and patient-reported outcomes from SIBAT, and MADRS suicidal thoughts item (item 10).

- Baseline characteristics were comparable across treatment arms.[3,4]

	ASPIRE-1[3]		ASPIRE-2[4]	
	ESK+SOC (n=112)	PBO+SOC (n=112)	ESK+SOC (n=114)	PBO+SOC (n=113)
Age, years, mean (SD)	40.8 (13.17)	37.9 (12.54)	40.2 (12.73)	41.4 (13.43)
Female, n (%)	65 (58.0)	73 (65.2)	69 (60.5)	67 (59.3)
MADRS total score, mean (SD)	41.3 (5.87)[a]	41.0 (6.29)	39.5 (5.19)	39.9 (5.76)
CGI-SS-r, %	90.0[a]	87.5	90.3	92.1
Moderately suicidal, n (%)	29 (26.1)	28 (25.0)	35 (30.7)	33 (29.2)
Markedly suicidal, n (%)	38 (34.2)	42 (37.5)	48 (42.1)	42 (37.2)
Severely suicidal, n (%)	29 (26.1)	27 (24.1)	17 (14.9)	28 (24.8)
Extremely suicidal, n (%)	4 (3.6)	1 (0.9)	3 (2.6)	1 (0.9)
Prior suicide attempts, n (%)	66 (59.5)[a]	68 (60.7)	78 (68.4)	72 (63.7)
Attempted suicide within the last month	32 (28.6)	31 (27.7)	36 (31.6)	24 (21.2)
SOC-ADs as randomized, n (%)				
AD monotherapy	59 (52.7)	65 (58.0)	45 (39.5)	43 (38.1)
AD + augmentation therapy	53 (47.3)	47 (42.0)	69 (60.5)	70 (61.9)

[a]n=111.

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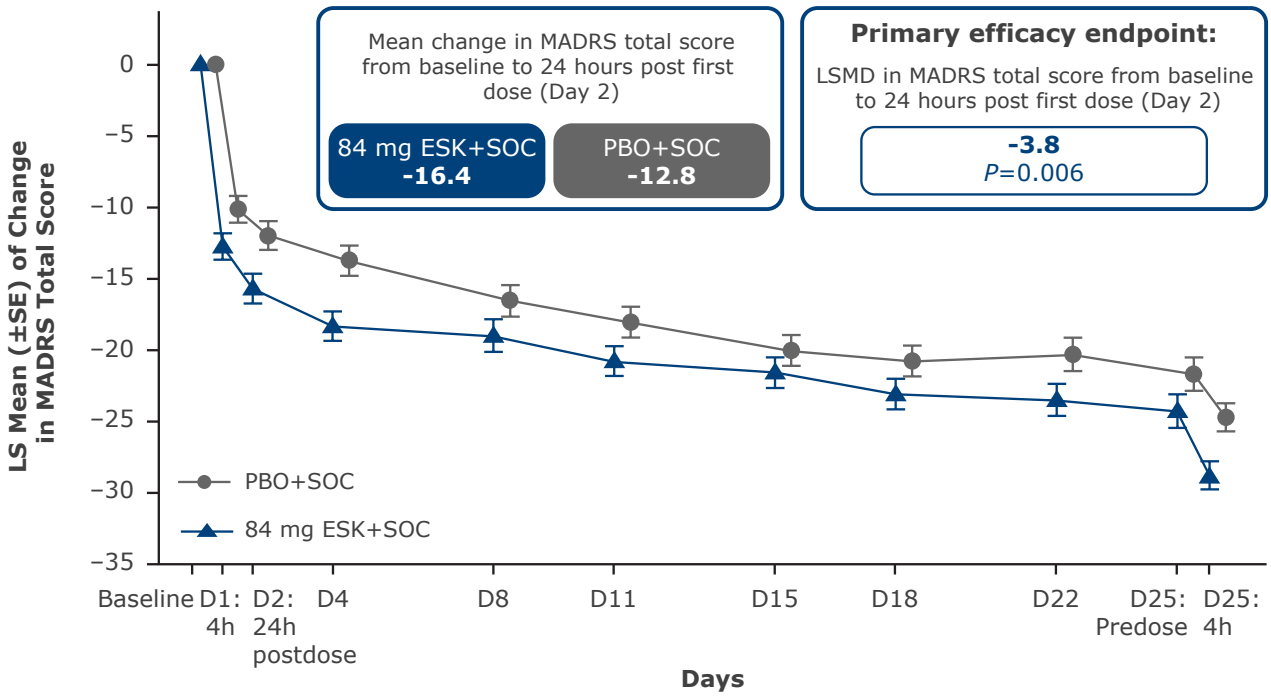
- Statistically significant improvement in change from baseline of mean MADRS total score at 24 hours after first dose was noted in ESK+SOC vs PBO+SOC.[3,4]
  - Treatment effect of ESK+SOC on depressive symptoms was observed at 4 hours after the initial dose and at all time points compared to PBO+SOC.

ASPIRE-1[3]



No. of Patients											
PBO+SOC	112	112	111	110	108	103	99	94	92	92	88
84 mg ESK+SOC	111	110	111	109	104	100	104	102	103	96	94

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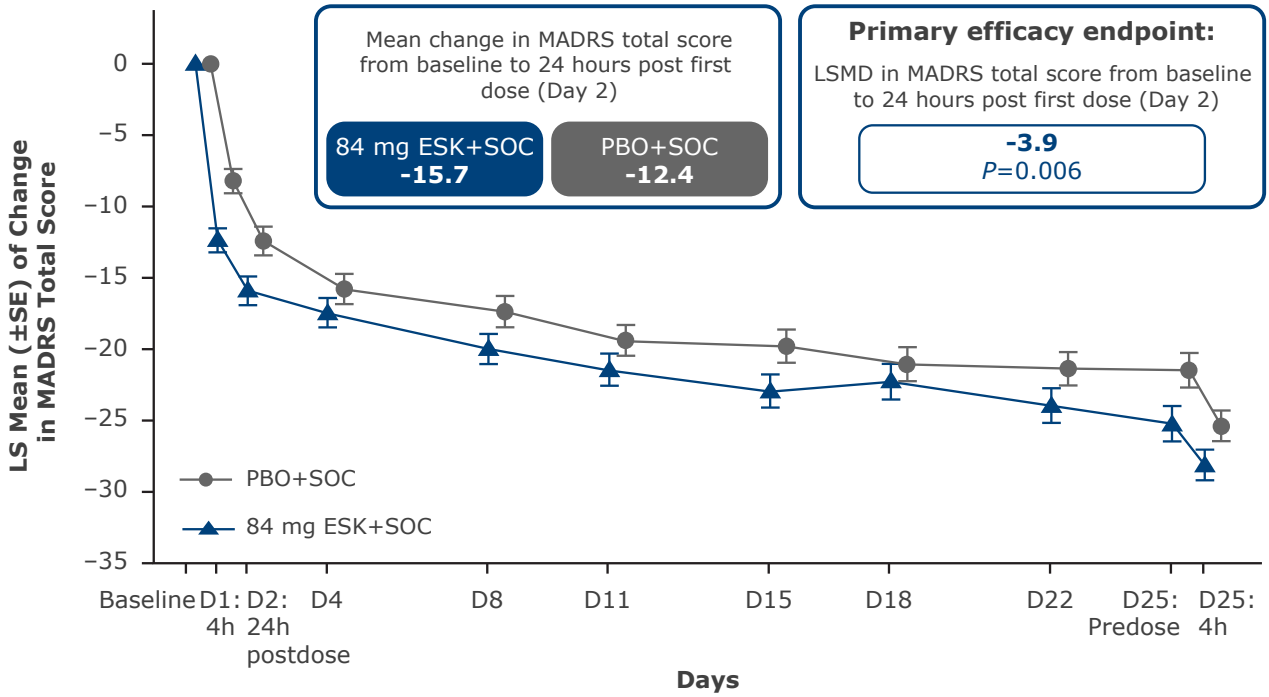
ASPIRE-2[4]



No. of Patients											
PBO+SOC	113	112	111	111	105	99	99	90	94	88	87
84 mg ESK+SOC	114	112	110	107	99	95	91	84	90	85	87

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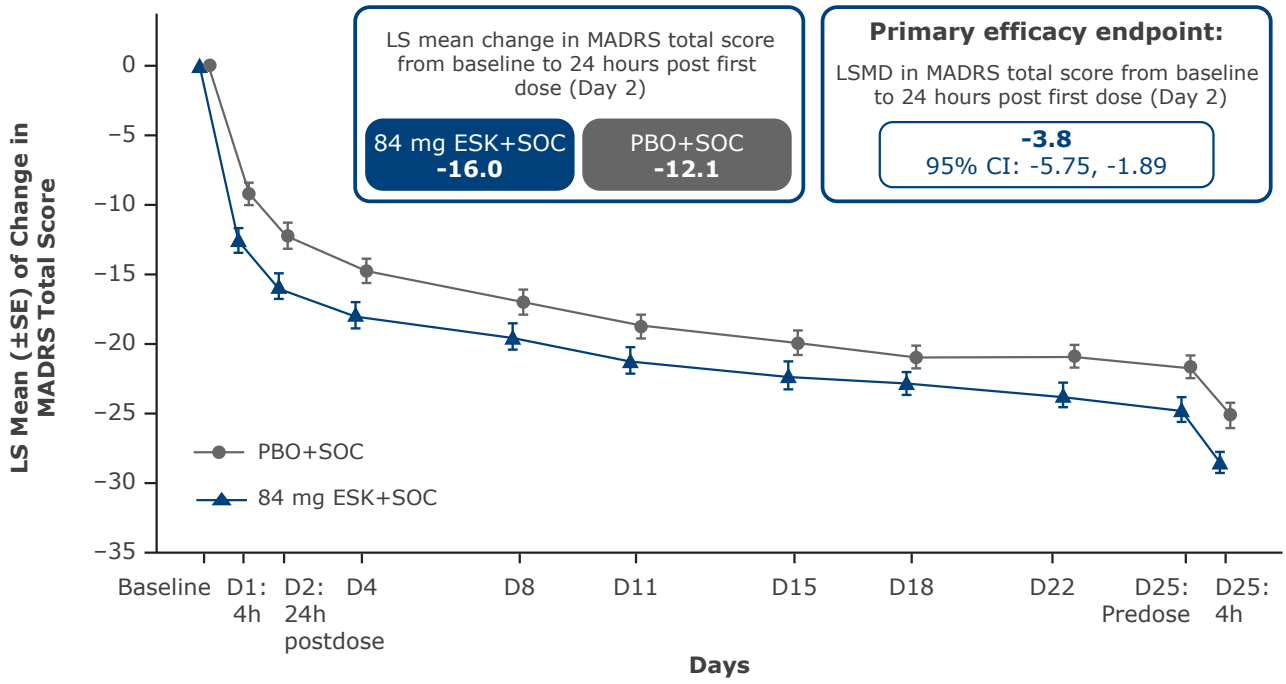
ASPIRE-1 and ASPIRE-2 Pooled Analysis[5]

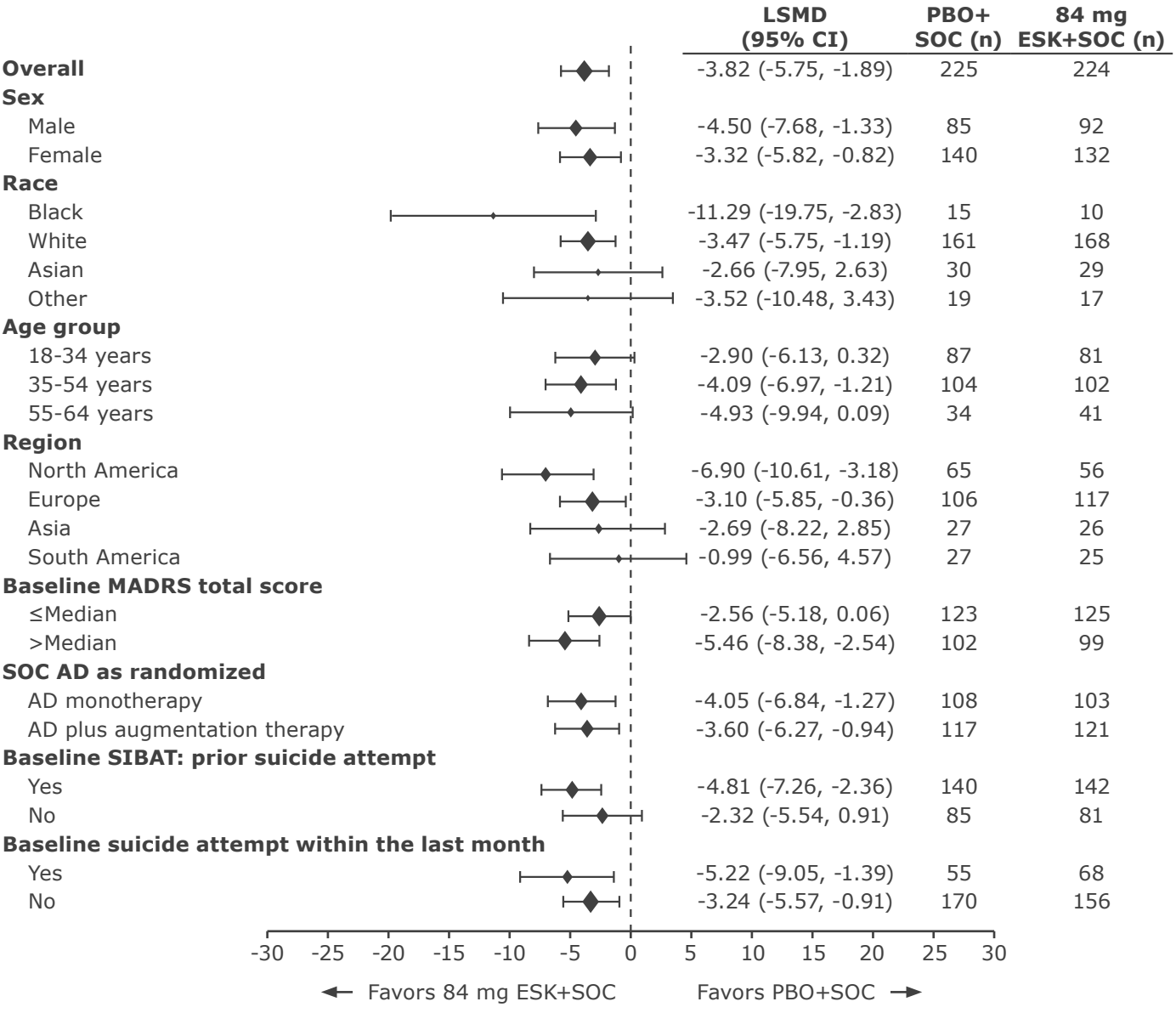


No. of Patients											
PBO+SOC	225	224	222	221	213	202	198	184	186	180	175
84 mg ESK+SOC	225	222	221	216	203	195	195	186	193	181	177

Subgroup Analysis of the Pooled Primary Endpoint

Subgroup Analysis of the Pooled Primary Efficacy Endpoint

- Change in baseline MADRS total score at 24 hours after the first dose was consistent with the primary analysis for all prespecified subgroups.[5]



AD, antidepressant; CI, confidence interval; ESK, esketamine; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; SIBAT, Suicide Ideation and Behavior Assessment Tool; SOC, standard of care.

ESK nasal spray has not been studied or proven to be effective in preventing suicide.

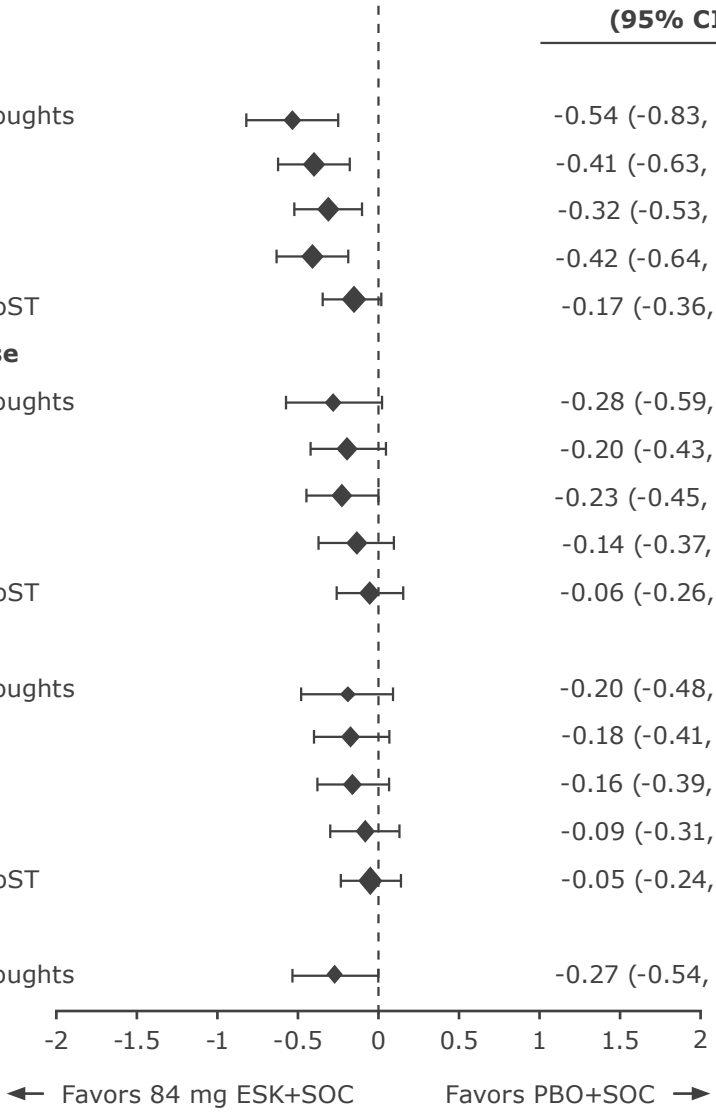
- While improvements in the severity of suicidality scores were noted in ESK+SOC and PBO+SOC arms at 24 hours after the first dose, the difference was not statistically significant.[3,4]

	ASPIRE-1[3]		ASPIRE-2[4]	
	ESK+SOC (n=112)	**PBO+SOC (n=112)**	**ESK+SOC (n=114)**	**PBO+SOC (n=113)**
Change from baseline in CGI-SS-r total score, median (range)	-1.0 (-6; 2)	-1.0 (-5; 1)	-1.0 (-6; 2)	-1.0 (-5; 2)
	P=0.107		*P*=0.379	

Pooled Analysis of Secondary Suicidality Endpoints

Pooled Analysis of Secondary Suicidality Endpoints

- ESK+SOC treatment was directionally favored for all other indices of suicidality[a] (using the item response theory model) at 4 hours and 24 hours after first dose and on day 25.[3-5]



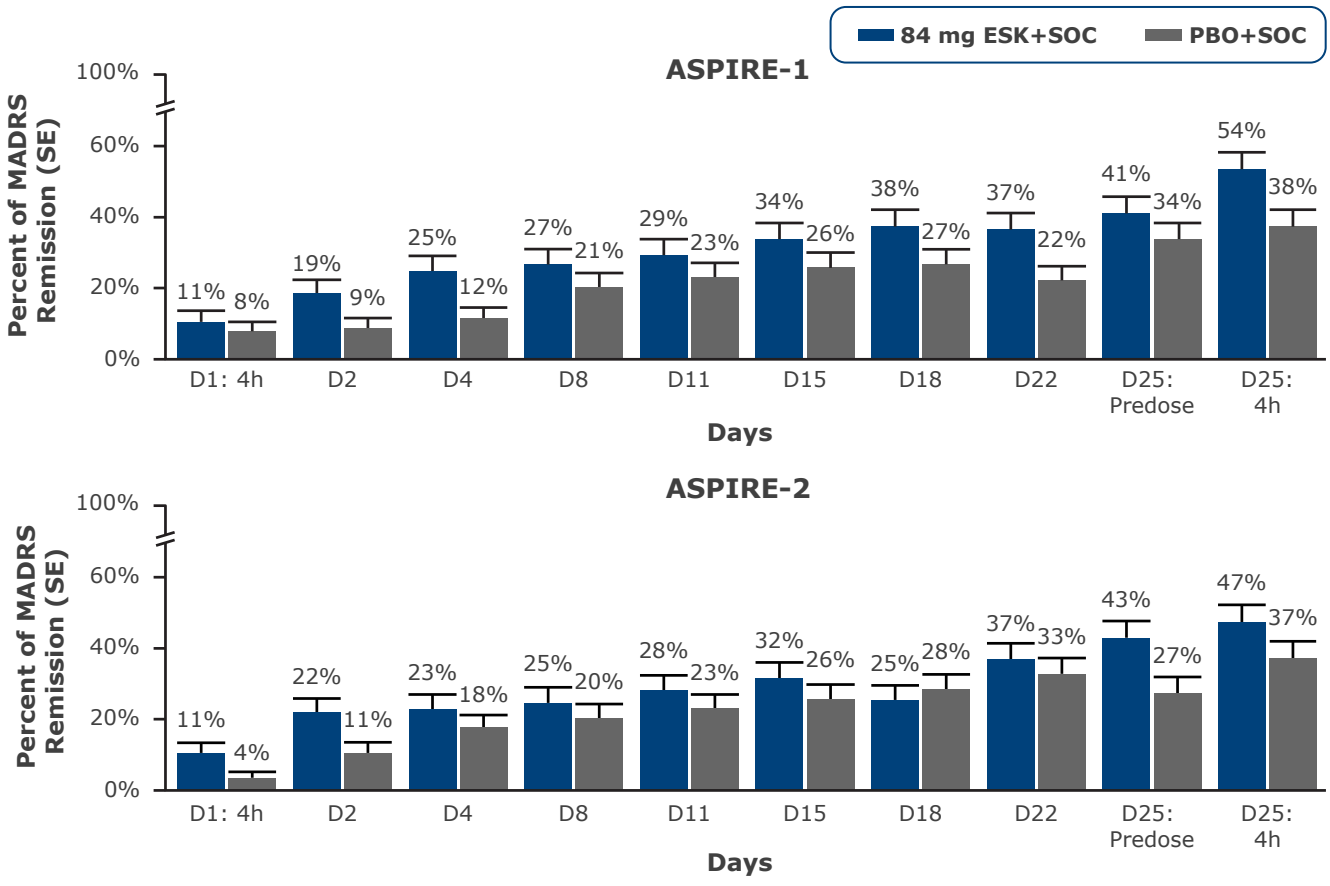
	LSMD (95% CI)	PBO+ SOC (n)	84 mg ESK+SOC (n)
Day 1: 4h			
MADRS suicidal thoughts	-0.54 (-0.83, -0.26)	224	222
CGI-SS-r	-0.41 (-0.63, -0.18)	224	221
CGI-SR-I	-0.32 (-0.53, -0.11)	224	221
CGI FoST	-0.42 (-0.64, -0.19)	224	221
Patient-reported FoST	-0.17 (-0.36, 0.01)	222	219
Day 2: 24h postdose			
MADRS suicidal thoughts	-0.28 (-0.59, 0.02)	225	224
CGI-SS-r	-0.20 (-0.43, 0.04)	225	224
CGI-SR-I	-0.23 (-0.45, -0.00)	225	224
CGI FoST	-0.14 (-0.37, 0.09)	225	224
Patient-reported FoST	-0.06 (-0.26, 0.15)	224	223
Day 25: Predose			
MADRS suicidal thoughts	-0.20 (-0.48, 0.08)	225	225
CGI-SS-r	-0.18 (-0.41, 0.06)	225	225
CGI-SR-I	-0.16 (-0.39, 0.06)	225	225
CGI FoST	-0.09 (-0.31, 0.13)	225	225
Patient-reported FoST	-0.05 (-0.24, 0.14)	224	225
Day 25: 4h			
MADRS suicidal thoughts	-0.27 (-0.54, -0.01)	225	225

[a]Includes CGI-SS-r, the MADRS suicidal thoughts item, CGI-SR-I, and clinician-rated and patient-reported FoST.

CGI-SR-I, Clinical Global Impression - Imminent Suicide Risk; CGI-SS-r, Clinical Global Impression - Severity of Suicidality - revised; CI, confidence interval; ESK, esketamine; FoST, Frequency of Suicidal Thinking; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; SOC, standard of care.

ESK nasal spray has not been studied or proven to be effective in preventing suicide.

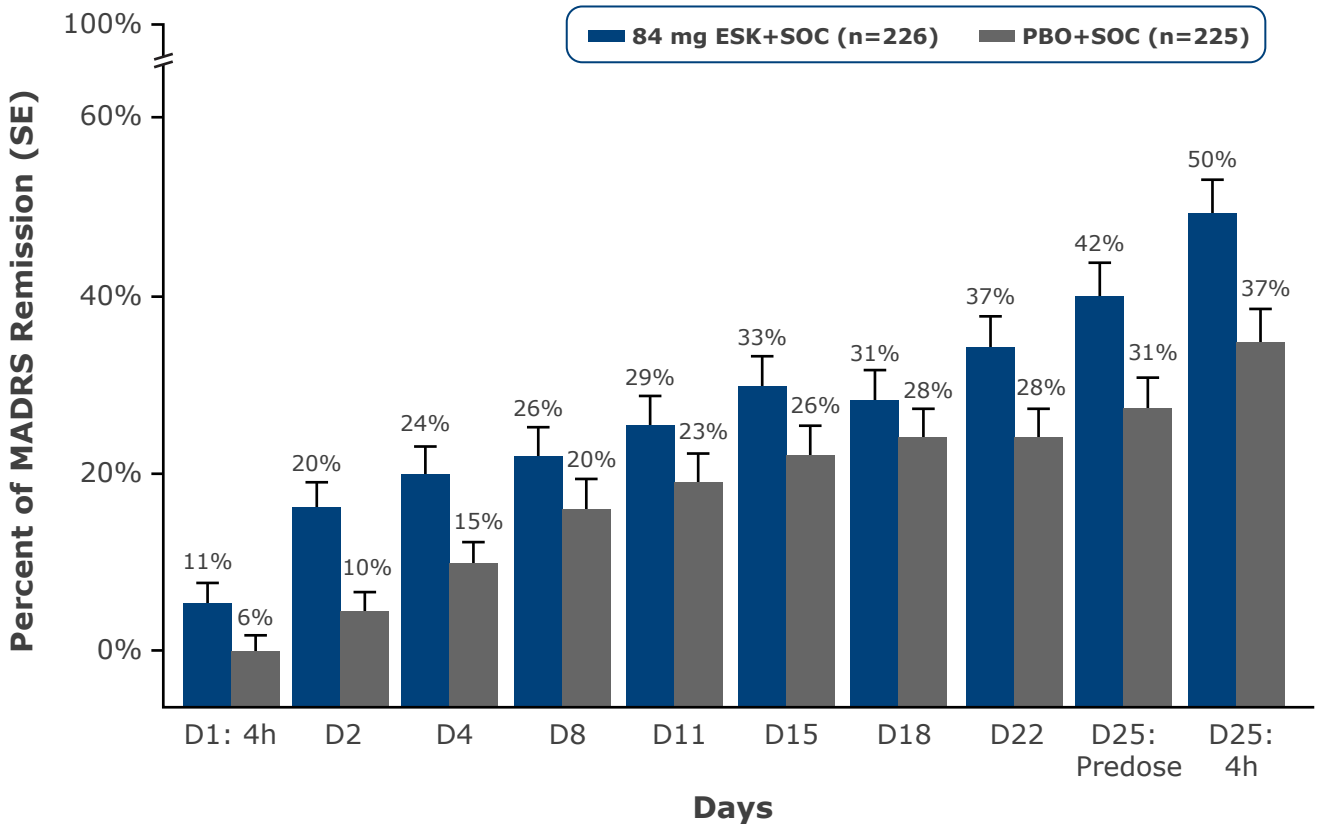
- More patients achieved remission (MADRS total score of ≤12) in the ESK+SOC vs PBO+SOC at all timepoints during the double-blind phase.[3,4]



Pooled Analysis of Remission

Pooled Analysis of Remission

- More patients achieved remission (MADRS total score of ≤12) in the ESK+SOC vs PBO+SOC at all timepoints during the double-blind phase.[5]



ESK, esketamine; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; SE, standard error; SOC, standard of care.

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Adverse Event	ASPIRE-1[3]		ASPIRE-2[4]	
	ESK+SOC (n=113)	PBO+SOC (n=112)	ESK+SOC (n=114)	PBO+SOC (n=113)
≥1 TEAE during double-blind phase, n (%)	100 (88.5)	83 (74.1)	104 (91.2)	87 (77.0)
Discontinuations of study drug due to TEAEs, n (%)	5 (4.4)	5 (4.5)	9 (7.9)	3 (2.7)
Serious TEAEs, n (%)	4 (3.5)[a]	6 (5.4)[b]	5 (4.4)[c]	6 (5.3)[d]
Deaths in the double-blind phase, n	0	0	0	0
Deaths in the follow-up phase, n	1[e]	0	0	0

[a]Included suicidal depression (n=2), depression, suicide attempt, and diabetic ketoacidosis (n=1 each).

[b]Included suicidal ideation (n=2), depression suicidal, depression, suicide attempt, aggression, and hypertransaminasemia (n=1 each).

[c]Included suicide attempt (n=3), suicidal ideation, and depersonalization/derealization disorder (n=1 each).

[d]Included suicide attempt (n=3), suicidal ideation (n=2), depression, arrhythmia, pericardial effusion, and pneumothorax (n=1 each).

[e]Completed suicide.

Most Common (≥10% in Either Group) TEAEs

Most Common (≥10% in Either Group) TEAEs

ASPIRE-1[3]		
Events Reported in the Double-blind Phase, n (%)	**ESK+SOC (n=113)**	**PBO+SOC (n=112)**
Dizziness	40 (35.4)	10 (8.9)
Dissociation	33 (29.2)	4 (3.6)
Nausea	23 (20.4)	15 (13.4)
Headache	21 (18.6)	20 (17.9)
Somnolence	21 (18.6)	11 (9.8)
Blood pressure increased	19 (16.8)	6 (5.4)
Constipation	15 (13.3)	5 (4.5)
Dysgeusia	16 (14.2)	11 (9.8)

ASPIRE-2[4]		
Events Reported in the Double-blind Phase, n (%)	**ESK+SOC (n=114)**	**PBO+SOC (n=113)**
Dizziness	47 (41.2)	21 (18.6)
Dissociation	44 (38.6)	9 (8.0)
Nausea	38 (33.3)	16 (14.2)
Dysgeusia	29 (25.4)	18 (15.9)
Somnolence	26 (22.8)	12 (10.6)
Headache	25 (21.9)	26 (23.0)
Paresthesia	23 (20.2)	7 (6.2)
Vomiting	18 (15.8)	5 (4.4)
Anxiety	17 (14.9)	7 (6.2)
Vision blurred	17 (14.9)	6 (5.3)
Sedation	16 (14.0)	3 (2.7)
Paresthesia oral	14 (12.3)	3 (2.7)
Euphoric mood	13 (11.4)	1 (0.9)
Hypoesthesia	12 (10.5)	1 (0.9)

ESK, esketamine; PBO, placebo; SOC, standard of care; TEAE, treatment-emergent adverse event.

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AD	Antidepressant	**MDD**	Major depressive disorder
CGI-SR-I	Clinical Global Impression - Imminent Suicide Risk	**OCD**	Obsessive compulsive disorder
CGI-SS-r	Clinical Global Impression - Severity of Suicidality - revised	**PBO**	Placebo
CI	Confidence interval	**SBP**	Systolic blood pressure
DBP	Diastolic blood pressure	**SD**	Standard deviation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)	**SE**	Standard error
ESK	Esketamine	**SIBAT**	Suicide Ideation and Behavior Assessment Tool
FoST	Frequency of Suicidal Thinking	**sNDA**	Supplemental New Drug Application
LS	Least squares	**SOC**	Standard of care
LSMD	Least squares mean difference	**TEAE**	Treatment-emergent adverse event
MADRS	Montgomery-Åsberg Depression Rating Scale	**US FDA**	United States Food and Drug Administration

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A literature search of MEDLINE® and EMBASE® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 23 January 2020.

This response contains a summary of phase 3 studies in adults with MDD and active suicidal ideation with intent and an ongoing phase 2 study in adolescents. The citation for the phase 2 study in adults[9] is located within the References tab.

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1. Janssen Research & Development, LLC. A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in adults subjects assessed to be at imminent risk for suicide. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [1/24/2018]. Available from: https://clinicaltrials.gov/ct2/show/NCT03097133 NLM Identifier: NCT03097133.
2. Janssen Research & Development, LLC. A study of the efficacy and safety of intranasal esketamine in the rapid reduction of symptoms of major depressive disorders, in adult at imminent risk for suicide. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [1/24/2018]. Available from: https://clinicaltrials.gov/ct2/show/NCT03039192 NLM Identifier: NCT03039192.
3. Fu DJ, Canuso CM, Ionescu DF, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE-1 study. Poster presented at: 32nd European College of Neuropsychopharmacology (ECNP); September 7-10, 2019; Copenhagen, Denmark.
4. Ionescu DF, Canuso CM, Fu DJ, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE-2 study. Poster presented at: 32nd European College of Neuropsychopharmacology (ECNP); September 7-10, 2019; Copenhagen, Denmark.
5. Canuso CM, Fu DJ, Ionescu DF, et al. Esketamine nasal spray for rapid reduction of depressive symptoms in adult patients with major depressive disorder at imminent risk for suicide: results from the phase 3 program. Poster presented at: 58th Annual meeting of American College of Neuropsychopharmacology (ACNP); December 8-11, 2019; Orlando, FL.
6. Nash AI, Turkoz I, Fu DJ, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in adult patients at imminent risk for suicide: a post hoc analysis of North American subjects. Poster presented at: 58th Annual meeting of American College of Neuropsychopharmacology (ACNP); December 8-11, 2020; Orlando, FL.
7. Pandina G, Kosik-Gonzalez C, Canuso CM. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in adolescents at imminent suicidal risk: rationale, design and progress of a phase 2 study. Poster presented at: The 17th European Symposium on Suicide and Suicidal Behavior (ESSSB); September 5-8, 2018; Ghent, Belgium.
8. Janssen Research & Development, LLC. A double-blind, randomized, psychoactive placebo-controlled, study to evaluate the efficacy and safety of 3 fixed doses (28 mg, 56 mg and 84 mg) of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric subjects assessed to be at imminent risk for suicide. In: ClinicalTrials.gov [Internet]. Besthesda (MD): National Library of Medicine (US). 2000- [cited 2018 October 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03185819 NLM Identifier: NCT03185819.
9. Canuso C, Singh J, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study [published online ahead of print]. *Am J Psychiatry* 2018. doi:10.1176/appi.ajp.2018.17060720.2018.