Esketamine Short-term Trials in Treatment-Resistant Depression

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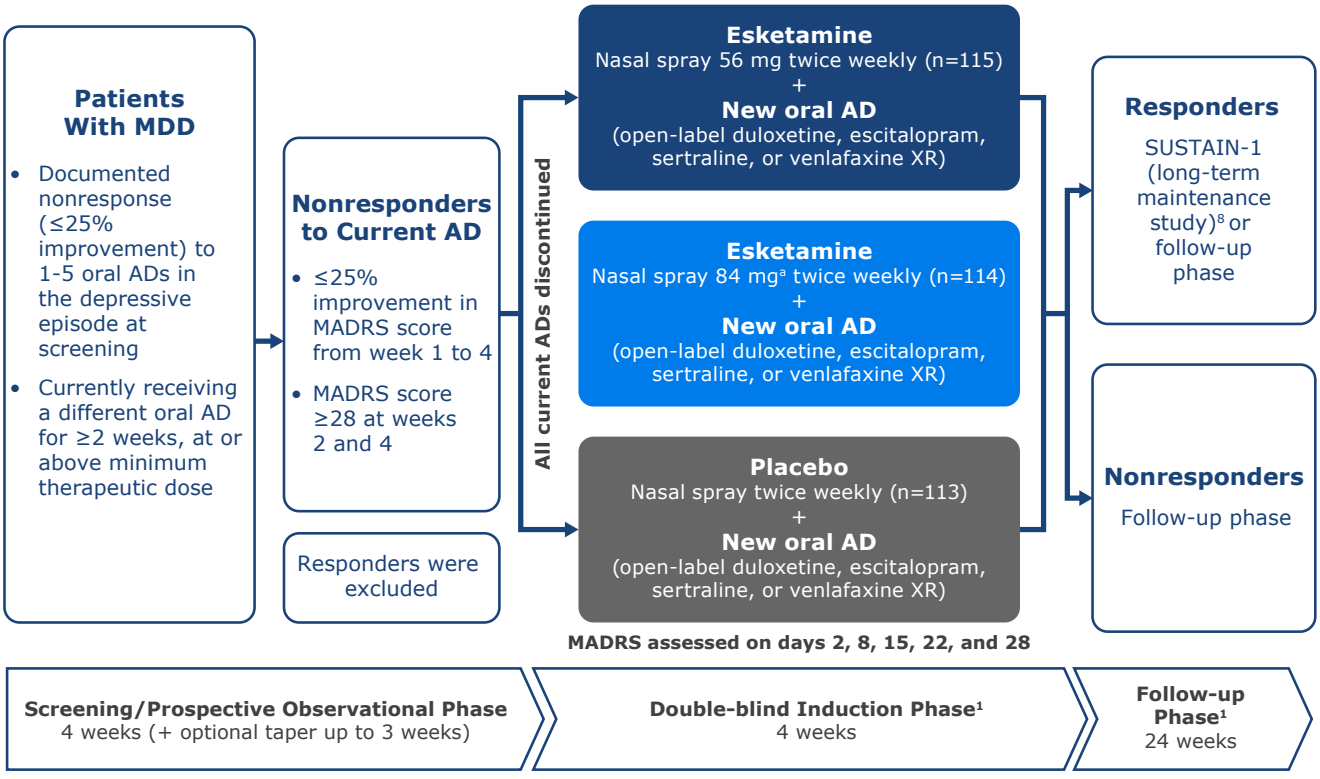
- TRANSFORM-1 (NCT02417064) was a phase 3, 1:1:1 randomized, double-blind, active-controlled, fixed-dose, multicenter study.[2]
- A prespecified interim analysis was performed 4 weeks after randomizing 121 patients to re-estimate sample size in order to achieve the desired power and minimize type I error.[2]



[a]Patients were started at 56 mg on day 1 and increased to 84 mg on day 4 to improve tolerability.

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Inclusion Criteria[2]	**Exclusion Criteria**[2]
• Age 18-64 years • Single-episode (≥2 years) or recurrent MDD, without psychotic features, per DSM-5 and clinical assessment, confirmed by MINI • IDS-C_{30} score ≥34 • Nonresponse (≤25% improvement) to ≥1 but ≤5 oral ADs of adequate dose, duration, and adherence in current MDD episode, and taking a different oral AD for ≥2 previous weeks at or above the minimum therapeutic dose • Current MDD episode, depression symptom severity, and AD response in the current depressive episode must be confirmed using a Site Independent Qualification Assessment	• Homicidal ideation/intent or suicidal ideation with some intent to act for ≤6 months, per the investigator's judgment or C-SSRS • Current or prior DSM-5 diagnosis of psychotic disorder or MDD with psychosis; bipolar or related disorders; OCD; autism spectrum disorder; intellectual disability; or borderline, antisocial, histrionic, or narcissistic personality disorder • History of uncontrolled hypertension; seizures; or moderate or severe substance or alcohol use disorder per DSM-5 criteria • Nonresponse in the current MDD episode to esketamine or ketamine, to all 4 of the oral AD treatment options, or an adequate course of ECT • Received vagal nerve stimulation or deep brain stimulation in the current episode

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Primary Efficacy Endpoint[2]

- Change from baseline (day 1) to the end of the double-blind induction phase (day 28) in MADRS total score

Key Secondary Efficacy Endpoints[2]

- Early onset of sustained clinical response
  - Defined as ≥50% improvement in MADRS total score by day 2 that continued through day 28, with 1 excursion (ie, ≥25% improvement at day 8, 15, or 22)
- Change from baseline in SDS total score at day 28
- Change from baseline in PHQ-9 total score at day 28

Other Secondary Endpoints[2]

- Proportion of responders (≥50% reduction from baseline in MADRS total score) and remitters (MADRS score ≤12) at day 28

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- Overall 346 patients were randomized.[2]
- Demographics and baseline characteristics were similar across treatment arms.[2]

	Esketamine 56 mg + AD (n=115)	Esketamine 84 mg + AD (n=114)	AD + Placebo (n=113)
Age, years, mean (SD)	46.4 (11.2)	45.7 (11.1)	46.8 (11.4)
Female, n (%)	81 (70.4)	79 (69.3)	81 (71.7)
Race, n (%)			
Black or African American	7 (6.1)	7 (6.1)	5 (4.4)
White	91 (79.1)	85 (74.6)	86 (76.1)
Other	8 (7.0)	12 (10.5)	10 (8.8)
Duration of current episode, weeks, mean (SD)	202.8 (277.3)	212.7 (327.6)	193.1 (264.1)
MADRS score, mean (SD)	37.4 (4.8)	37.8 (5.6)	37.5 (6.2)
Number of previous AD medications, %			
1-2	79 (69.9)	59 (51.8)	67 (59.3)
≥3	34 (30.1)	55 (48.2)	46 (40.7)
Class of oral AD, n (%)			
SNRI	65 (56.5)	67 (58.8)	64 (56.6)
SSRI	50 (43.5)	47 (41.2)	49 (43.4)

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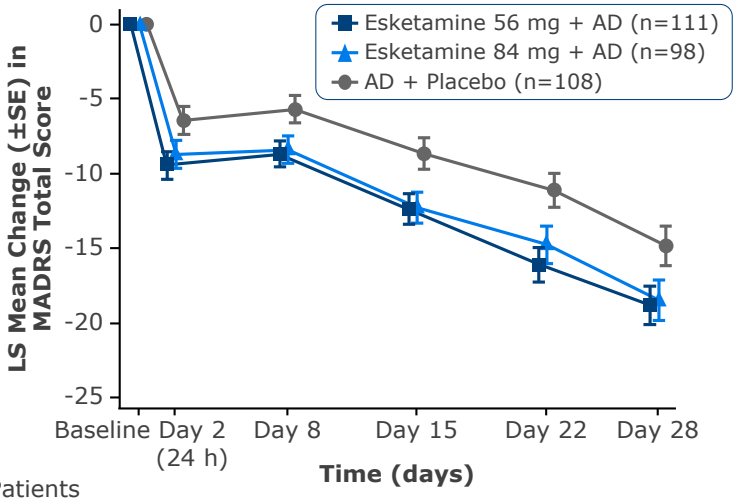
- **Change in mean MADRS total score** from baseline to day 28 was not statistically significant; however, both esketamine + AD arms showed a clinically meaningful[5-7] and numerically greater change vs AD + placebo.[2]



No. of Patients						
Esketamine 56 mg + AD	115	105	114	110	107	111
Esketamine 84 mg + AD	114	104	107	99	96	98
AD + Placebo	113	101	111	106	105	108

- **Mean change from baseline at day 28[2]**
  - Esketamine 84 mg + AD: -18.8
  - Esketamine 56 mg + AD: -19.0
  - AD + placebo: -14.8
- **LSMD (median unbiased estimate) from placebo[2]**
  - Esketamine 84 mg + AD: -3.2 (95% CI: -6.88, 0.45; *P*=0.088)
  - Esketamine 56 mg + AD: -4.1 (95% CI: -7.67, -0.49; nominal *P*=0.027)
  - A predefined gatekeeping procedure was established to evaluate the efficacy of esketamine 84 mg before proceeding to evaluate esketamine 56 mg. Since statistical significance was not demonstrated, esketamine 56 mg + AD could not be formally evaluated.
- **Treatment differences based on MADRS total score** were more pronounced after the interim analysis was conducted.[2]

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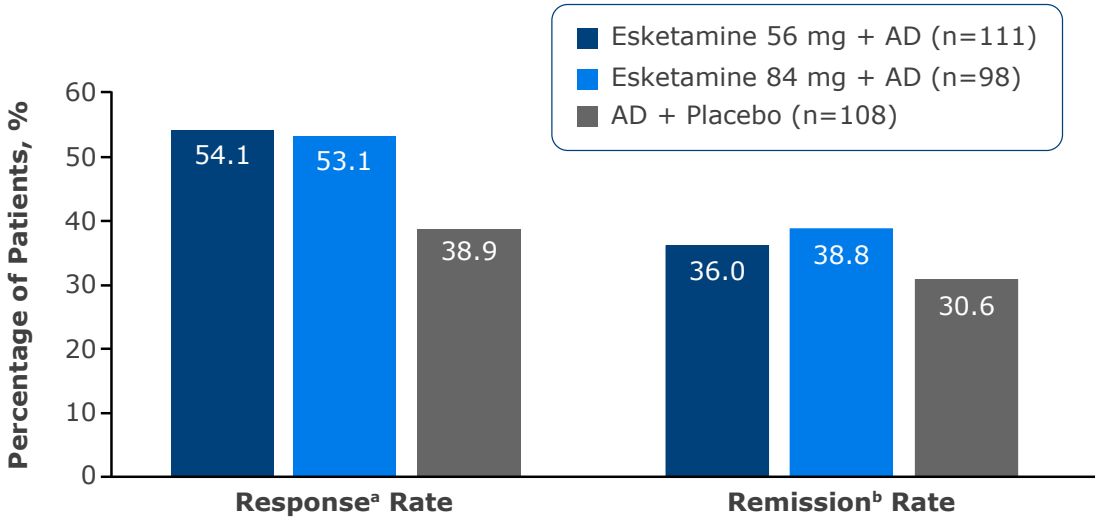
- **Response[a] and remission[b] rates** at day 28 were greater with esketamine (56 mg and 84 mg) + AD vs AD + placebo.[2]
  - NNT for response was 7 for both esketamine + AD arms and for remission was 18 and 12, respectively.



- All key secondary endpoints, including onset of clinical response by day 2, SDS total score, and PHQ-9 total score, **numerically favored** the esketamine + AD arms vs AD + placebo.[2]
- An improvement in the median **CGI-S scores** from baseline to day 28 was noted in all 3 treatment arms (both esketamine + AD arms, -2.0; AD + placebo, -1.0).[2]

[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS score ≤12.

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- The **most common AEs** (≥20% in any treatment arm) in both esketamine + AD arms included nausea, dissociation, dizziness, headache, and somnolence; all were more frequent than in the AD + placebo arm.[2]
- Most AEs were **mild to moderate** in severity and were transient and resolved on the same dosing day.[2]
- There were no deaths in the study.[2]
- Two patients in the esketamine 56 mg + AD arm each experienced 1 SAE during the double-blind phase (possibly related: worsening of depression on day 15; probably related: headache on day 12).[2]
- Treatment discontinuation due to AEs:[2]
  - **Esketamine 56 mg + AD**: 1 (0.9%) patient discontinued treatment due to depression.
  - **Esketamine 84 mg + AD**: 7 (6.0%) patients discontinued treatment due to anxiety, disturbance in attention, extrasystoles, headache, mania, motion sickness, panic attack, tachycardia (n=1 event each) and dizziness, nausea, vomiting (n=2 events each).
  - **AD + Placebo**: 2 (1.8%) patients discontinued treatment due to erectile dysfunction and worsening insomnia (n=1 event each).

TEAEs ≥10% in Any Treatment Arm

TEAEs ≥10% in Any Treatment Arm During the Double-blind Phase[2]

Event, n (%)	Esketamine 56 mg + AD (n=115)	Esketamine 84 mg + AD (n=116)	AD + Placebo (n=113)
Nausea	31 (27.0)	37 (31.9)	12 (10.6)
Dissociation	30 (26.1)	32 (27.6)	4 (3.5)
Dizziness	32 (27.8)	26 (22.4)	10 (8.8)
Vertigo	24 (20.9)	24 (20.7)	2 (1.8)
Headache	23 (20.0)	24 (20.7)	19 (16.8)
Somnolence	24 (20.9)	21 (18.1)	13 (11.5)
Dysgeusia	17 (14.8)	20 (17.2)	17 (15.0)
Hypoesthesia	14 (12.2)	16 (13.8)	2 (1.8)
Paresthesia	19 (16.5)	11 (9.5)	3 (2.7)
Hypoesthesia oral	16 (13.9)	12 (10.3)	2 (1.8)
Vomiting	7 (6.1)	14 (12.1)	2 (1.8)
Fatigue	12 (10.4)	8 (6.9)	5 (4.4)

AD, antidepressant; TEAE, treatment-emergent adverse event.

TEAEs ≥10% in Any Treatment Arm

Postdose Monitoring[2]

- **Sedation**
  - Sedative effects were generally mild (MOAA/S score=4).
  - The MOAA/S score was ≤3 at any time postdose in 9.6% of patients in the esketamine 56 mg + AD arm, 12.1% in the esketamine 84 mg + AD arm, and 0.9% in the AD + placebo arm.
  - Symptoms resolved by 1-1.5 hours postdose.
- **Transient Blood Pressure Increases**
  - Occurred after each esketamine dose and peaked at 40 minutes postdose.
  - Mean maximum increase before dosing to any postdose time point:

Change in Blood Pressure	Esketamine 56 mg + AD	Esketamine 84 mg + AD	AD + Placebo
Systolic blood pressure, mm Hg	+14.3	+15.0	+7.2
Diastolic blood pressure, mm Hg	+8.9	+9.4	+5.3

  - Blood pressure typically returned to the predose range by 1.5 hours postdose.
- **Dissociative Symptoms and Perceptual Effects**
  - Per the CADSS, symptoms were observed shortly after the esketamine dose, peaked at 40 minutes, and resolved by 1.5 hours postdose.
  - Events and symptoms of psychosis were not observed.
- **Discharge Readiness**
  - Discharge readiness was assessed per the CGADR:

Proportion Considered Ready for Discharge	Esketamine 56 mg + AD	Esketamine 84 mg + AD	AD + Placebo
1 hour postdose, %	≥56	≥44	≥88
1.5 hours postdose, %	≥90	≥87	≥97

Other Safety Assessments[2]

- **Suicidal Ideation**
  - Treatment-emergent post-baseline suicidal ideation was reported in 10.4% of patients in the esketamine 56 mg + AD arm, 7.1% in the esketamine 84 mg + AD arm, and 11.5% in the AD + placebo arm per the C-SSRS score.

- **Discontinuations[2]**
  - The discontinuation rate in the esketamine 84 mg + AD arm (16.4%) was 3 times higher than in the esketamine 56 mg + AD (5.1%) and AD + placebo (5.3%) arms.
  - Eleven of the 19 patients in the higher esketamine dosage arm withdrew during day 1 while on the esketamine 56 mg dose; withdrawals were not due to any new or dose-related safety findings.
- The authors noted **factors that may have contributed to the lack of statistical significance** between esketamine 84 mg + AD and AD + placebo:[2]
  - A 3-fold higher withdrawal rate in the esketamine 84 mg + AD arm and a lower overall effect size than assumed in the protocol.
  - The AD + placebo arm had a greater improvement in depressive symptoms than was anticipated.
  - Initiatives implemented prior to and independent of the interim analysis to enhance the quality of study conduct may have impacted the results of patients enrolled after the interim analysis, resulting in a greater treatment difference observed.

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TRANSFORM-3[3]

Phase 3, Double-blind, Randomized, Active-Controlled, Multicenter, Flexible-Dose Study

N=138

Key Inclusion Criteria[3]

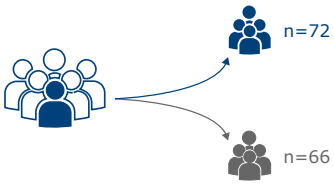
- Age ≥65 years
- Recurrent MDD or single-episode nonpsychotic MDD (≥2 years)
- Nonresponse to ≥2 ADs in current episode
- IDS-C_{30} score ≥31
- MMSE score ≥25 (≥22 for less than equivalent of HS education)

Key Exclusion Criteria[3]

- Homicidal or suicidal ideation
- Bipolar or personality disorders
- Uncontrolled hypertension
- OCD
- Nonresponse to all 4 study ADs or ECT
- Seizures
- Substance or alcohol abuse

Study Design[3]

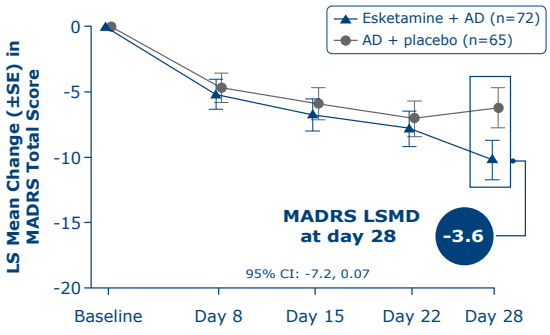
Esketamine nasal spray 28, 56, or 84 mg + **Newly initiated oral AD** (duloxetine, escitalopram, sertraline, or venlafaxine XR)



Newly initiated oral AD (duloxetine, escitalopram, sertraline, or venlafaxine XR) + **Placebo** nasal spray

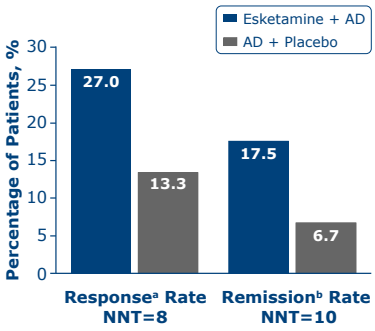
Primary Efficacy Endpoint[3]

Change in mean MADRS total score from baseline to day 28 was clinically meaningful[5-7] but not statistically significant with esketamine + AD vs AD + placebo



Secondary Efficacy Endpoints[3]

Response[a] and remission[b] rates at day 28 were greater with esketamine + AD vs AD + placebo



Safety[3]

TEAEs ≥20%

- Observed more frequently in the esketamine + AD arm
- Dizziness
- TEAEs were mostly **mild to moderate**, and generally **resolved** by the end of the study

- **Treatment discontinuation due to TEAEs:**
  - Esketamine + AD: **5.6%**
  - AD + placebo: **1.8%**

[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS score ≤12.

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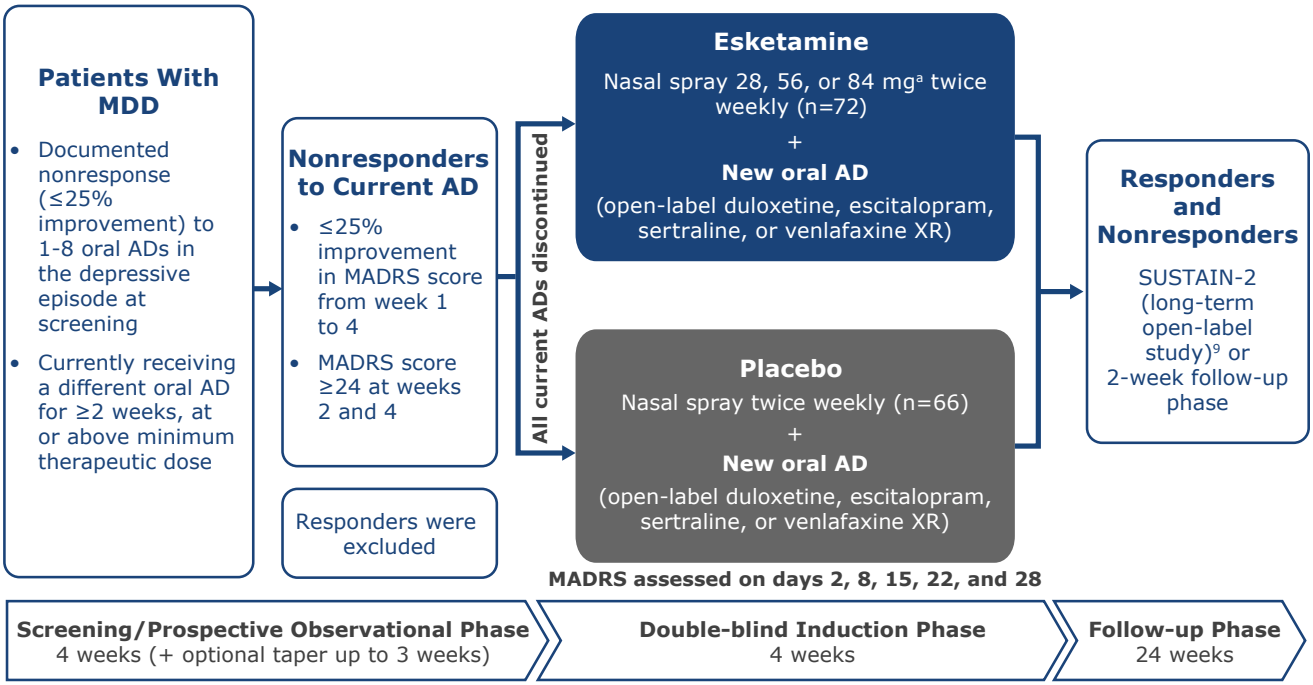
- TRANSFORM-3 (NCT02422186) was a phase 3, 1:1 randomized, double-blind, active-controlled, flexible-dose, multicenter study conducted in 13 countries in elderly patients.[3]



[a]All patients started with esketamine 28 mg or placebo on day 1; the second dose (day 4) of esketamine was 28 or 56 mg and all subsequent doses were 28, 56, or 84 mg based on efficacy and tolerability. Dose increase in esketamine was not permitted past day 15.

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Inclusion Criteria[3]	**Exclusion Criteria[3]**
• Age ≥65 years • Single-episode (≥2 years) or recurrent MDD, without psychotic features, per DSM-5 and clinical assessment, confirmed by MINI • IDS-C_{30} score ≥31 • MMSE total score ≥25 (≥22 for patients with less than the equivalent of a high school education) • Nonresponse to ≥1 AD but ≤8 ADs in current depressive episode at the start of screening/ prospective observational phase • Nonresponse to ≥2 ADs prior to randomization • Medically stable based on clinical laboratory tests performed during screening/observational phase	• Homicidal ideation/intent or suicidal ideation with some intent to act for ≤6 months, per the investigator's judgment or C-SSRS • Current or prior DSM-5 diagnosis of psychotic disorder or MDD with psychosis; bipolar or related disorders; OCD; autism spectrum disorder; intellectual disability; or borderline, antisocial, histrionic, or narcissistic personality disorder • History of uncontrolled hypertension; seizures; or moderate or severe substance or alcohol use disorder per DSM-5 criteria • Nonresponse in the current MDD episode to esketamine or ketamine, to all 4 of the oral AD treatment options, or an adequate course of ECT • Received vagal nerve stimulation or deep brain stimulation in the current episode

Primary Efficacy Endpoint[3]

- Change from baseline (day 1) to the endpoint (day 28) in MADRS total score

Additional Efficacy Endpoints[3]

- Rates of response and remission at day 28
- Change from baseline in CGI-S total score at day 28
- Change from baseline in SDS total score at day 28
- Change from baseline in PHQ-9 total score at day 28

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- Overall 138 patients were randomized to treatment.[3]
- Demographics and baseline characteristics were similar across treatment arms.[3]

	Esketamine + AD (n=72)	AD + Placebo (n=65)
Age, years, mean (SD)	70.6 (4.79)	69.4 (4.15)
Age category 65-74 years, n (%)	59 (81.9)	57 (87.7)
Female, n (%)	45 (62.5)	40 (61.5)
Race, n (%)		
White	66 (91.7)	64 (98.5)
Multiple	4 (5.6)	0 (0)
Screening IDS-C_{30} total score, mean	44.2	43.1
Duration of current episode, weeks, mean (SD)	163.1 (277.04)	274.1 (395.47)
Baseline MADRS score, mean	35.5	34.8
Number of previous AD medications, n (%)		
1	15 (20.8)	6 (9.2)
2	31 (43.1)	32 (49.2)
3	13 (18.1)	17 (26.2)
4	12 (16.7)	4 (6.2)
≥5	1 (1.4)	6 (9.2)
Class of oral AD, n (%)		
SNRI	31 (43.1)	30 (46.2)
SSRI	41 (56.9)	35 (53.8)

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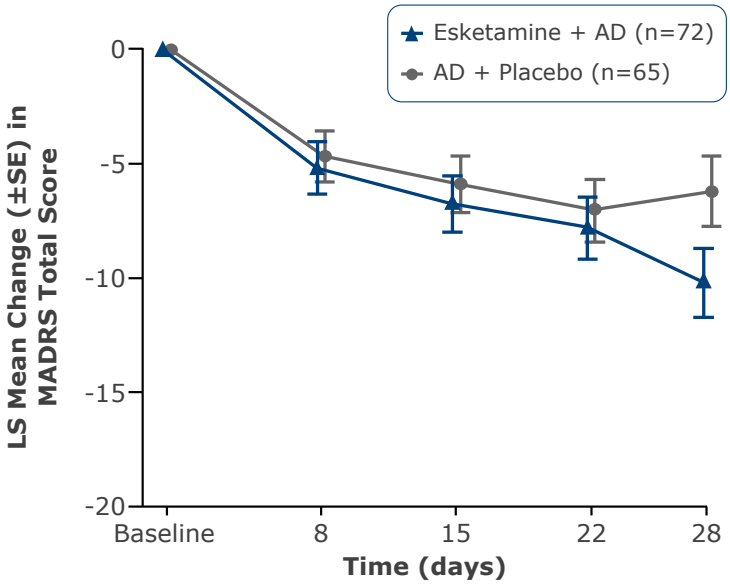
- While not statistically significant, **change in mean MADRS total score** from baseline to day 28 was clinically meaningful[5-7] and numerically greater with esketamine (28, 56, or 84 mg) + AD vs AD + placebo.[3]



No. of Patients					
Esketamine + AD	72	66	68	60	63
AD + Placebo	65	63	62	56	60

- **Mean change from baseline at day 28[3]**
  - Esketamine + AD: -10.0
  - AD + Placebo: -6.3
- **LSMD (median unbiased estimate) from placebo[3]**
  - -3.6 (95% CI: -7.2, 0.07); *P*=0.059

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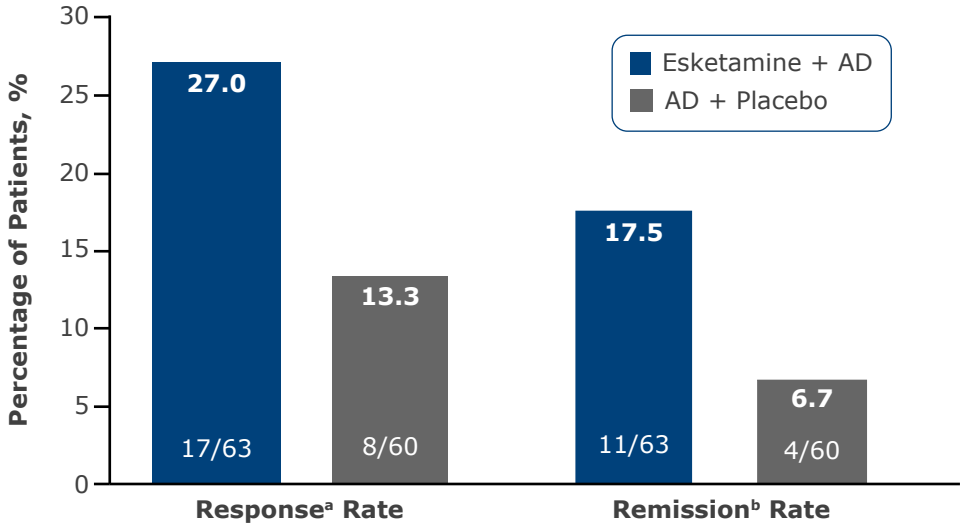
- **Response[a] and remission[b] rates** at day 28 were greater with esketamine (28 mg, 56 mg, 84 mg) + AD vs AD + placebo.[3]
  - NNT for response was 8 and that for remission was 10.



- All key secondary endpoints, including CGI-S, SDS total score, and PHQ-9 total score, **numerically favored** the esketamine + AD arm vs AD + placebo.[3]
- A numerical improvement in the median **CGI-S scores** from baseline to day 28 was noted in both treatment arms (esketamine + AD, -1.0; AD + placebo, 0).[3]

[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS ≤12.

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- Additional efficacy analyses found that patients aged 65-74 years vs ≥75 years in the esketamine + AD arm had **greater improvement in MADRS total score** (LSMD: -4.9; nominal *P*=0.017 vs -0.4; nominal *P*=0.930).[3]
- In a post hoc analysis, patients in the esketamine + AD arm who had an earlier onset of depression (<55 years of age) vs later onset of depression (≥55 years of age) had **greater improvement in MADRS total score** (LSMD: -6.1; nominal *P*=0.006 vs 3.1; nominal *P*=0.407).[3]
- In an interim analysis conducted during the study, more patients were assessed post-interim analysis (Stage 2, n=86) vs pre-interim analysis (Stage 1, n=51) resulting in a treatment difference between the 2 phases. An unweighted analysis showed a LSMD of -4.0 (95% CI: -7.71, -0.25) between esketamine + AD vs AD + placebo.[3]
- A slower dose titration occurred in this trial compared to other trials. The percentage of patients in Stage 1 and Stage 2 who received 84 mg at day 25 was 52.2% and 71.8%, respectively.[3]
- Patients in this study could enter a long-term, open-label safety and efficacy study.[9] Of the 111/138 patients who entered into this study, 88 were nonresponders who received an additional 4 weeks of induction treatment. MADRS total scores continued to decrease in 93% of these nonresponders.[3]

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- The **most common AE** (≥20%) in the esketamine + AD arm was dizziness, which was more frequent than in the AD + placebo arm.[3]
- Most AEs were **mild to moderate** in severity and resolved on the same dosing day.[3]
- There were no deaths in the study.[3]
- Three patients in the esketamine + AD arm (anxiety, blood pressure increased, hip fracture) and 2 patients in the AD + placebo arm (gait disturbance, dizziness) experienced 1 SAE during the double-blind phase.[4]
- **Treatment discontinuation** due to ≥1 TEAE:[3]
  - **Esketamine + AD**: 4 (5.6%)
  - **AD + Placebo**: 2 (3.1%)

TEAEs ≥10% in Either Treatment Arm

TEAEs ≥10% in Either Treatment Arm During the Double-blind Phase[3]

Event, n (%)	Esketamine + AD (n=72)	AD + Placebo (n=65)
Dizziness	15 (20.8)	5 (7.7)
Nausea	13 (18.1)	3 (4.6)
Blood pressure increased	9 (12.5)	3 (4.6)
Fatigue	9 (12.5)	5 (7.7)
Headache	9 (12.5)	2 (3.1)
Dissociation	9 (12.5)	1 (1.5)
Vertigo	8 (11.1)	2 (3.1)

AD, antidepressant; TEAE, treatment-emergent adverse event.

Postdose Monitoring[3]

- **Sedation**
  - The MOAA/S score ≤3 at any time postdose was reported in ≤3.4% of patients in the esketamine + AD arm on each treatment day.
- **Transient Blood Pressure Increases**
  - Occurred after each esketamine dose and peaked at 40 minutes postdose.
  - Mean maximum increase before dosing to any postdose time point:

Change in Blood Pressure	Esketamine + AD	AD + Placebo
Systolic blood pressure, mm Hg	+16.0	+11.1
Diastolic blood pressure, mm Hg	+9.5	+6.8

  - Blood pressure generally returned near predose levels.
- **Dissociative Symptoms and Perceptual Effects**
  - Per the CADSS, symptoms were observed shortly after the esketamine dose, peaked at 40 minutes, and generally resolved by 1.5 hours postdose.
- **Discharge Readiness**
  - Discharge readiness was assessed per the CGADR:

Proportion Considered Ready for Discharge	Esketamine + AD	AD + Placebo
1 hour postdose, %	50	85
1.5 hours postdose, %	90	95

  - All patients were ready for discharge by 3 hours in the esketamine + AD arm and 3.25 hours in the AD + placebo arm.

Other Safety Assessments[3]

- **Suicidal Ideation**
  - Suicidal ideation, based on the C-SSRS score, decreased from baseline to day 28 in both arms.
  - Treatment-emergent post-baseline suicidal ideation was reported in 11.4% of patients in the esketamine + AD arm and 13.8% of patients in the AD + placebo arm per the C-SSRS score.
  - No suicidal attempts or behavior was observed.

Abbreviations

AD	Antidepressant	**MINI**	Mini International Neuropsychiatric Interview
AE	Adverse event	**MMSE**	Mini Mental Status Exam
CADSS	Clinician-Assessed Dissociative Symptom Scale	**MOAA/S**	Modified Observer's Assessment of Alertness/Sedation
CGADR	Clinical Global Assessment of Discharge Readiness	**NNT**	Number needed to treat
CGI-S	Clinical Global Impression—Severity	**OCD**	Obsessive compulsive disorder
CI	Confidence interval	**PHQ-9**	Patient Health Questionnaire—9-Item
C-SSRS	Columbia-Suicide Severity Rating Scale	**SAE**	Serious AE
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition	**SD**	Standard deviation
ECT	Electroconvulsive therapy	**SDS**	Sheehan Disability Scale
HS	High School	**SE**	Standard error
IDS-C_{30}	Inventory of Depressive Symptomatology-Clinician Rated—30-item	**SNRI**	Serotonin-norepinephrine reuptake inhibitor
LS	Least squares	**SSRI**	Selective serotonin reuptake inhibitor
LSMD	Least squares mean difference	**TEAE**	Treatment-emergent AE
MADRS	Montgomery-Åsberg Depression Rating Scale	**TRD**	Treatment-resistant depression
MDD	Major depressive disorder	**XR**	Extended release

Literature Search

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

This response contains a summary of short-term phase 3 studies in TRD. Phase 2 studies[10] are not included in this scientific response.

Thank you for your interest in SPRAVATO® (esketamine). The information is presented in response to your unsolicited inquiry. This information is taken from the references cited, but is not intended to serve as a substitute for review of these references. This information is not intended to advocate the use of our product in any manner other than as described in the product monograph. Please refer to the SPRAVATO® Product Monograph available at http://www.janssen.com/canada/products for full prescribing information.

For any questions, please contact Janssen Medical Information at:
1.800.567.3331 or 1.800.387.8781 or http://www.janssenmedicalinformation.ca

References

1. 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(6):428-438.
2. Fedgchin M, Trivedi M, Daly E, 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(10):616-630.
3. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM 3. *Am J Geriat Psychiatry*. 2020;28(2):121-141.
4. Data on File. Esketamine. Internal Communication.
5. Kim J, Farchione T, Potter A, et al. Esketamine for treatment-resistant depression - first FDA-approved antidepressant in a new class. [published online May 22, 2019]. *N Engl J Med*. doi:10.1056/NEJMp1903305.
6. Montgomery SA, Möller HJ. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? *Int Clin Psychopharmacol*. 2009;24(3):111-118.
7. Montgomery SA, Nielsen RZ, Poulsen LH, et al. A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. *Hum Psychopharmacol*. 2014;29(5):470-482.
8. 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. [published online ahead of print June 5, 2019]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2019.1189.
9. 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):e1-e10. doi: 10.4088/JCP.4019m12891.
10. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: results of a double-blind, doubly-randomized, placebo-controlled study. *JAMA Psychiatry*. 2018;75(2):139-148.