SPRAVATO® (esketamine)
Short-term adjunctive trials in treatment-resistant depression

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- The efficacy and safety of SPRAVATO was assessed in 3 short-term, phase 3, randomized, double-blind, active-controlled clinical studies in patients with TRD.[1-3] Patients participating in the phase 3 clinical development program were generally outpatients.[4]
- A short term, phase 3 trial was conducted in patients mostly in China.[5]

TRANSFORM-2[1]

- In patients 18-64 years of age, the SPRAVATO + new oral AD arm showed greater improvement from baseline to day 28 in mean MADRS total score compared to the new oral AD + placebo nasal spray arm (-21.4 vs -17.0; LSMD, -4.0; 95% CI, -7.31 to -0.64; *P*=0.020).
- The most common TEAEs (≥20% in either arm) were dissociation, nausea, vertigo, dysgeusia, dizziness, and headache.

TRANSFORM-1[2]

- In patients 18-64 years of age, both SPRAVATO (56 mg and 84 mg) + AD arms showed a clinically meaningful[7-9] and numerically greater change from baseline to day 28 in mean MADRS total score compared to the AD + placebo arm (-19.0 vs -18.8 vs -14.8, respectively; LSMD [median unbiased estimate] from placebo, -4.1 vs -3.2, respectively); however, statistical significance was not demonstrated with SPRAVATO 84 mg + AD (95% CI, -6.88 to 0.45; *P*=0.088), and therefore SPRAVATO 56 mg + AD could not be formally evaluated.
- The most common TEAEs (≥20% in any treatment arm) were nausea, dissociation, dizziness, vertigo, headache, and somnolence.

TRANSFORM-3[3]

- Though not statistically significant, in elderly patients ≥65 years of age, the SPRAVATO + AD arm showed a clinically meaningful[7-9] improvement, and a numerically greater decrease in MADRS total score from baseline to day 28 compared to the AD + placebo arm (-10.0 vs -6.3; LSMD [median unbiased estimate], -3.6; 95% CI, -7.2 to 0.07; *P*=0.059).
- The most common TEAE (≥20% in either treatment arm) was dizziness.

NCT03434041[5]

- A phase 3, multicenter study conducted mainly in China (22 sites in China, 5 sites in United states) failed to achieve statistical significance for primary efficacy endpoint.

Note: AD, antidepressant; CI, confidence interval; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression.

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TRANSFORM-2[1]

Phase 3, double-blind, randomized, active-controlled, flexible-dose study

Treatment-resistant depression

N=223

Key inclusion criteria[1]

- Age 18-64 years
- Moderate to severe nonpsychotic MDD
- Nonresponse to ≥2 ADs in current episode
- IDS-C_{30} score ≥34

Key exclusion criteria[1]

- 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[1]

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

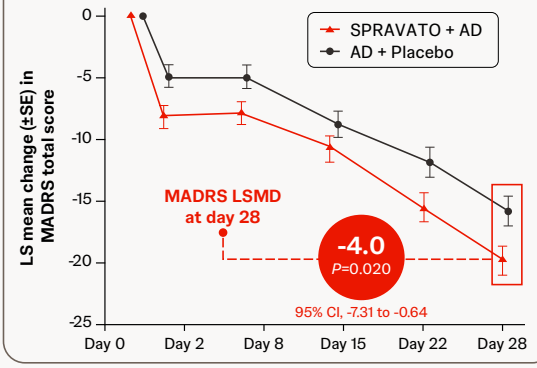
n=114

n=109

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

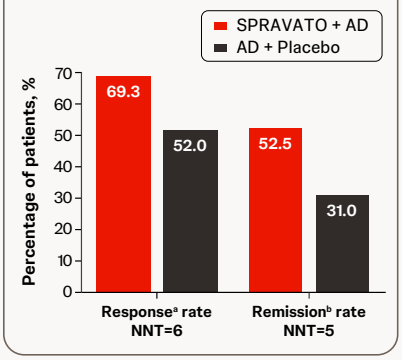
Primary efficacy endpoint[1]

Change in mean MADRS total score from baseline to day 28 was statistically significantly greater with SPRAVATO + AD vs AD + placebo



Secondary efficacy endpoints[1]

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



Safety[1]

TEAEs ≥20%

- Dissociation
- Nausea
- Vertigo
- Dysgeusia
- Dizziness
- Headache

- Observed more frequently in the SPRAVATO + AD arm
- Mostly **mild to moderate**, appeared shortly after dosing
- Generally **resolved** by 1.5 hours postdose

- **Treatment discontinuation due to TEAEs:**
  - SPRAVATO + AD: **7%**
  - AD + Placebo: **0.9%**

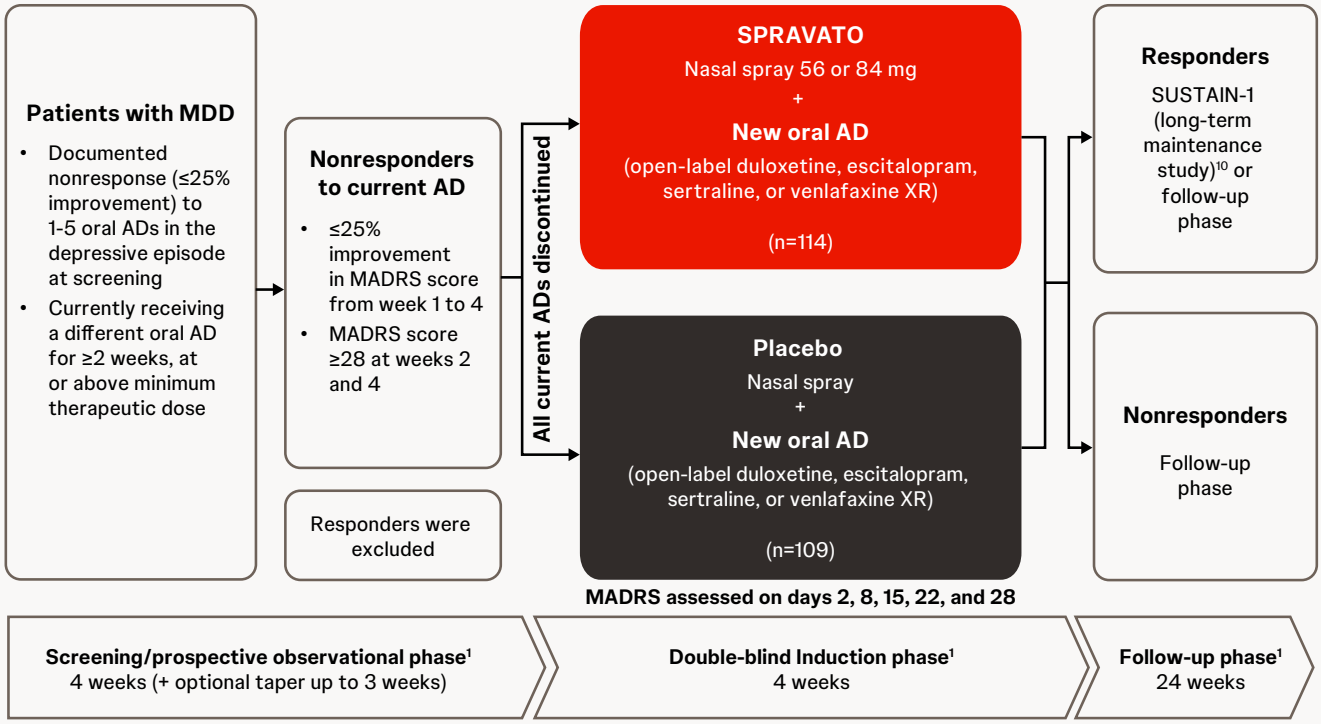
[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS score ≤12.

Note: AD, antidepressant; CI, confidence interval; ECT, electroconvulsive therapy; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician Rated—30-item; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NNT, number needed to treat; OCD, obsessive compulsive disorder; SE, standard error; TEAE, treatment-emergent adverse event; XR, extended release.

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- TRANSFORM-2 (NCT02418585) was a phase 3, 1:1 randomized, double-blind, active-controlled, flexible-dose, multicenter study conducted in 39 sites across 5 countries in patients with TRD.[1]



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Inclusion criteria[1]	**Exclusion criteria**[1]
• 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 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, in the past 6 months • Nonresponse in the current MDD episode to SPRAVATO 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[1]

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

Key secondary efficacy endpoints[1]

- 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[1]

- Proportion of responders (≥50% reduction from baseline in MADRS total score) and remitters (MADRS score ≤12) at day 28[1]
- CGI-S ranks of change[1]
- Patient-reported outcomes as determined by the number of patients reporting impairment in each dimension of EQ-5D-5L, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, at baseline and on days 15 and 28.[14]
  - Health Status Index was calculated from each dimension's response and ranged from 0 (dead) to 1 (full health).

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- Overall, 223 patients were randomized and received the study drugs.[1]
- Demographics and baseline characteristics were similar across treatment arms.[1]

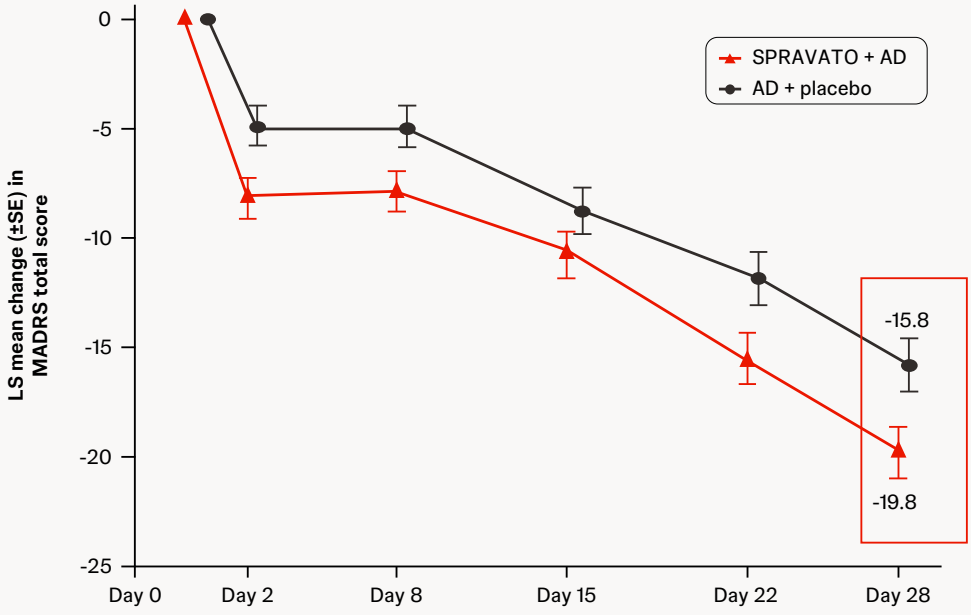
	SPRAVATO + AD (n=114)	AD + placebo (n=109)
Age, years, mean (SD)	44.9 (12.58)	46.4 (11.14)
Female, n (%)	75 (65.8)	63 (57.8)
Race, n (%)		
Black or African American	6 (5.3)	5 (4.6)
White	106 (93.0)	102 (93.6)
Other	2 (1.8)	2 (1.8)
Duration of current episode, weeks, mean (SD)	111.4 (124.28)	118.0 (187.37)
MADRS score, mean (SD)	37.0 (5.69)	37.3 (5.66)
Number of previous AD medications,[a] n (%)		
1-2	78 (68.4)	72 (66.1)
≥3	36 (31.6)	37 (39.9)
Class of oral AD, n (%)		
SNRI	77 (67.5)	75 (68.8)
SSRI	37 (32.5)	34 (31.2)

[a]Taken for ≥6 weeks, and nonresponse (defined as ≤25% improvement) during the current episode in addition to 1 prospective AD.

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- **Change in mean MADRS total score** from baseline to day 28 was significantly greater with SPRAVATO + AD vs AD + placebo.[1]



	Day 0	Day 2	Day 8	Day 15	Day 22	Day 28
SPRAVATO + AD	114	109	109	107	103	101
AD + placebo	109	102	105	102	104	100

Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO® dosage from 84 mg to 56 mg twice weekly.
Adapted from The American Journal of Psychiatry, 176, 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, 428-438, Copyright 2019, and adapted with permission from copyright holder.

Primary efficacy endpoints[1]	**SPRAVATO (56 or 84 mg) + AD**	**AD + placebo**
Mean change from baseline at day 28	-21.4	-17.0
LS mean change from baseline at day 28	-19.8	-15.8
LSMD between treatment arms	-4.0 (95% CI, -7.31 to -0.64)	
	P=0.020	

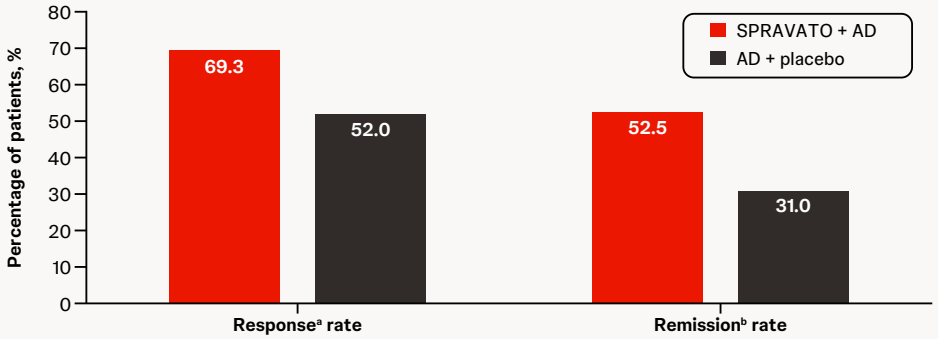
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- The proportion of patients with **early onset of sustained clinical response** was greater with SPRAVATO + AD vs AD + placebo.[1]
  - As the difference was not statistically significant, changes in SDS and PHQ-9 total scores from baseline to day 28 could not be formally evaluated.

Key secondary endpoints	SPRAVATO + AD (n=114)	AD + placebo (n=109)
Early onset of sustained clinical response, n (%)	9 (7.9)	5 (4.6)
	P=0.321	
Change in SDS score from baseline to day 28, mean	-13.6	-9.4
	LSMD: -4.0	
Change in PHQ-9 score from baseline to day 28, mean	-13.0	-10.2
	LSMD: -2.4	

- **In post hoc analyses, response[a] and remission[b] rates** at day 28 were greater with SPRAVATO + AD (69.3% and 52.5%) vs AD + placebo (52.0% vs 31.0%)[1]
  - NNT for response[a] was 6 and for remission[b] was 5



- An improvement in the median **CGI-S scores** from baseline to day 28 was noted in both treatment arms (-2.0 in both arms)[1]
- On Day 28, a numerically lower percentage of patients reported impairment in the SPRAVATO + AD group vs the AD + placebo group in all 5 EQ-5D-5L dimensions: mobility (10.6% vs 25.0%), self-care (13.5% vs 32.0%), usual activities (51.9% vs 72.0%), pain/discomfort (35.6% vs 54.0%), and anxiety/depression (69.2% vs 78.0%).[14]
  - At Day 28, the mean (SD) changes in the weighted Health Status Index score relative to baseline was higher for the SPRAVATO + AD group vs the AD + placebo group (0.310 [0.219] vs 0.235 [0.252]).

[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 the SPRAVATO + AD arm included dissociation, nausea, vertigo, dysgeusia, dizziness, and headache; all were more frequent than in the AD + placebo arm.[1]
- Most AEs were **mild to moderate** in severity and were transient, with an onset shortly after dosing and a resolution by 1.5 hours postdose.[1]
- One death due to a road traffic accident was reported in the SPRAVATO + AD arm and was determined by the investigator as doubtfully treatment related.[1]
- No other fatal or nonfatal study drug-related SAEs occurred.[1]
- **Treatment discontinuation** due to AEs:[1]
  - **SPRAVATO + AD:** 8 (7%) patients discontinued treatment due to anxiety, depression, depressive symptom, panic attack, drug intolerance, feeling drunk, dizziness, headache, vertigo, nausea, road traffic accident, and multiple injuries.
  - **AD + placebo:** 1 (0.9%) patient discontinued treatment due to generalized rash.

TEAEs ≥10% in either treatment arm

TEAEs ≥10% in either treatment arm during the double-blind phase[1]

Event, n (%)	SPRAVATO + AD (n=114)	AD + placebo (n=109)
Dissociation	30 (26.1)	4 (3.7)
Nausea	30 (26.1)	7 (6.4)
Vertigo	30 (26.1)	3 (2.8)
Dysgeusia	28 (24.3)	13 (11.9)
Dizziness	24 (20.9)	5 (4.6)
Headache	23 (20.0)	19 (17.4)
Somnolence	15 (13.0)	7 (6.4)
Vision blurred	14 (12.2)	3 (2.8)
Paresthesia	13 (11.3)	1 (0.9)
Anxiety	12 (10.4)	5 (4.6)

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

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Postdose monitoring[1]

- **Sedation**
  - The MOAA/S score was ≤4 at any time postdose in 57.4% of patients in the SPRAVATO + AD arm and in 10.1% of patients in the AD + placebo arm.
  - Generally, symptoms spontaneously resolved by 1-1.5 hours postdose.
  - Sedation was not associated with hypoxemia.
- **Transient blood pressure increases**
  - Occurred after each SPRAVATO dose and peaked at 40 minutes postdose.
  - Mean maximum increase before dosing to any postdose time point:

Change in blood pressure	SPRAVATO + AD	AD + placebo
Systolic blood pressure, mm Hg	+11.6	+5.0
Diastolic blood pressure, mm Hg	+8.1	+4.5

  - Blood pressure typically returned to the predose range by 1.5-2 hours postdose.
- **Dissociative symptoms and perceptual effects**
  - Per the CADSS, symptoms were observed shortly after the SPRAVATO dose, peaked at 40 minutes, resolved by 1.5 hours postdose, and attenuated with repeated dosing.
    - Mean change in CADSS score from predose to 40 minutes postdose was 7.8 on day 1 and 3.5 on day 25.
  - Events and symptoms of psychosis were not observed.

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- **Discharge readiness**[1]
  - Discharge readiness was assessed per the CGADR:

Discharge readiness per CGADR	SPRAVATO + AD	AD + placebo
1 hour postdose, %	≥44.3	≥92.0
1.5 hours postdose, %	93.2	98.9

  - All patients were ready for discharge by 3 hours postdose.

Other safety assessments[1]

- **Suicidal ideation**
  - Per the C-SSRS score, suicidal ideation decreased from baseline to day 28 in both arms.
  - Treatment-emergent suicidal ideation was reported in 5.4% of patients in the SPRAVATO + AD arm and 6.4% of patients in the AD + placebo arm.
  - Treatment-emergent suicidal behavior was not observed in either arm.

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TRANSFORM-1[2]

Phase 3, double-blind, randomized, active-controlled, multicenter, fixed-dose study

Treatment-resistant depression

N=342

Key inclusion criteria[2]

- Age 18-64 years
- Recurrent MDD or single-episode nonpsychotic MDD (≥2 years)
- Nonresponse to ≥2 ADs in current episode
- IDS-C_{30} score ≥31

Key exclusion criteria[2]

- 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[2]

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

56 mg n=115

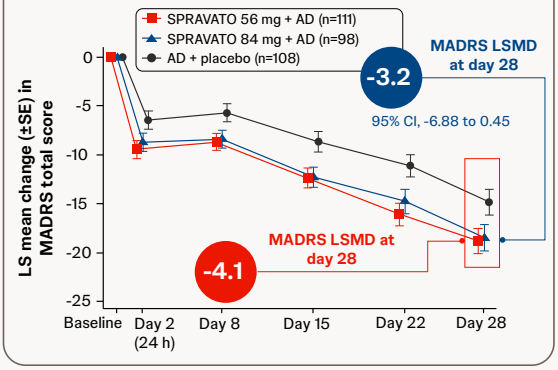
84 mg n=114

n=113

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

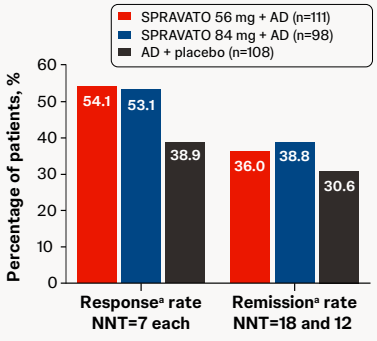
Primary efficacy endpoint[2]

Change in mean MADRS total score from baseline to day 28 was clinically meaningful[7-9] but not statistically significant with SPRAVATO + AD arms vs AD + placebo



Secondary efficacy endpoints[2]

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



Safety[2]

TEAEs ≥20%

- Nausea
- Dissociation
- Dizziness
- Vertigo
- Headache

- Observed more frequently in the SPRAVATO + AD arm
- Mostly **mild to moderate**, and generally **resolved** in the same dosing day

- **Treatment discontinuation due to TEAEs:**
  - SPRAVATO 56 mg + AD: **0.9%**
  - SPRAVATO 84 mg + AD: **6.0%**
  - AD + placebo: **1.8%**

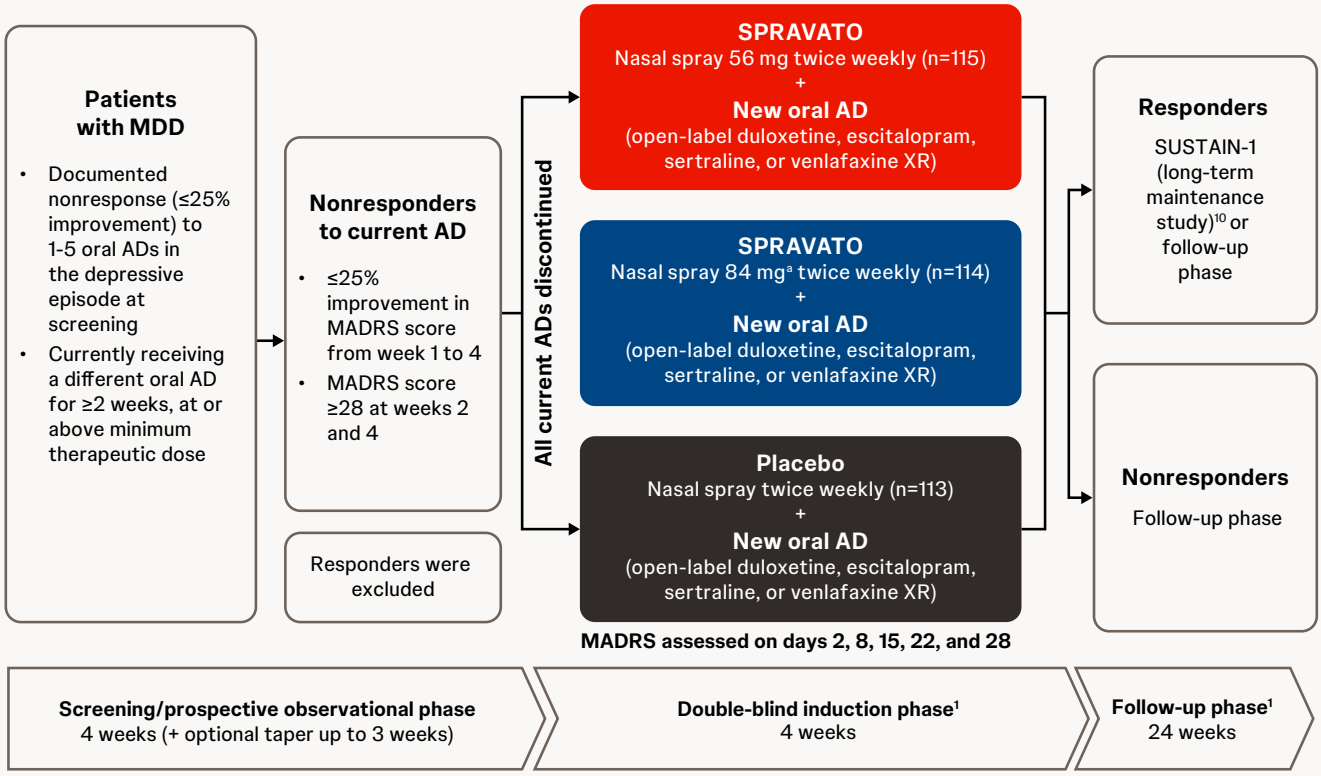
[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS score ≤12.

Note: AD, antidepressant; CI, confidence interval; ECT, electroconvulsive therapy; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician Rated—30-item; LS, least squares; LSMD, least squares mean difference; MADRS,Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NNT, number needed to treat; OCD, obsessive compulsive disorder; SE, standard error; TEAE, treatment-emergent adverse event; XR, extended release.

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- TRANSFORM-1 (NCT02417064) was a phase 3, 1:1:1 randomized, double-blind, active-controlled, fixed-dose, multicenter study in patients with TRD.[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 SPRAVATO 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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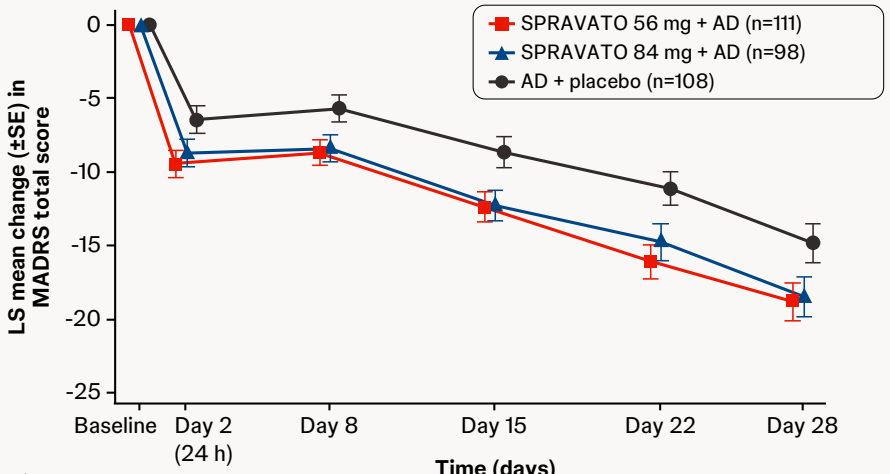
- Overall 346 patients were randomized.[2]
- Demographics and baseline characteristics were similar across treatment arms.[2]

	SPRAVATO 56 mg + AD (n=115)	SPRAVATO 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 SPRAVATO + AD arms showed a clinically meaningful[7-9] and numerically greater change vs AD + placebo.[2]



No. of patients						
SPRAVATO 56 mg + AD	115	105	114	110	107	111
SPRAVATO 84 mg + AD	114	104	107	99	96	98
AD + placebo	113	101	111	106	105	108

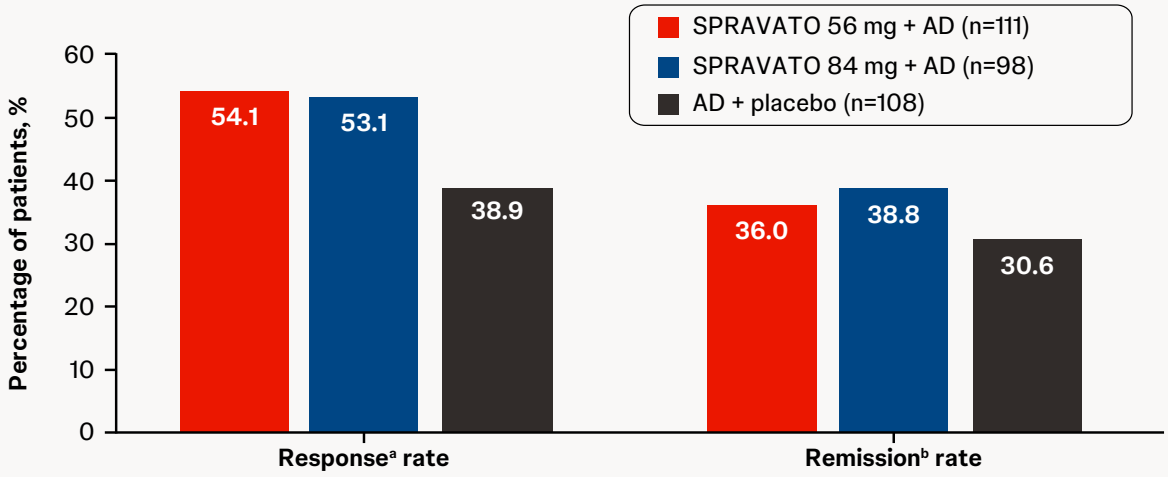
Fedgchin M, Trivedi, M, Daly EJ, et al., Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1), International Journal of Neuropsychopharmacology, 2019, 22, 10, 616-630, This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium.

- **Mean change from baseline at day 28**[2]
  - SPRAVATO 84 mg + AD: -18.8
  - SPRAVATO 56 mg + AD: -19.0
  - AD + placebo: -14.8
- **LSMD (median unbiased estimate) from placebo**[2]
  - SPRAVATO 84 mg + AD: -3.2 (95% CI, -6.88 to 0.45; *P*=0.088)
  - SPRAVATO 56 mg + AD: -4.1 (95% CI, -7.67 to -0.49; nominal *P*=0.027)
  - A predefined gatekeeping procedure was established to evaluate the efficacy of SPRAVATO 84 mg before proceeding to evaluate SPRAVATO 56 mg. Since statistical significance was not demonstrated, SPRAVATO 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 SPRAVATO (56 mg and 84 mg) + AD vs AD + placebo.[2]
  - NNT for response was 7 for both SPRAVATO + 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 SPRAVATO + 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 SPRAVATO + 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 SPRAVATO + 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 SPRAVATO 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]
  - **SPRAVATO 56 mg + AD:** 1 (0.9%) patient discontinued treatment due to depression.
  - **SPRAVATO 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 (%)	SPRAVATO 56 mg + AD (n=115)	SPRAVATO 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.

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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 SPRAVATO 56 mg + AD arm, 12.1% in the SPRAVATO 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 SPRAVATO dose and peaked at 40 minutes postdose.
  - Mean maximum increase before dosing to any postdose time point:

Change in blood pressure	SPRAVATO 56 mg + AD	SPRAVATO 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 SPRAVATO 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	SPRAVATO 56 mg + AD	SPRAVATO 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 SPRAVATO 56 mg + AD arm, 7.1% in the SPRAVATO 84 mg + AD arm, and 11.5% in the AD + placebo arm per the C-SSRS score.

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- **Discontinuations**[2]
  - The discontinuation rate in the SPRAVATO 84 mg + AD arm (16.4%) was 3 times higher than in the SPRAVATO 56 mg + AD (5.1%) and AD + placebo (5.3%) arms.
  - Eleven of the 19 patients in the higher SPRAVATO dosage arm withdrew during day 1 while on the SPRAVATO 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 SPRAVATO 84 mg + AD and AD + placebo:[2]
  - A 3-fold higher withdrawal rate in the SPRAVATO 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

Treatment-resistant depression

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]

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

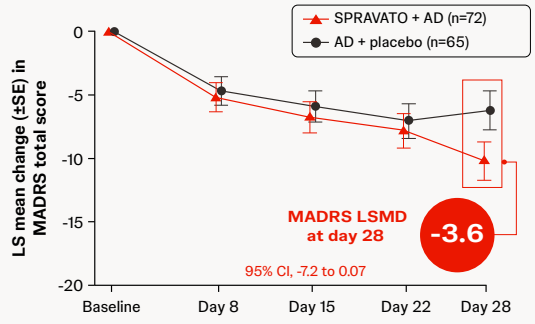
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n=66

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

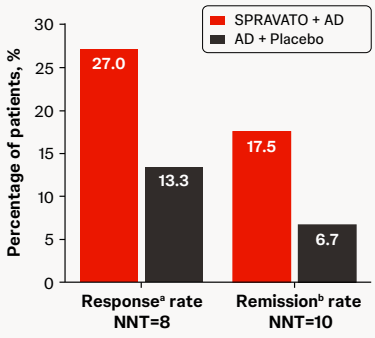
Primary efficacy endpoint[3]

Change in mean MADRS total score from baseline to day 28 was clinically meaningful[7-9] but not statistically significant with SPRAVATO + AD vs AD + placebo



Secondary efficacy endpoints[3]

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



Safety[3]

TEAEs ≥20%

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

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

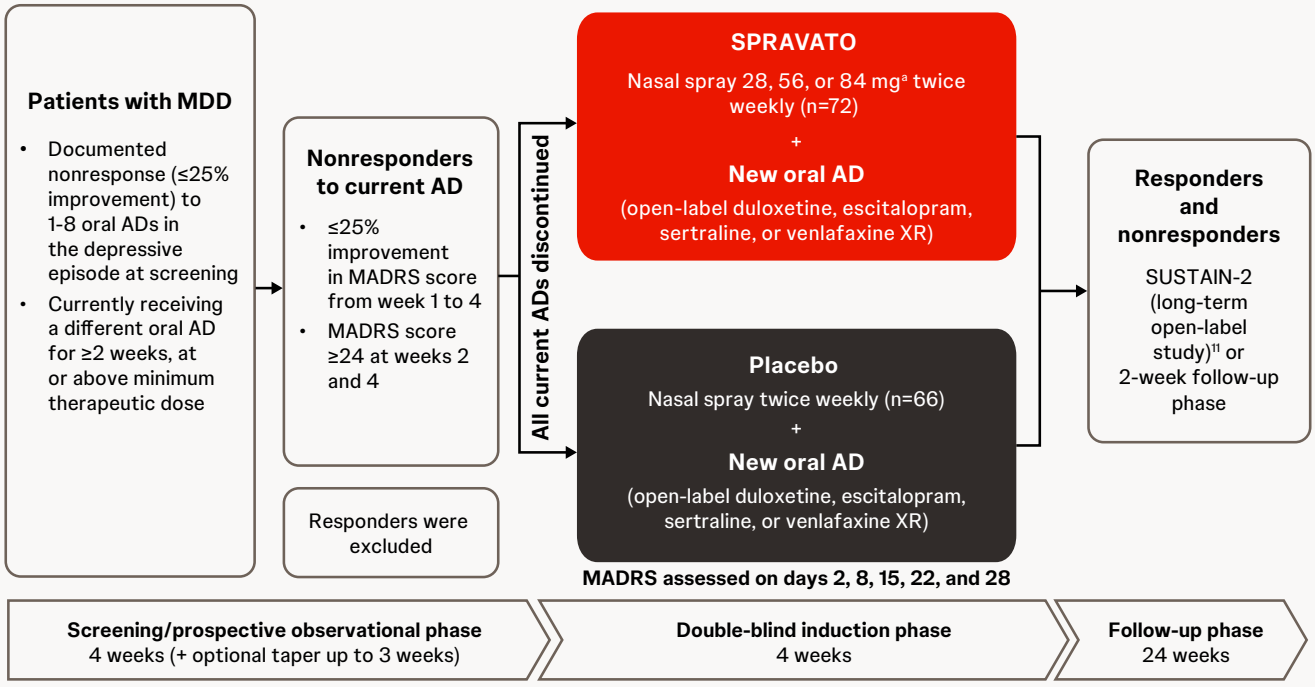
[a]Response was defined as ≥50% reduction from baseline in MADRS total score; [b]Remission was defined as MADRS score ≤12.

Note: AD, antidepressant; CI, confidence interval; ECT, electroconvulsive therapy; IDS-C_{30}, Inventory of Depressive Symptomatology-Clinician Rated—30-item; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MMSE, Mini Mental Status Exam; NNT, number needed to treat; OCD, obsessive compulsive disorder; SE, standard error; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression; XR, extended release.

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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 with TRD.[3]



[a]All patients started with SPRAVATO 28 mg or placebo on day 1; the second dose (day 4) of SPRAVATO was 28 or 56 mg and all subsequent doses were 28, 56, or 84 mg based on efficacy and tolerability. Dose increase in SPRAVATO 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 HS 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 SPRAVATO 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[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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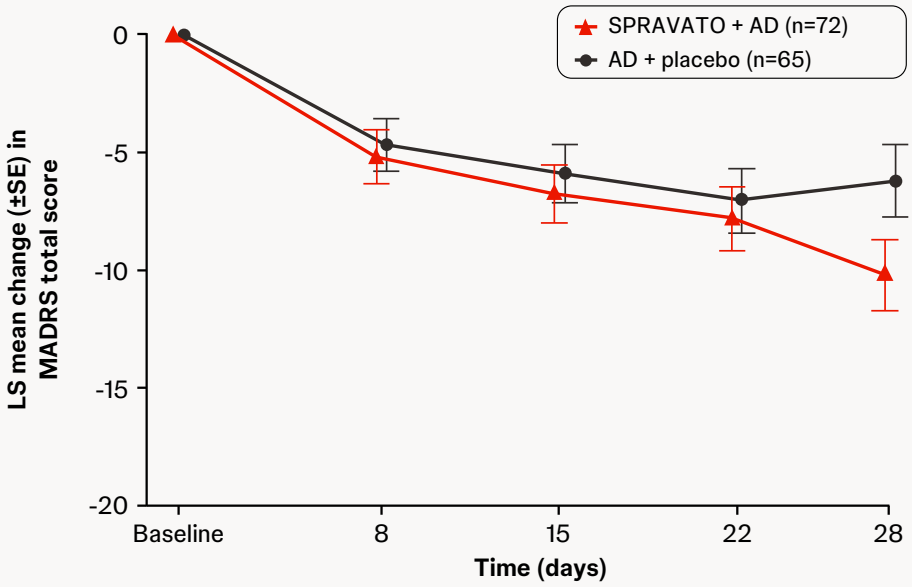
- Overall 138 patients were randomized to treatment.[3]
- Demographics and baseline characteristics were similar across treatment arms.[3]

	SPRAVATO + 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[7-9] and numerically greater with SPRAVATO (28, 56, or 84 mg) + AD vs AD + placebo.[3]



No. of patients					
SPRAVATO + AD	72	66	68	60	63
AD + placebo	65	63	62	56	60

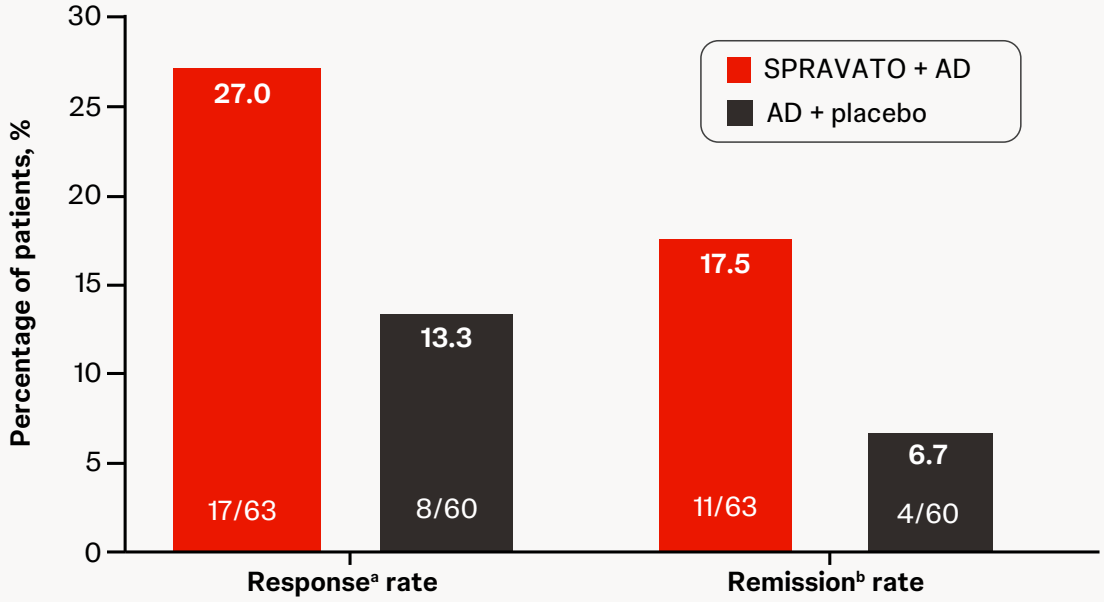
Reprinted from The American Journal of Geriatric Psychiatry, 28, Ochs-Ross R, Daly EJ, Zhang Y, et al., Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3, 121-141, Copyright 2020, with permission from Elsevier.

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

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- **Response[a] and remission[b] rates** at day 28 were greater with SPRAVATO (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 SPRAVATO + 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 (SPRAVATO + AD, -1.0; AD + placebo, 0).[3]

SPRAVATO® (esketamine)
Short-term adjunctive trials in treatment-resistant depression

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- Additional efficacy analyses found that patients aged 65-74 years vs ≥75 years in the SPRAVATO + 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 SPRAVATO + 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, to -0.25) between SPRAVATO + 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.[11] 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 SPRAVATO + 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 SPRAVATO + 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]
  - **SPRAVATO + 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 (%)	SPRAVATO + 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.

SPRAVATO® (esketamine)
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Postdose monitoring[3]

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

Change in Blood Pressure	SPRAVATO + 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 SPRAVATO 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	SPRAVATO + 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 SPRAVATO + 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 SPRAVATO + AD arm and 13.8% of patients in the AD + placebo arm per the C-SSRS score.
  - No suicidal attempts or behavior was observed.

SPRAVATO® (esketamine)
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NCT03434041[5]

Randomized, double-blind, multicenter active-controlled study in patients mainly in china

Treatment-resistant depression

N=252

Key inclusion criteria[5]

- Age 18-64 years
- Single-episode or recurrent MDD without psychotic features
- Nonresponse to 1-5 oral ADs during the current episode
- MADRS score ≥28

Key exclusion criteria[5]

- Nonresponse to SPRAVATO, ketamine, all 4 study ADs, and ECT
- Received vagal nerve stimulation or deep brain stimulation
- Bipolar or personality disorders
- Homicidal or suicidal ideation

Study design[5]

SPRAVATO nasal spray 56 or 84 mg + **Oral AD** (duloxetine, escitalopram, sertraline, or venlafaxine XR)

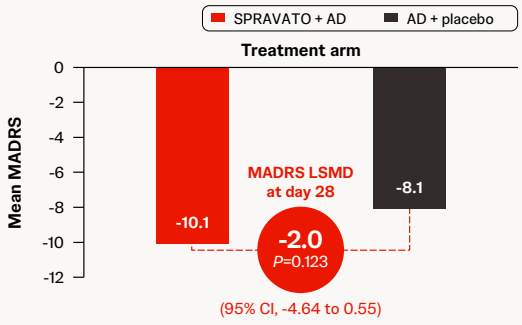
n=126

n=126

Oral AD (duloxetine, escitalopram, sertraline, or venlafaxine XR) + **Placebo** nasal spray

Primary efficacy endpoint[5]

At day 28, the LSMD was not statistically significant between the SPRAVATO + AD and AD + placebo groups



Key secondary efficacy endpoints[5]

Mean change in MADRS total score from baseline to 24 hours (day 2):

- SPRAVATO + AD = -8.0
- AD + placebo = -4.4
- LSMD, -3.3 (95% CI, -5.33 to -1.33)

Mean change in SDS total score from baseline to day 28:

- SPRAVATO + AD = -6.3
- AD + placebo = -5.3
- LSMD, 1.0 (95% CI, -2.96 to 0.97)

Safety[5]

- All-cause mortality was 1 (0.8%) in the SPRAVATO + AD arm and none in AD + placebo arm

TEAEs ≥20%

Observed more frequently in the SPRAVATO + AD arm

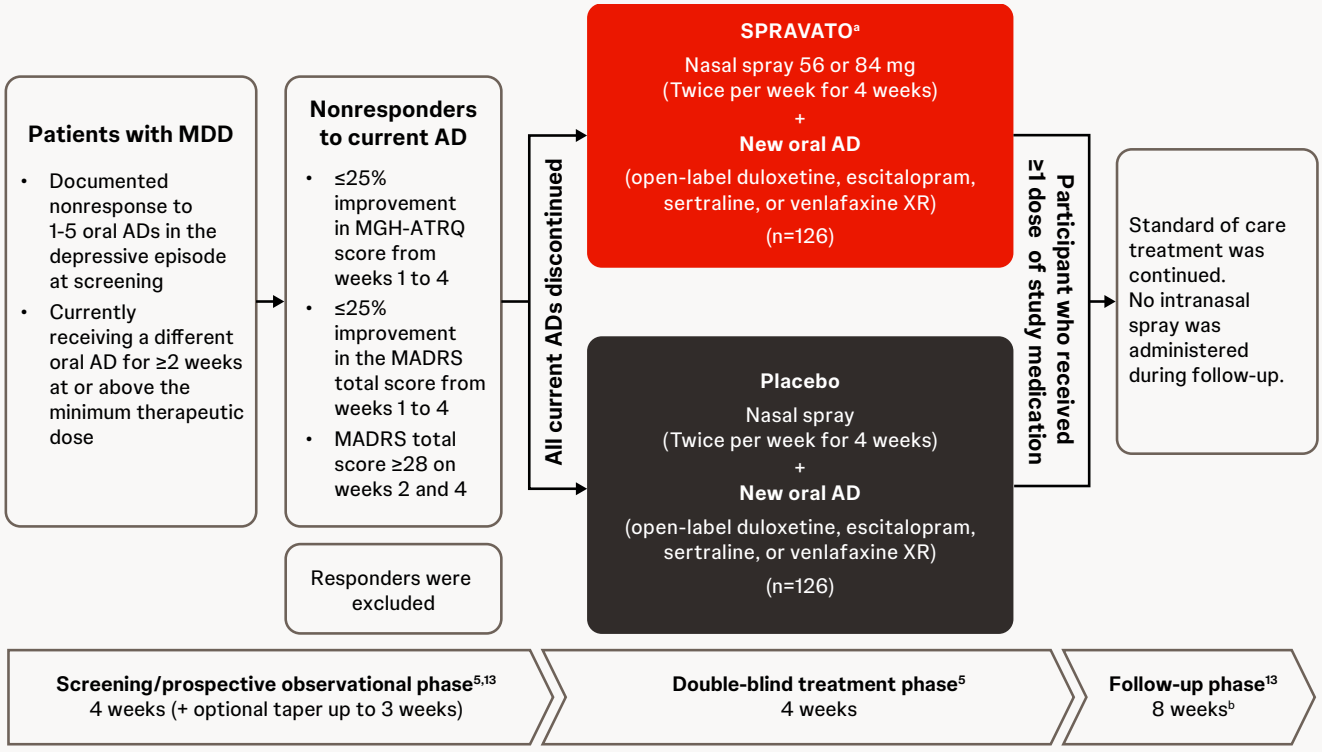
- Dizziness
- Dissociation
- Nausea
- Increased blood pressure

Note: AD, antidepressant; CI, confidence interval; ECT, electroconvulsive therapy; LSMD, Least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SDS, Sheehan Disability Scale; TEAE, treatment-emergent adverse event; XR, extended release.

SPRAVATO® (esketamine)
Short-term adjunctive trials in treatment-resistant depression

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- ESKETINTRD3006 (NCT03434041) was a phase 3, randomized, double-blind, active-controlled, multicenter study conducted in patients with TRD.[5]



[a]SPRAVATO was initiated at 56 mg on day 1. The dose could be maintained at 56 mg or increased to 84 mg per the investigator's discretion. Participants received 1 of the 4 ADs on day 1, which was continued for 4 weeks.
[b]Participants received oral AD only during the 8-week–follow-up period unless it was determined clinically inappropriate.

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Inclusion criteria[5,6]	**Exclusion criteria**[5]
• Age 18-64 years • Recurrent or single episode of MDD without psychotic features per DSM-5 and clinical assessment confirmed by MINI • Nonresponse to 1-5 oral ADs during the current MDD episode, and taking a different oral AD for ≥2 previous weeks at or above the minimum therapeutic dose assessed by MGH-ATRQ • Current MDD episode with ≤25% improvement in the MADRS total score from weeks 1 to 4 and MADRS total score ≥28 on weeks 2 and 4 • AD treatment response must be confirmed by C-VISA • Medically stable based on physical examination, medical history, vital signs, pulse oximetry, 12-lead ECG, and clinical laboratory tests	• Nonresponse in the current MDD episode to SPRAVATO, ketamine, to all 4 oral AD treatment options, or an adequate course of ECT • Received vagal nerve stimulation or deep brain stimulation in the current episode • Current or prior DSM-5 diagnosis of psychotic disorder or MDD with psychotic features or related disorders; OCD; autism spectrum disorder; intellectual disability; or borderline, antisocial, histrionic, or narcissistic personality disorder • Homicidal ideation/intent or suicidal ideation with some intent to act within the past 6 months or history of suicidal behavior within past year • History of moderate to severe substance or alcohol use disorder per DSM-5 criteria, in the past 6 months including a lifetime history of ketamine, phencyclidine, lysergic acid diethylamide, or 3,4-methlyenedioxy-methamphetamine hallucinogen-related use disorder

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Short-term adjunctive trials in treatment-resistant depression

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Primary efficacy endpoint[5]

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

Key secondary efficacy endpoints[5]

- Change in MADRS total score from baseline (day 1, predose) to 24 hours after first dose (day 2)
- Change in SDS total score from baseline to day 28

Other secondary endpoints[5]

- CGI-S score change
- GAD-7 score change
- EQ-5D-5L score change

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- Overall, 252 patients were randomized.[5]
- Demographics and baseline characteristics were similar across treatment arms.[5]

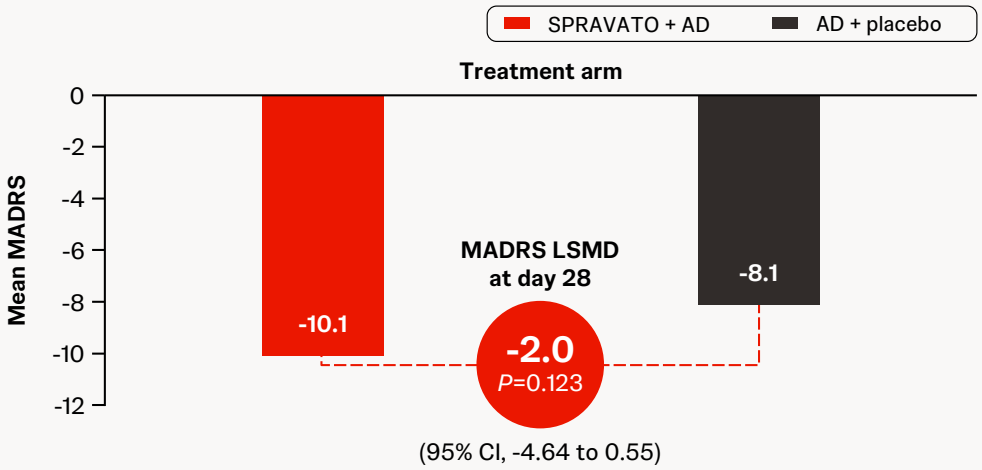
	SPRAVATO + AD (n=124)	AD + placebo (n=126)
Age, years, mean (SD)	36.9 (12.04)	37.8 (12.36)
Sex, n (%)		
Female	58 (46.8)	55 (43.7)
Male	66 (53.2)	71 (56.3)
Race, n (%)		
Asian	112 (88.9)	112 (88.9)
White	12 (9.5)	9 (7.1)
Black or African American	1 (0.8)	4 (3.2)
Region of enrollment, n (%)		
China	110 (88.7)	112 (88.9)
United States	14 (11.3)	14 (11.1)
Duration of current episode, weeks, mean (SD)	225.3 (317.75)	218.6 (274.20)
MADRS total score, mean (SD)	36.5 (5.21)	35.9 (4.50)
CGI-S, mean (SD)	5.1 (0.61)	5.2 (0.68)
SDS total score, mean (SD)	22.9 (5.18)	22.5 (5.20)
Class of oral AD, n (%)		
SNRI	68 (54.8)	69 (54.8)
SSRI	56 (45.2)	57 (45.2)
Number of previous treatment failures in current episode, n (%)		
1	38 (30.6)	38 (30.2)
2	46 (37.1)	47 (37.3)
3	29 (23.4)	31 (24.6)
4	7 (5.6)	8 (6.3)
5	4 (3.2)	2 (1.6)

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Primary efficacy endpoint[5]

- **Change in mean (SD) MADRS total score** from baseline to day 28 in the SPRAVATO + AD vs placebo + AD group was -10.1 (10.80) vs -8.1 (10.26); LSMD, -2.0 (95% CI, -4.64 to 0.55).



Secondary efficacy endpoint[5,6]

- Results of secondary endpoint are given in table below:

Parameters	SPRAVATO + AD	AD + placebo
Change in MADRS total score from baseline to 24 hours post-first dose (day 2), mean (SD)	-8.0 (9.01)	-4.4 (7.66)
	LSMD, -3.3 (95% CI, -5.33 to -1.33)	
Change in SDS total score from baseline to day 28, mean (SD)	-6.3 (7.54)	-5.3 (7.03)
	LSMD, -1.0 (95% CI, -2.96 to 0.97)	
Change in CGI-S from baseline to day 28, median (range)	-1.0 (-5 to 1)	-1.0 (-5 to 1)
	LSMD, -0.2 (95% CI, -0.46 to 0.10)	
Change in GAD-7 from baseline to day 28, mean (SD)	-4.3 (5.65)	-2.9 (5.28)
	LSMD, -1.6 (95% CI, -2.78 to -0.36)	

- The proportion of patients who reported problems in all 5 individual domains of **EQ-5D-5L** decreased from baseline to day 28 in both treatment groups.

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- All-cause mortality and AEs during the double-blind phase are reported in the table below[5]:

Events, n (%)	SPRAVATO + AD (n=126)	AD + placebo (n=126)
≥1 TEAE	120 (95.2)	89 (70.6)
TEAEs ≥10% (both arms)		
Dizziness	97 (77.0)	25 (19.8)
Dissociation	75 (59.5)	8 (6.3)
Nausea	53 (42.1)	17 (13.5)
Increased blood pressure	38 (30.2)	13 (10.3)
Hypoesthesia	25 (19.8)	1 (0.8)
Vomiting	23 (18.3)	2 (1.6)
Vision blurred	23 (18.3)	1 (0.8)
Somnolence	20 (15.9)	11 (8.7)
Headache	16 (12.7)	14 (11.1)
Dysgeusia	14 (11.1)	6 (4.8)
TEAEs possibly related to intranasal drug	117 (92.9)	55 (43.7)
TEAEs leading to discontinuation of study medication	7 (5.6)	2 (1.6)
All-cause mortality	1 (0.8)	0 (0.0)
Treatment-emergent SAEs		
Depression	1 (0.8)	3 (2.4)
Suicide attempt	1 (0.8)	0 (0.0)
Completed suicide	1 (0.8)	0 (0.0)

C-SSRS[5]

- Treatment-emergent post-baseline suicidal ideation were reported in 12 and 14 patients receiving SPRAVATO + AD and AD + placebo, respectively, and suicidal behavior was reported in 1 patient who received SPRAVATO + AD.

C-SSRS[5]

- In the SPRAVATO + AD vs AD + placebo groups, 72.8% (n=91) vs 4.8% (n=6) of patients, had an increase of >4 in the CADSS total score from pre-dose at any time during the double-blind phase.

PWC-20[5]

- No clear signs of withdrawal were observed 2 weeks after cessation of treatment with SPRAVATO + AD.

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AD	Antidepressant	**MDD**	Major depressive disorder
AE	Adverse event	**MGH- ATRQ**	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
CADSS	Clinician-Assessed Dissociative Symptom Scale	**MINI**	Mini International Neuropsychiatric Interview
CGADR	Clinical Global Assessment of Discharge Readiness	**MMSE**	Mini Mental Status Exam
CGI-S	Clinical Global Impression-Severity	**MOAA/S**	Modified Observer's Assessment of Alertness/Sedation
CI	Confidence interval	**NNT**	Number needed to treat
C-SSRS	Columbia-Suicide Severity Rating Scale	**OCD**	Obsessive compulsive disorder
C-VISA	Clinical Validation Inventory for Study Admission	**PHQ-9**	Patient Health Questionnaire— 9-Item
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition	**PWC-20**	20-Item Physician Withdrawal Checklist
ECG	Electrocardiogram	**SAE**	Serious adverse event
ECT	Electroconvulsive therapy	**SD**	Standard deviation
EQ-5D-5L	European Quality of Life-5 Dimension-5 Level	**SDS**	Sheehan Disability Scale
GAD-7	Generalized Anxiety Disorder 7-item	**SE**	Standard error
HS	High school	**SNRI**	Serotonin-norepinephrine reuptake inhibitor
IDS-C30	Inventory of Depressive Symptomatology-Clinician Rated— 30-item	**SSRI**	Selective serotonin reuptake inhibitor
LS	Least squares	**TEAE**	Treatment-emergent adverse event
LSMD	Least squares mean difference	**TRD**	Treatment-resistant depression
MADRS	Montgomery-Åsberg Depression Rating Scale	**XR**	Extended release

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A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 10 April 2026.

This response contains a summary of short-term phase 3 studies in TRD. Phase 2 studies[12] are not included in this scientific response.

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