# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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## Overview

The efficacy and safety of SPRAVATO nasal spray + an oral AD was assessed in 3 long-term, phase 3, multicenter studies (SUSTAIN-1, SUSTAIN-2, and SUSTAIN-3) in patients with TRD.[1,2,3] Patients participating in the phase 3 clinical development program were generally outpatients.[4]

## SUSTAIN-1

- SUSTAIN-1 was a longer-term, phase 3, multicenter, double-blind, randomized withdrawal study conducted to evaluate SPRAVATO + an oral AD in sustaining antidepressant effects in patients with TRD who were in stable remission after 16 weeks of SPRAVATO + AD.[1]
- In patients who were stable remitters, SPRAVATO + AD significantly delayed relapse compared to an AD + placebo ($P$=0.003).[1]
- Treatment with SPRAVATO + AD decreased the risk of relapse by 51% (estimated HR: 0.49; 95% CI: 0.29-0.84) among stable remitters.[1]
- No new safety concerns were observed with repeated weekly or every-other-week dosing of SPRAVATO + AD when compared with earlier short-term studies.[5-7]

## SUSTAIN-2

- SUSTAIN-2 was a long-term, open-label, phase 3 study conducted to evaluate the safety and tolerability of SPRAVATO + AD in patients with TRD.[2]
- In patients ≥18 years of age treated with SPRAVATO + AD for up to 1 year, TEAEs occurred in 723 patients (90.1%), and 55 patients (6.9%) had events that were considered serious.[2]
- The majority of TEAEs were mild or moderate in intensity, occurred on dosing days, and usually resolved on the same day.[2]

## SUSTAIN-3

- SUSTAIN-3 was an open-label, phase 3 study to evaluate the long-term safety and efficacy of flexibly-dosed SPRAVATO plus oral AD in patients with TRD. Mean (median, range) exposure to SPRAVATO was 42.9 months (45.8, range 0-79 months).[3]
- No new safety signals were observed with long-term intermittent dosing of SPRAVATO.[3]
  - The most common AEs (≥20%) were headache, dizziness, nausea, dissociation, nasopharyngitis, somnolence, dysgeusia, and back pain.[3]
- Improvement in depressive symptoms were observed and maintained throughout treatment.[3]
  - Overall, 35.6% (162/455) and 49.6% (551/1110) of patients were in remission (MADRS total score ≤12) at the end of IND and OP/M phases, respectively.[3]

**Note:** AD, antidepressant; CI, confidence interval; HR, hazard ratio; IND, induction, MADRS, Montgomery-Åsberg Depression Rating Scale; OP/M, optimization/maintenance; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression.

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## SUSTAIN-1[1]

**Phase 3, Double-blind, Active-controlled, Long-term, Randomized Withdrawal, Maintenance-of-effect Study**

**Study in TRD**

**N = 297**

## Key inclusion criteria[1]

**Direct-entry**

- Age 18-64 years
- Moderate-to-severe nonpsychotic MDD
- Nonresponse to ≥1 but ≤5 ADs in current episode
- IDS-$C_{30}$ score ≥34

**Transfer-entry**

- Achieved response in the 2 short-term studies

## 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]

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

Esketamine nasal spray + New oral AD

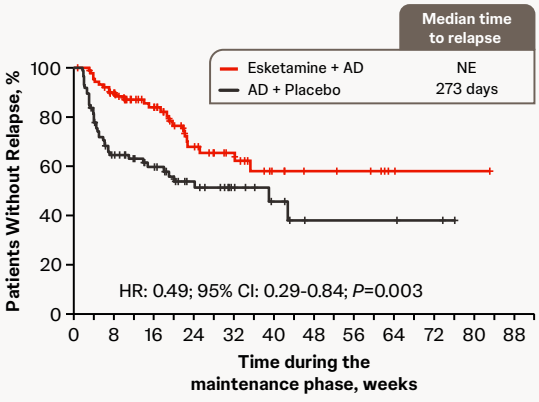
16 weeks IND + optimization → Stable remitters and stable responders → n=152

Stable remitters and stable responders → n=145

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

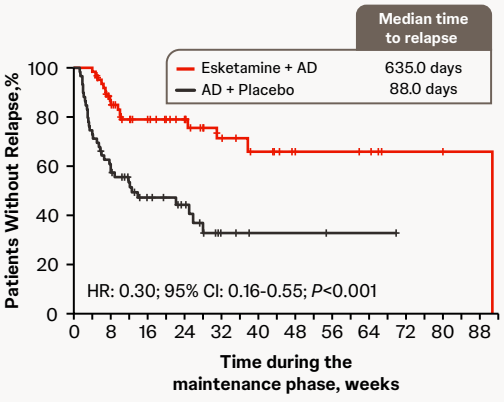
## Primary efficacy endpoint[1]

**SPRAVATO + AD significantly delayed relapse and decreased the risk of relapse by 51% in stable remitters**




## Secondary efficacy endpoint[1]

**SPRAVATO + AD significantly delayed relapse and reduced the risk of relapse by 70% in stable responders**




## Safety[1]

**TEAEs ≥20%**

- Dysgeusia
- Somnolence
- Vertigo
- Dizziness
- Dissociation

- Observed more frequently in the SPRAVATO + AD arm
- Most AEs were **mild to moderate** and generally **resolved** on the same dosing day
- **Treatment discontinuation due to AEs:**
  - 2.6% with SPRAVATO + AD
  - 2.1% with AD + placebo

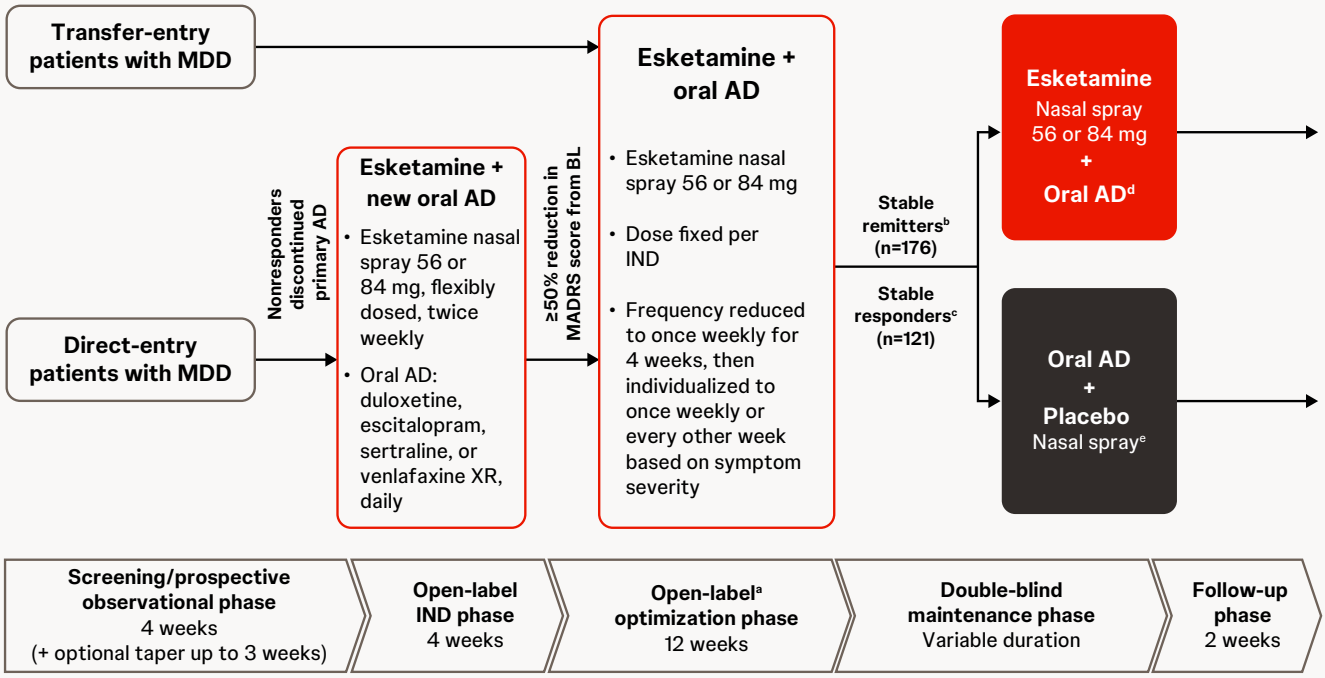
**Note:** AD, antidepressant; AE, adverse event; CI, confidence interval; ECT, electroconvulsive therapy; HR, hazard ratio; IDS-$C_{30}$, Inventory of Depressive Symptomatology-Clinician Rated-30-item; IND, induction; MDD, major depressive disorder; NE, not estimable; OCD, obsessive compulsive disorder; TEAE, treatment-emergent adverse event; XR, extended release.

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- SUSTAIN-1 (NCT02493868) was a phase 3, double-blind, active-controlled, randomized withdrawal, maintenance-of-effect, multicenter study conducted in 99 sites across 16 countries in patients with TRD.[1]




[a]Double-blind for transfer-entry patients (oral AD + either esketamine or placebo).
[b]MADRS score ≤12 for ≥3 of the last 4 weeks, with 1 MADRS score >12 or 1 missing assessment permitted at week 13 or 14.
[c]≥50% reduction in MADRS score from BL in the past 2 weeks, without remission.
[d]Stable remitters, n=90; stable responders, n=62.
[e]Stable remitters, n=86; stable responders, n=59.

**Note:** BL, baseline

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| Inclusion criteria[1] | Exclusion criteria[1] |
|---|---|
| **Direct-entry patients:**<br>• Age 18-64 years<br>• Single-episode (≥2 years) or recurrent MDD, without psychotic features, per DSM-5 and clinical assessment, confirmed by MINI<br>• IDS-$C_{30}$ score ≥34 and MADRS score ≥28<br>• Nonresponse to ≥1 but ≤5 oral ADs of adequate dose, duration, and adherence in current MDD episode, per MGH-ATRQ and documented records, and taking a different oral AD for ≥2 previous weeks at or above the minimum therapeutic dose<br>• Current MDD episode, depression symptom severity, and AD response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment<br><br>**Transfer-entry patients:**<br>• Completed and demonstrated response (≥50% reduction from BL in the MADRS score) after double-blind IND phase from two short-term studies[5,6] | • Homicidal ideation/intent, or suicidal ideation with some intent to act, for ≤6 months, per the investigator's judgment or per C-SSRS or history of suicidal behavior within the past year<br>• Bipolar or related disorders; comorbid OCD; intellectual disability; or borderline, antisocial, histrionic, or narcissistic personality disorder<br>• History of uncontrolled hypertension or certain cardiovascular conditions; seizures; or moderate or severe substance or alcohol use disorder per DSM-5, in the past 6 months<br>• Nonresponse in the current episode to SPRAVATO or ketamine, to all 4 of the oral AD treatment options, or an adequate course of ECT<br>• Received vagal nerve stimulation or deep brain stimulation in the current episode |

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### Primary efficacy endpoint

- Time to relapse among stable remitters during the maintenance phase.[1]
  - Relapse was defined as MADRS score ≥22 for 2 consecutive assessments separated by 5-15 days or hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or any other clinically relevant event suggestive of relapse.[1]
  - Relapse was assessed by a relapse adjudication committee on weeks 1, 2, and 4 during screening and observation and weekly during the IND, optimization, maintenance, and follow-up phases.[1]

### Secondary efficacy endpoint[1]

- Time to relapse among stable responders without remission during the maintenance phase.

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- Demographics and BL characteristics were similar across treatment arms.[1]

| Characteristic | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | SPRAVATO + AD (n=90) | AD + placebo (n=86) | SPRAVATO + AD (n=62) | AD + placebo (n=59) |
| Age, years, mean (SD) | 45.4 (12.12) | 46.2 (11.16) | 47.2 (11.00) | 46.7 (9.76) |
| Sex, female, n (%) | 58 (64.4) | 59 (68.6) | 38 (61.3) | 42 (71.2) |
| Race, n (%) | | | | |
| Black | 4 (4.4) | 6 (7.0) | 2 (3.2) | 1 (1.7) |
| White | 80 (88.9) | 76 (88.4) | 57 (91.9) | 55 (93.2) |
| Other | 3 (3.3) | 2 (2.3) | 3 (4.8) | 3 (5.1) |
| Duration of current episode, weeks, mean (SD) | 112.2 (171.30) | 110.5 (147.41) | 121.6 (193.85) | 141.8 (254.43) |
| MADRS score, mean (SD) | 37.4 (5.20) | 37.6 (4.66) | 40.1 (5.56) | 38.9 (4.92) |
| Number of previous AD medications, n (%) | | | | |
| ≤2 | 71 (78.9) | 62 (73.8) | 41 (66.1) | 34 (57.6) |
| >2 | 19 (21.1) | 22 (26.2) | 21 (33.9) | 25 (42.4) |
| Class of oral AD, n (%) | | | | |
| SNRI | 62 (68.9) | 58 (67.4) | 35 (56.5) | 36 (61.0) |
| SSRI | 28 (31.1) | 28 (32.6) | 27 (43.5) | 23 (39.0) |

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## Treatment exposure[1]

- The median exposure to the study drug was as follows:

| Median study drug exposure, weeks | SPRAVATO + AD | AD + placebo |
|---|---|---|
| Stable remitters[a] | 17.7 | 10.2 |
| Stable responders[b] | 19.4 | 10.1 |

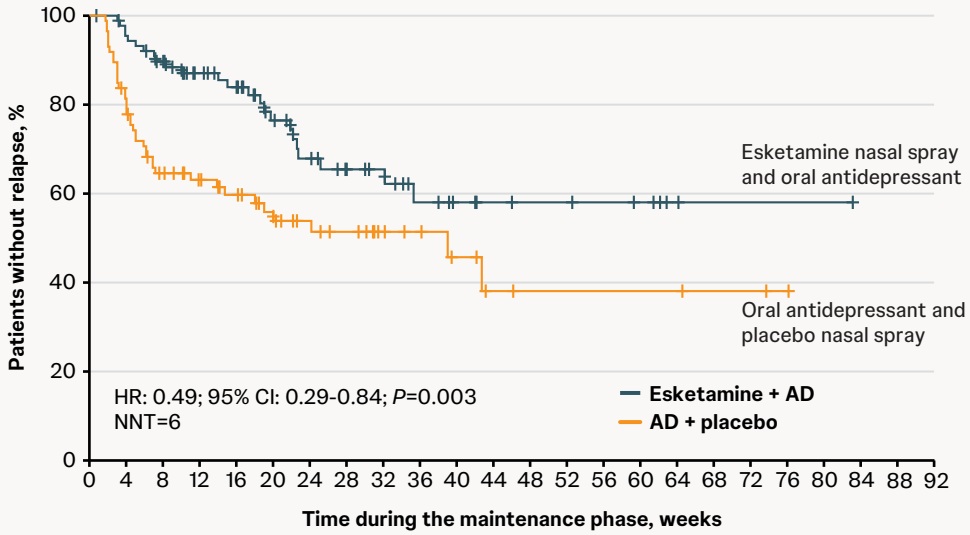
[a]Stable remission was defined as an MADRS score ≤12 for ≥3 of the last 4 weeks, with 1 MADRS score >12 or 1 missing assessment permitted at week 13 or 14.
[b]Stable response was defined as a ≥50% reduction in MADRS score from BL in the past 2 weeks, without remission.

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- Among stable remitters,[a] SPRAVATO + AD significantly delayed relapse compared to AD + placebo and reduced the risk of relapse by 51%.[1]




**No. at risk**

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esketamine + AD | 90 | 84 | 74 | 58 | 53 | 39 | 31 | 25 | 20 | 14 | 10 | 8 | 7 | 7 | 6 | 5 | 2 | 1 | 1 | 1 | 0 |
| AD + placebo | 86 | 69 | 52 | 41 | 34 | 28 | 22 | 19 | 12 | 10 | 7 | 4 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 1 | 0 | 0 |


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- Among stable remitters, 26.7% (24/90) of patients in the SPRAVATO + AD group and 45.3% (39/86) in the AD + placebo group relapsed; hospitalization was the reason for relapse in 12.5% (3/24) and 0% of patients in the 2 groups, respectively.[9]

**Censored patients – discontinuation (maintenance phase)**

[a]Stable remission was defined as MADRS score ≤12 for ≥3 of the last 4 weeks, with 1 MADRS score >12 or 1 missing assessment permitted at week 13 or 14.

## Censored patients – discontinuation (maintenance phase)

- Censoring was done for patients who remained relapse free at the end of the study (after the defined number of relapse events occurred) or who withdrew early without relapse in the maintenance phase.[1]
- Thirteen patients (stable remission, n=8; stable response, n=5) in the SPRAVATO + AD group and 12 patients (stable remission, n=9; stable response, n=3) in the AD + placebo group were censored because they discontinued the maintenance phase before having a relapse and before the end of the study.[1]
- Treatment withdrawal in the maintenance phase was due to[9]:

| SPRAVATO + AD | AD + placebo |
|---|---|
| • Withdrawal by subject, n=5<br>• Other, n=4<br>• AE, n=1<br>• Lost to follow-up, n=1<br>• Pregnancy, n=1<br>• Protocol violation, n=1 | • Other, n=5<br>• Withdrawal by subject, n=4<br>• AE, n=2<br>• Noncompliance with study drug, n=1 |

AD, antidepressant; AE, adverse event.

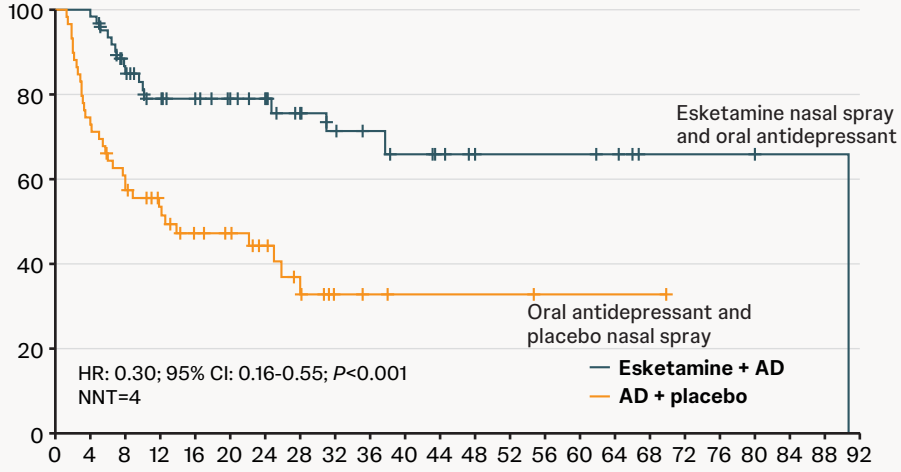
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## Secondary efficacy endpoint[1]

- Among stable responders,[a] SPRAVATO + AD significantly delayed relapse compared to AD + placebo and reduced the risk of relapse by 70%; among the 50 patients who relapsed, there were no hospitalizations in either group.[1,9]
- There were fewer relapse events in stable responders (n=16) vs stable remitters[b] (n=24) who stayed on SPRAVATO + AD; however, the percentage of relapses was similar (25.8% vs 26.7%, respectively) between the groups.[1]
- A higher percentage of relapse events was noted in stable responders vs stable remitters who discontinued SPRAVATO and switched to placebo nasal spray (57.6% vs 45.3%); this is believed to be because this patient population was more vulnerable to relapse due to the fact that they had not achieved stable remission.[1,4]




**No. at risk**

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esketamine + AD | 62 | 62 | 49 | 38 | 35 | 31 | 26 | 20 | 15 | 13 | 11 | 9 | 7 | 6 | 6 | 6 | 5 | 2 | 2 | 2 | 2 | 1 | 1 | 0 |
| AD + placebo | 59 | 44 | 35 | 26 | 19 | 17 | 13 | 9 | 4 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |


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[a]Stable response was defined as a ≥50% reduction in MADRS score from BL in the past 2 weeks, without remission.
[b]Stable remission was defined as an MADRS score ≤12 for ≥3 of the last 4 weeks, with 1 MADRS score >12 or 1 missing assessment permitted at week 13 or 14.
[c]The median time to relapse for SPRAVATO + AD should be interpreted with caution, as it is influenced by a single patient who participated in the maintenance phase beyond week 88 and relapsed prior to the end of the study.

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- The **most common AEs** in the SPRAVATO + AD arm (≥20%) during the maintenance phase included dysgeusia, vertigo, dissociation, somnolence, and dizziness and were more frequent than in the AD + placebo arm.[1]
- Most AEs were **mild to moderate** in severity, observed after dosing, and resolved on the same day.[1]
- No fatal events were reported during the study.[1]
- Study drug-related **SAEs** were reported in 6 patients in the SPRAVATO + AD arm only during the IND phase and included the following:[1]
  - Autonomic nervous system imbalance
  - Disorientation
  - Lacunar stroke
  - Hypothermia
  - Sedation
  - Simple partial seizures
  - Suicidal ideation
- **Treatment discontinuation** due to AEs during the maintenance phase are listed below:[1]
  - **SPRAVATO + AD**: 4 (2.6%) patients discontinued treatment due to worsening depression (n=3), and anxiety and transient confusional state (n=1).
  - **AD + placebo**: 3 (2.1%) patients discontinued treatment due to worsening depression.

**TEAEs in the maintenance phase in ≥10% patients in either treatment arm**

**TEAEs in the maintenance phase in ≥10% patients in either treatment arm[1]**

| Event, n (%) | SPRAVATO + AD (n=152) | AD + placebo (n=145) |
|---|---|---|
| Dysgeusia | 41 (27.0) | 10 (6.9) |
| Vertigo | 38 (25.0) | 8 (5.5) |
| Dissociation | 35 (23.0) | 0 |
| Somnolence | 32 (21.1) | 3 (2.1) |
| Dizziness | 31 (20.4) | 7 (4.8) |
| Headache | 27 (17.8) | 14 (9.7) |
| Nausea | 25 (16.4) | 1 (0.7) |
| Vision blurred | 24 (15.8) | 1 (0.7) |
| Hypoesthesia oral | 20 (13.2) | 0 |

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

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### Transient BP increases[1]

- The increases occurred after SPRAVATO treatment, typically peaked at 40 minutes postdose, and generally returned to the predose range by 1.5 hours postdose.
- Treatment-emergent transient hypertension during maintenance is summarized below:

| BP | SPRAVATO + AD | AD + placebo |
|---|---|---|
| SBP ≥180 mm Hg, n (%) | 1 (0.7) | 0 |
| DBP ≥110 mm Hg, n (%) | 2 (1.3) | 0 |

### Suicidal ideation[1]

- The proportion of patients who reported no suicidal ideation or behavior at BL (C-SSRS score=0) and a higher post-BL C-SSRS score of ≥1 is summarized below:

| Higher post-BL C-SSRS score of ≥1, n (%) | SPRAVATO + AD | AD + placebo |
|---|---|---|
| IND phase | 42 (11.6) | - |
| Optimization phase | 22 (5.7) | - |
| Maintenance phase | 3 (2.4) | 6 (4.5) |

- Patients experiencing relapse did not have a significant elevation in C-SSRS scores.
- Treatment-emergent suicidal behavior was not observed in either arm.

### Present-state dissociative symptoms[1]

- Per the CADSS, symptoms were observed shortly after the SPRAVATO dose, peaked at 40 minutes, generally resolved by 1.5 hours postdose, and attenuated with repeated dosing.
- Events or symptoms of psychosis were not observed.

### Withdrawal syndrome[1]

- Per the PWC-20, no evidence of a distinct withdrawal syndrome was observed during the 2 weeks following SPRAVATO cessation.

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## SUSTAIN-2[2]

**Phase 3, open-label, multicenter, long-term (up to 1 year exposure) study**

**Study in TRD**

**N=802**

## Key inclusion criteria[2]

**Direct-entry**
- Age ≥18 years
- DSM-5 diagnosis of MDD without psychotic features
- MADRS total score ≥22 at screening
- Nonresponse to ≥2 oral ADs (via the MGH-ATRQ)

**Transfer-entry**
- Completed double-blind IND phase of an acute study of elderly patients with TRD

## Key exclusion critria[2]

- Homicidal or suicidal ideation
- Borderline, antisocial, histrionic, or narcissistic personality disorder
- Bipolar disorder or OCD
- Nonresponse to all 4 study ADs or SPRAVATO or ketamine
- Clinically significant CVD or uncontrolled hypertension
- Substance or alcohol abuse

## Study design[2]

Direct-Entry Patients (n=691) | Transfer-Entry Nonresponders (n=88)

Transfer-Entry Responders (n=23)

Open-label IND (4 Weeks) (n=779)

Open-label OP/M (48 Weeks) (n=603)

**Esketamine** flexibly dosed, twice weekly (28, 56, or 84 mg based on age)
+
**Oral AD** (duloxetine, escitalopram, sertraline, or venlafaxine XR)

Transfer-entry patients continued same AD

Responders (n=580) →

**Esketamine Transfer entry:** 28 mg (week 5) → 56 or 84 mg until week 8. Treatment reduced to weekly for 4 weeks, then weekly or every other week
+
**Oral AD**

## Safety endpoint[2]

**TEAEs during the IND + OP/M phases**

- **≥1 TEAE:** 90.1%
  - Most TEAEs were **mild or moderate** and **resolved** on the day of dosing
- TEAEs in ≥10% of patients:
  - Dizziness
  - Dissociation
  - Nausea
  - Headache
  - Somnolence
  - Dysgeusia
  - Hypoesthesia
  - Vertigo
  - Vomiting
  - Viral URTI
- **≥1 SAE:** 6.9%
- **TEAEs leading to discontinuation** of:
  - SPRAVATO: 9.5%
  - Oral AD: 4.1%
- **Deaths:** 2 (1 doubtfully related to SPRAVATO)

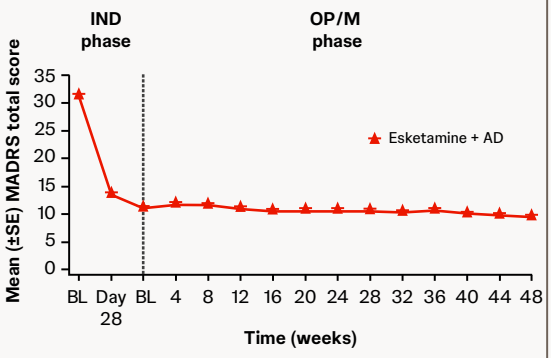
## Other safety outcomes[2]

- Treatment-emergent **dissociative symptoms**, **sedation**, and **BP increases** generally resolved by 1.5 hours postdose
- **Cognitive performance** either improved or remained stable through week 44
- There were no cases of **interstitial or ulcerative cystitis**
- New occurrences of **suicidal ideation:** 14.5%
- **Nasal tolerability** was acceptable

## Efficacy results[2]

- MADRS total score improved throughout the IND phase and was maintained through the OP/M phase

**Mean MADRS total score over time**



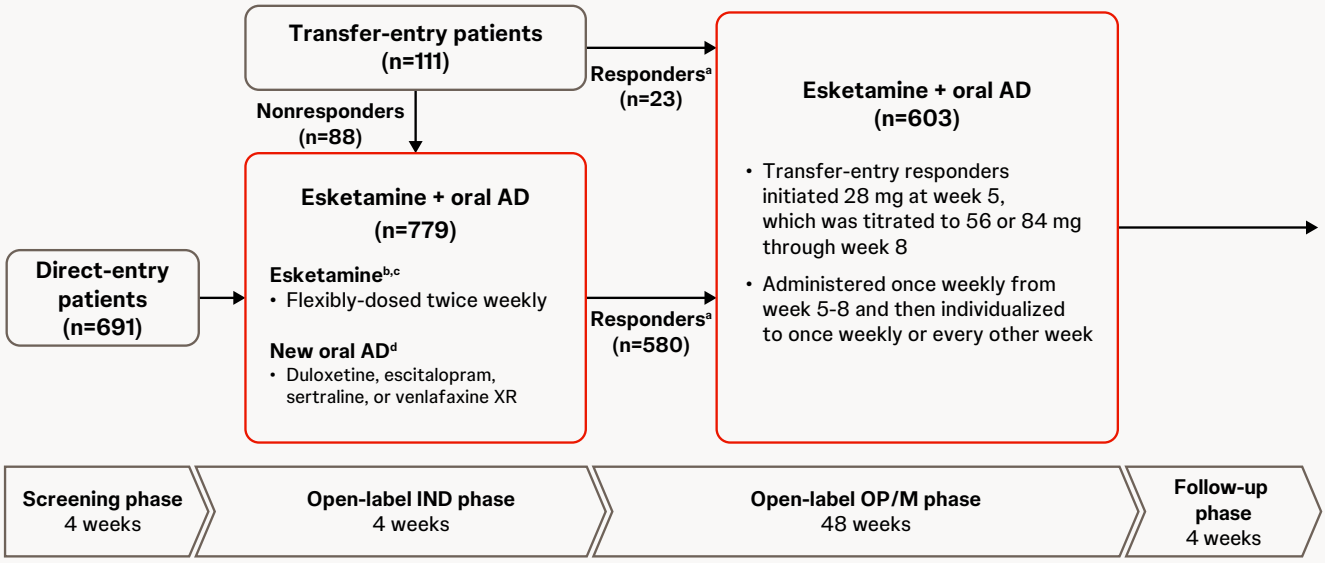

**Note:** AD, antidepressant; CVD, cardiovascular disease; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; IND, induction; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire; OCD, obsessive compulsive disorder; OP/M, optimization/maintenance; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression; URTI, upper respiratory tract infection; XR, extended release.

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- SUSTAIN-2 (NCT02497287) was a phase 3, open-label, multicenter study conducted to evaluate the long-term (up to 1 year of exposure) safety, tolerability, and efficacy of SPRAVATO nasal spray (28, 56, or 84 mg) plus a newly initiated oral AD in patients with TRD.[2]




[a]Response: ≥50% reduction in MADRS total score.
[b]Per protocol, esketamine was not recommended in patients <65 years old with a repeated BP measurement >140/90 mm Hg or in patients ≥65 years old with a repeated BP measurement >150/90 mm Hg. Esketamine was discontinued in patients <65 years old with BP ≥200/120 mm Hg or in patients ≥65 years old with BP ≥190/110 mm Hg.
[c]Dose adjusted based on clinician's judgment. Patients <65 years old received 56 mg esketamine followed by 56 or 84 mg; patients ≥65 years old received 28 mg esketamine followed by 28, 56, or 84 mg.
[d]Transfer-entry patients continued the same AD as in the acute trial.

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| Inclusion criteria[2] | Exclusion criteria[2] |
|---|---|
| **Direct-entry patients:**<br>• Age ≥18 years<br>• DSM-5 diagnosis of MDD without psychotic features<br>• MADRS total score of ≥22 at screening<br>• Nonresponse to ≥2 ADs in the current episode of depression, assessed retrospectively via the MGH-ATRQ and medication records<br><br>**Transfer-entry patients:**<br>• Completed the double-blind IND phase of an acute study of elderly patients with TRD[7]<br>• Aforementioned criteria for direct-entry patients | • History of prior nonresponse to all 4 oral ADs or SPRAVATO or ketamine<br>• Bipolar or related disorders; comorbid OCD; intellectual disability; autism spectrum disorder; or borderline, antisocial, histrionic, or narcissistic personality disorder<br>• Homicidal or suicidal ideation with intent to act within 6 months prior to start of screening, per investigator's judgment or based on C-SSRS<br>• History of moderate or severe substance or alcohol abuse (DSM-5 criteria) within 6 months before screening, except nicotine or caffeine<br>• Clinically significant CVD or history of uncontrolled hypertension or hypertensive crisis |

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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### Safety endpoints[2]

- Assessment of TEAEs throughout the study.
- Assessment of cognitive function at predose BL and specified predose timepoints through computerized cognitive test battery (Cogstate) and HVLT-R.
- Suicidal ideation and behavior measured with C-SSRS, dissociative symptoms scored with CADSS, psychotic and affective symptoms measured with the positive symptom subscale of BPRS+, and sedation using MOAA/S.
- Bladder symptoms monitored using BPIC-SS.
- Potential withdrawal symptoms assessed using PWC-20 (after IND and maintenance endpoints and at weeks 1, 2, and 4 of follow-up).
- Clinical laboratory tests, vital signs assessment, ECG, nasal examination, and nasal symptom questionnaire were evaluated at prespecified timepoints; respiratory and pulse oximetry monitored at each dosing session.

### Efficacy endpoints[2]

- Change in MADRS total score from IND and maintenance BL to endpoint.
- Proportion of responders (≥50% reduction in MADRS total score) and remitters (MADRS total score ≤12).

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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| **Characteristic**[2] | **Enrolled patients (n=802)** |
|---|---|
| Age, years, mean (SD) | 52.2 (13.69) |
| Sex, female, n (%) | 502 (62.6) |
| Race, n (%) | |
| White | 686 (85.5) |
| Asian | 81 (10.1) |
| Black or African American | 15 (1.9) |
| Other | 16 (2.0) |
| Nonresponse to 2 prior ADs, n (%) | 465 (58.0) |
| History of suicidal ideation in past 6 months, n (%) | 215 (26.9) |
| AD use,[a] n (%) | |
| Duloxetine | 251 (31.3) |
| Escitalopram | 237 (29.6) |
| Sertraline | 157 (19.6) |
| Venlafaxine XR | 156 (19.5) |

[a]Number of evaluable patients, n=801.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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- **Median exposure** to SPRAVATO was 22.9 weeks.[2]
- Most TEAEs were **mild or moderate** in intensity, occurred on dosing days, and **resolved** on the same day.[2]

| TEAEs,[a] n (%) | 4-week IND phase (n=779) | 48-week OP/M phase (n=603) | IND and OP/M phases (N=802) |
|---|---|---|---|
| Patients with ≥1 TEAE | 653 (83.8) | 516 (85.6) | 723 (90.1) |
| Patients with ≥1 SAE | 17 (2.2) | 38 (6.3) | 55 (6.9)[b] |
| TEAEs leading to SPRAVATO discontinuation | 53 (6.8) | 23 (3.8) | 76 (9.5) |
| TEAEs leading to oral AD discontinuation | 20 (2.6) | 14 (2.3) | 33 (4.1) |
| **Most common TEAEs (≥10% of patients in the combined phases group)** | | | |
| Dizziness | 228 (29.3) | 135 (22.4) | 264 (32.9) |
| Dissociation | 182 (23.1) | 113 (18.7) | 221 (27.6) |
| Nausea | 157 (20.2) | 84 (13.9) | 201 (25.1) |
| Headache | 137 (17.6) | 114 (18.9) | 200 (24.9) |
| Somnolence | 94 (12.1) | 85 (14.1) | 134 (16.7) |
| Dysgeusia | 77 (9.9) | 54 (9.0) | 95 (11.8) |
| Hypoesthesia | 79 (10.1) | 40 (6.6) | 95 (11.8) |
| Vertigo | 68 (8.7) | 43 (7.1) | 88 (11.0) |
| Vomiting | 56 (7.2) | 45 (7.5) | 87 (10.8) |
| Viral URTI | 19 (2.4) | 70 (11.6) | 82 (10.2) |

[a]All enrolled analysis set (IND and OP/M phases combined): patients who received ≥1 dose of nasal spray study medication or oral AD.
[b]Five SAEs were considered SPRAVATO-related by the investigator: anxiety and delusion (both in 1 patient), delirium (n=1), suicidal ideation (n=1), and suicidal attempt (n=1).

- There were 2 deaths: one considered by investigators to be doubtfully related to SPRAVATO (60-year-old man who died due to acute cardiac and respiratory failure) and the other not considered by investigators to be related to SPRAVATO (suicide-related death in a 55-year-old woman).[2]

**Most common TEAEs leading to discontinuation of SPRAVATO in ≥2 patients**

**Most common TEAEs[a] leading to discontinuation of SPRAVATO in ≥2 patients[2]**

| TEAEs, n (%) | 4-week IND phase (n=779) | 48-week OP/M phase (n=603) | IND and OP/M phases (N=802) |
|---|---|---|---|
| Anxiety | 9 (1.2) | 0 | 9 (1.1) |
| Suicidal ideation | 3 (0.4) | 4 (0.7) | 7 (0.9) |
| Depression | 3 (0.4) | 3 (0.5) | 6 (0.7) |
| Dizziness | 6 (0.8) | 0 | 6 (0.7) |
| BP increased | 4 (0.5) | 2 (0.3) | 6 (0.7) |
| Dissociation | 5 (0.6) | 0 | 5 (0.6) |
| Muscular weakness | 4 (0.5) | 0 | 4 (0.5) |
| Vomiting | 3 (0.4) | 0 | 3 (0.4) |
| Hypertension | 2 (0.3) | 1 (0.2) | 3 (0.4) |
| Suicide attempt | 1 (0.1) | 1 (0.2) | 2 (0.2) |
| Headache | 2 (0.3) | 0 | 2 (0.2) |
| Sedation | 2 (0.3) | 0 | 2 (0.2) |
| Somnolence | 2 (0.3) | 0 | 2 (0.2) |
| Nausea | 2 (0.3) | 0 | 2 (0.2) |
| Vertigo | 1 (0.1) | 1 (0.2) | 2 (0.2) |

[a]TEAE that started in the OP/M phase and resulted in discontinuation in the follow-up phase is counted as treatment-emergent in the OP/M phase.
IND, induction; OP/M, optimization/maintenance; TEAE, treatment-emergent adverse event.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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### Cognitive function[2]

- Group mean performance on all Cogstate and HVLT-R tests either improved or remained stable through week 44 for the entire study population.
- In patients ≥65 years of age, simple and choice RT slowed beginning at week 20 of the OP/M phase.
  - Among patients with RTs at BL that were within age-adjusted norms, 7 showed consistent slowing as the study progressed, and none had impaired RT at study endpoints and follow-up (z score <-1.5 on detection or identification tasks).

### Dissociative symptoms and sedation[2]

- Dissociative and perceptual changes, as measured by CADSS, peaked at 40 minutes postdose and generally resolved by 1.5 hours. The magnitude of change attenuated with repeated dosing.
- Clinically-relevant sedation (MOAA/S score ≤3) occurred in 8.4% of patients in the IND phase and 7.0% of patients in the OP/M phase.
  - The longest period of sedation started at 45 minutes postdose and lasted for 1.5 hours.

### Suicidal ideation[2]

- New occurrences of suicidal ideation and behavior was reported in 114/784 patients (14.5%) using the C-SSRS assessment.
- A total of 8 patients reported suicidal behavior.

### Withdrawal symptoms[2]

- Withdrawal symptoms, measured by the mean (SD) PWC-20, was 7.9 (6.91) at week 1 of follow-up, 8.0 (7.42) at week 2, and 7.7 (7.07) at week 4.
- In patients who discontinued the OP/M phase (n=110), the most common “withdrawal” symptom was fatigue-lethargy/lack of energy (25.0%) at week 1 and insomnia (22.7%) at study end.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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### Renal disorders[2]

- There were no reported cases of interstitial or ulcerative cystitis.
- TEAEs related to renal and urinary system disorders were reported in 136 (17.0%) patients and UTIs were reported in 8.1% of patients. Most cases of urinary symptoms were mild to moderate and resolved within 2 weeks.
- Overall, 14 patients had multiple episodes of BPIC-SS scores >18 (UTI/cystitis, n=6; dysuria and pollakiuria, n=2; history of benign prostate hyperplasia, n=1; signs of UTI on urinalysis, n=3; and no AEs/laboratory changes, n=2).

### Increases in BP[2]

- BP increases were reported 40 minutes postdose and generally returned to near BL values by 1.5 hours.
- Overall, 33 patients (4.1%) experienced SBP ≥180 mm Hg or DBP ≥110 mm Hg; 4 patients were withdrawn from the study due to increased BP.

### Nasal symptoms[2]

- Nasal tolerability was considered acceptable (≥99% of patients had a normal nasal examination).
- Responses to the Nasal Symptom Questionnaire:

| Nasal symptoms, % | IND | OP/M |
|---|---|---|
| Taste disturbance | 10.2 | 11.0 |
| Postnasal drip | 9.9 | 11.0 |
| Stuffy nose | 5.9 | 9.1 |

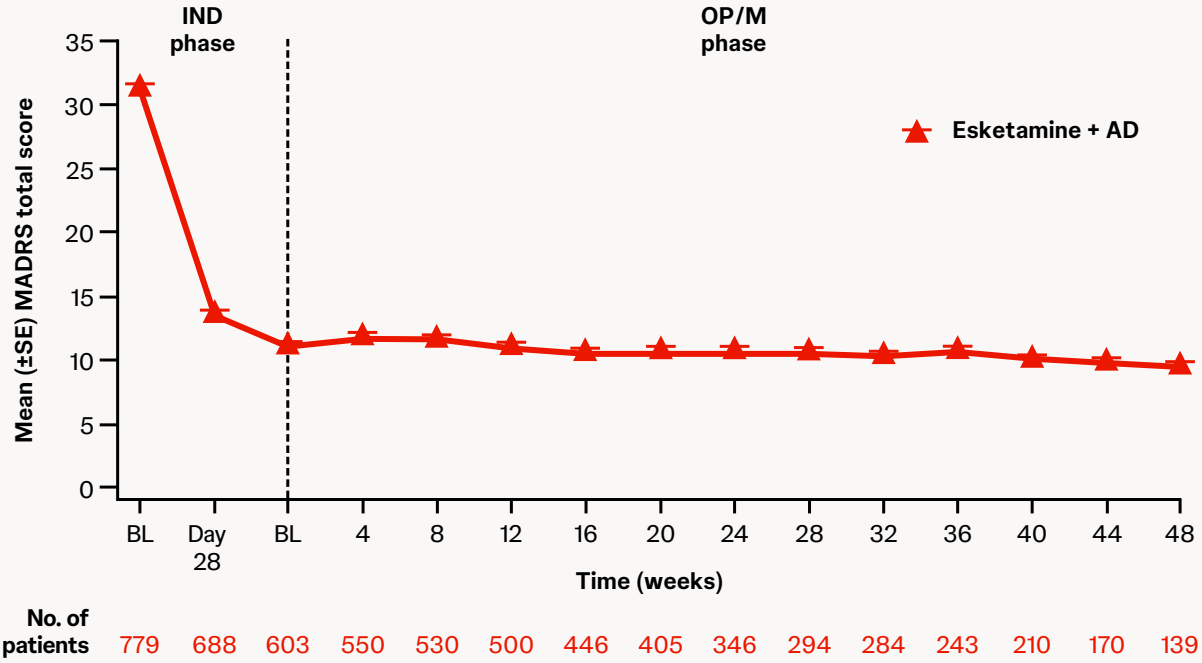
# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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- **MADRS total score** improved throughout the IND phase (mean [SD] change: -16.4 [8.76])and appeared to be maintained from OP/M BL to OP/M endpoint (mean [SD] change: 0.3 [8.12]).[2]

**Mean MADRS total score over time**




Full analysis sets: All patients who received ≥1 dose of esketamine or AD in the open-label IND or OP/M phases.
Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry.* 2020;81(3):19m12891. Copyright 2020. Physicians Postgraduate Press. Adapted by permission.

- The percentage of responders and remitters increased over time during the IND phase.[2]

| Efficacy response | IND | OP/M |
|---|---|---|
| Responders,[a] n/N (%) | 593/756 (78.4) | 461/603 (76.5) |
| Remitters,[b] n/N (%) | 357/756 (47.2) | 351/603 (58.2) |

[a]≥50% reduction in the MADRS total score.
[b]MADRS total score ≤12.

- In a post hoc analysis of SUSTAIN-2, sustained response was observed in 85.4% of patients from weeks 4 to 48 based on MADRS scores (≥50% improvement in total score from IND BL for ≥50% of all nonmissing scheduled visits between weeks 4 and 48 during the OP/M phase) and in 79.6% of patients from weeks 3 to 47 based on PHQ-9 scores (≥50% improvement in total score from IND BL for ≥50% of all nonmissing scheduled visits between weeks 3 and 47 during the OP/M phase).[10]

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# Long-term trials in treatment-resistant depression

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## SUSTAIN-3[3]

**Results from a phase 3, open-label, long-term safety study**

**Study in TRD**

**N=1148**

## Key eligibility criteria[3,8]

- Adults ≥18 years
- Previously participated in 1 of 6 phase 3, "parent" studies of SPRAVATO
  - Parent studies enrolled patients who met the definition of TRD (i.e., nonresponse to an adequate trial of at least 2 antidepressants in the current episode of depression, one of which was observed prospectively)

## Study design[3]

Patients from TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUSTAIN-2, and TRD-3006 (US only)

| Open-label IND (4 Weeks) (n=458) | Open-label OP/M (Variable Duration) (n=1110)[a] |
|---|---|
| **Esketamine** flexibly dosed twice weekly (28[b], 56, or 84 mg) | **Esketamine** (28[b], 56 or 84 mg) weekly, every other week, or every 4 weeks based on CGI-S and tolerability |

[a]690 patients entered directly into the maintenance phase and 420 out of 458 patients came over from the IND phase
[b]Only for patients aged ≥65 years

## Safety outcomes[3]

- Most frequent AEs (≥20% of patients) in SUSTAIN-3:
  - Headache: 36.9%
  - Dizziness: 33.9%
  - Nausea: 33.6%
  - Dissociation: 25.5%
  - Nasopharyngitis: 23.8%
  - Somnolence: 23.1%
  - Dysgeusia: 20.2%
  - Back pain: 20.0%
- SPRAVATO was discontinued in 6.4% of patients due to ≥1 AE.
- SAEs were reported in 18.8% of patients.

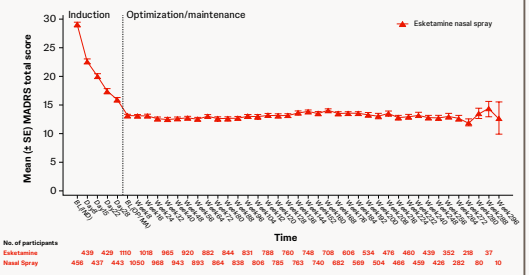
## Other safety outcomes[3]

- Neuropsychiatric events:
  - Overall dissociation: 25.5%
  - Cognition: No change or slight improvement from BL
  - Sedation: 8.2%
- Other AEs:
  - Increased BP: 14.5%
  - UTI: 15.8%
  - Hepatic AEs: 7.9%

## Efficacy results[3]

- MADRS total score improved throughout the IND phase and was maintained through the OP/M phase

**Mean MADRS total score over time**




- Improvements in SDS total score and PHQ-9 score were observed during the IND phase and were maintained through the OP/M phase.

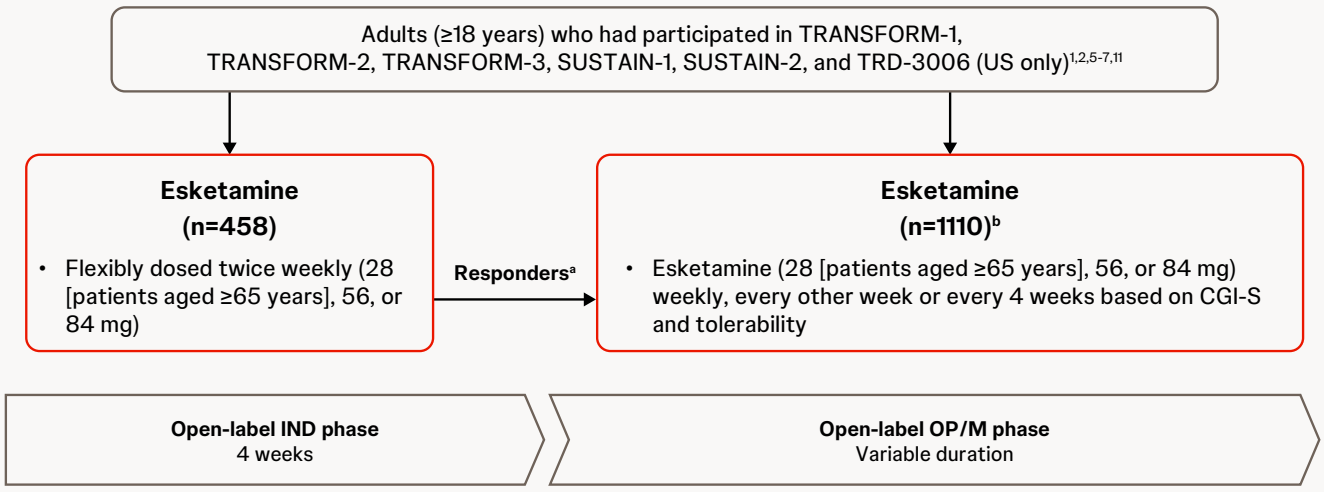
**Note:** CGI-S, Clinical Global Impressions - Severity scale; IND, induction; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OP/M, optimization/maintenance; PHQ-9, Patient Health Questionnaire 9-item; SAE, serious adverse event; SDS, Sheehan Disability Scale; SE, standard error; TEAE, treatment-emergent adverse event; TRD, treatment-resistant depression; US, United States; UTI, urinary tract infection.

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# Long-term trials in treatment-resistant depression

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- SUSTAIN-3 (NCT02782104) was a phase 3, open-label extension study conducted to evaluate the long-term safety and efficacy of individualized, intermittently-dosed SPRAVATO with an oral AD in patients with TRD.[3,8]




[a]Defined as ≥50% improvement from baseline MADRS score.
[b]690 patients entered directly into the maintenance phase and 420 out of 458 patients came over to the maintenance phase from the IND phase.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

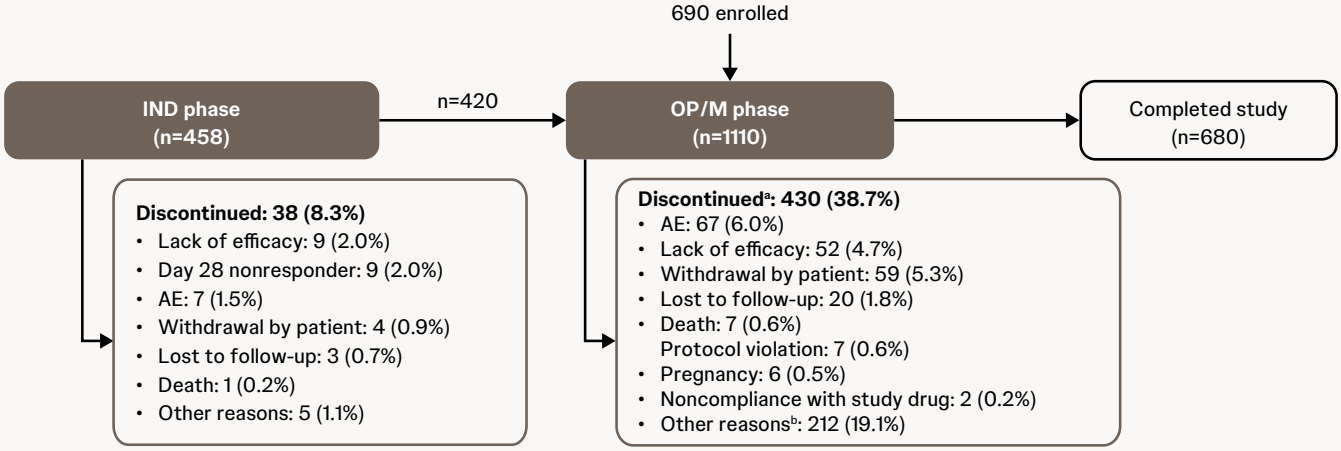
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- 1148 patients with TRD were enrolled in this study.[3]

| Characteristic | SPRAVATO (N=1148) |
|---|---|
| Age, mean (SD), years | 49.6 (12.3) |
| Sex, female, n (%) | 764 (66.6) |
| Race, n (%) | |
| White | 996 (86.8) |
| Black or African American | 45 (3.9) |
| Asian | 45 (3.9) |
| Other | 62 (5.4) |
| Patients with pre-existing hypertension, n (%) | 271 (23.6) |

- The patient disposition has been presented below.[3,8]




[a]Of the 9 patients who died during the IND and OP/M phases, none was considered related to SPRAVATO by the investigator.
[b]Included reasons such as participant/family choice, symptom improvement, relocation, investigator/sponsor decision, employment/school, and personal reasons.

- Mean (median, range) exposure to SPRAVATO was 42.9 months (45.8, range 0-79 months), with the duration of exposure ranging from ≥12 months (in 81.0% of patients), ≥36 months (in 63.4% of patients), to ≥60 months (in 28.0% of patients); total exposure was 3777 cumulative patient-years.[3]

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**Most frequently reported TEAEs (≥10% of patients)[3]**

| TEAEs, n (%) | SPRAVATO (N=1148) |
|---|---|
| Headache | 424 (36.9%) |
| Dizziness | 389 (33.9%) |
| Nausea | 386 (33.6%) |
| Dissociation | 293 (25.5%) |
| Nasopharyngitis | 273 (23.8%) |
| Somnolence | 265 (23.1%) |
| Dysgeusia | 232 (20.2%) |
| Back pain | 230 (20.0%) |
| Anxiety | 214 (18.6%) |
| Vertigo | 213 (18.6%) |
| Arthralgia | 188 (16.4%) |
| Diarrhea | 188 (16.4%) |
| Vomiting | 182 (15.9%) |
| UTI | 181 (15.8%) |
| Increased BP | 166 (14.5%) |
| Insomnia | 162 (14.1%) |
| Fatigue | 157 (13.7%) |
| URTI | 145 (12.6%) |
| COVID-19 | 141 (12.3%) |
| Influenza | 134 (11.7%) |
| Blurred vision | 124 (10.8%) |
| Cough | 118 (10.3%) |
| Hypoesthesia | 116 (10.1%) |

**TEAEs leading to discontinuation of SPRAVATO**

## TEAEs leading to discontinuation of SPRAVATO[3,8]

- Discontinuation of the study drug due to ≥1 AE was reported in 72/1148 (6.3%) patients[a].
- The most common TEAEs (>1 patient) leading to discontinuation of SPRAVATO in the IND and OP/M phases are presented below.

| TEAE, n (%) | SPRAVATO (N=1148) |
|---|---|
| Increased BP | 6 (0.5) |
| Dissociation | 5 (0.4) |
| Anxiety | 3 (0.3) |
| Depression | 3 (0.3) |
| Major depression | 3 (0.3) |
| Mania | 3 (0.3) |
| Fatigue | 2 (0.2) |
| Myocardial infarction | 2 (0.2) |
| Pneumonia | 2 (0.2) |
| Suicidal ideation | 2 (0.2) |
| Vertigo | 2 (0.2) |

[a]Additionally, 2 patients discontinued treatment due to intentional overdose and cholangio carcinoma. Study drug withdrawal was not selected for these 2 patients on the AEs forms, so they were not included in this table.
AE, adverse event; IND, induction; OP/M, optimization/maintenance; TEAE, treatment-emergent adverse event.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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### Dissociation[3]

- Overall, dissociation was reported in 25.5% (293/1148) of patients, and in 10.4% (365/3526) and 4.4% (5720/130,976) of dosing sessions during the IND and OP/M phases, respectively. Of those who experienced dissociation, only a few (0.6%) required concomitant medication(s) for dissociation.
  - In total, 99.8% of cases occurred and resolved on the same day of dosing.
  - No SAEs of dissociation were reported.
  - 5 patients discontinued treatment due to dissociation.

### Cognition[3]

- There were no clinically meaningful changes in cognition over time.
  - In patients aged ≥65 years, performance on tests for verbal and working memory as well as executive function remained stable or showed slight improvement from BL, with increased intraindividual variability.
  - There were small increases in simple and choice RTs during the OP/M phase for patients aged <65 and ≥65 years.

### Sedation[3]

- Overall, sedation was reported in 8.2% of patients (94/1148).
- Most (99.6%) sedation events were reported and resolved on the same dosing day. No SAEs or AEs of sedation resulted in study drug withdrawal.

### MOAA/S score[3]

- The MOAA/S score decreased within 15 minutes after dosing, stabilized between 30 to 45 minutes, and returned to near predose scores within an hour during both the IND and OP/M phases.
- Clinically relevant sedation (MOAA/S score of ≤3; moderate sedation, responds after being called loudly or repeatedly) was observed at least once in 6.1% (28/458) of patients during the IND phase and in 7.2% (80/1110) of patients during the OP/M phase.

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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### Increased BP[3]

- 6.5% of patients experienced either an increased SBP ≥180 mm Hg or DBP ≥110 mm Hg at any point during the study. This rate was higher among patients with a history of hypertension vs those without (SBP ≥180 mm Hg: 6.6% vs 1.5%; DBP ≥110 mm Hg: 9.2% vs 3.6%).
- Overall, TEAEs related to increased BP were reported in 14.5% of patients.
  - Most events (≥95%) occurred and resolved on the same day of dosing.
- An incidence of hypertensive emergency was reported in 1 (0.1%) patient.

### Urinary AEs[3]

- No cases of treatment-related interstitial/ulcerative cystitis were reported.
- UTIs occurred in 15.8% of patients.
- Other renal disorder-related AEs (≥1%) included dysuria (3.0%), cystitis (2.4%), pollakiuria (2.4%), nephrolithiasis (1.7%), micturition urgency (1.5%), urinary incontinence (1.5%), and hematuria (1.3%).

### Hepatic AEs[3]

- Hepatic AEs were reported in 7.9% of patients, the most frequent being elevated GGT (2.5%), elevated ALT (1.9%), elevated hepatic enzyme (1.6%), cases of hepatic steatosis (1.5%), cholelithiasis (1.4%), and elevated AST (1.3%). Three patients discontinued SPRAVATO due to elevated ALT, GGT, and hepatic enzyme (n=1 each).[3,8]

### Oxygen saturation[3]

- Oxygen saturation levels <93% after dosing at ≥2 consecutive assessments were observed in 1.1% of patients during the IND phase and 0.8% during the OP/M phase.
- Additionally, 4 patients (0.3%) reported decreased oxygen saturation as a TEAE; none required concomitant treatment or intervention, and all events were transient, asymptomatic, and resolved spontaneously before discharge during the postdose period.
- No AEs of respiratory depression were observed.

### C-SSRS[3]

- During the IND phase, the percentage of patients reporting no events of suicidal ideation or behavior (C-SSRS score=0) increased from 79.9% at BL to 93.2% at endpoint.
- During the OP/M phase, >90% of patients reported no suicidal ideation or behavior.

# SPRAVATO® (esketamine)
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### SAEs[3]

- SAEs occurred in 18.8% of patients.
- SAEs related to depression and suicidality were reported in 2.0% and 2.4% of patients, respectively.
- Other SAEs (>2 patients) included cholelithiasis (0.9%); COVID-19 (0.8%); pneumonia (0.6%); nephrolithiasis (0.5%); anxiety (0.4%); atrial fibrillation (0.4%); and myocardial infarction, back pain, cellulitis, UTI, intentional overdose, lower limb fracture, headache, cholecystitis, intervertebral disc protrusion, and osteoarthritis (0.3% each).[3,8]
- Most of the SAEs were considered doubtfully related or unrelated to SPRAVATO by the investigators.
- Death was reported in 9 patients (COVID-19 [n=3], pneumonia [n=2], suicide, myocardial infarction, multiple injuries, unknown [n=1 each]); none were considered to be related to SPRAVATO by investigators.

### Discharge readiness[3]

- According to investigators' assessments performed using Clinical Global Assessment of Discharge Readiness, 89% of patients were considered ready to be discharged from the clinic 1.5 hours after dosing at day 25 of the IND phase and 98% at week 276 of the OP/M phase.

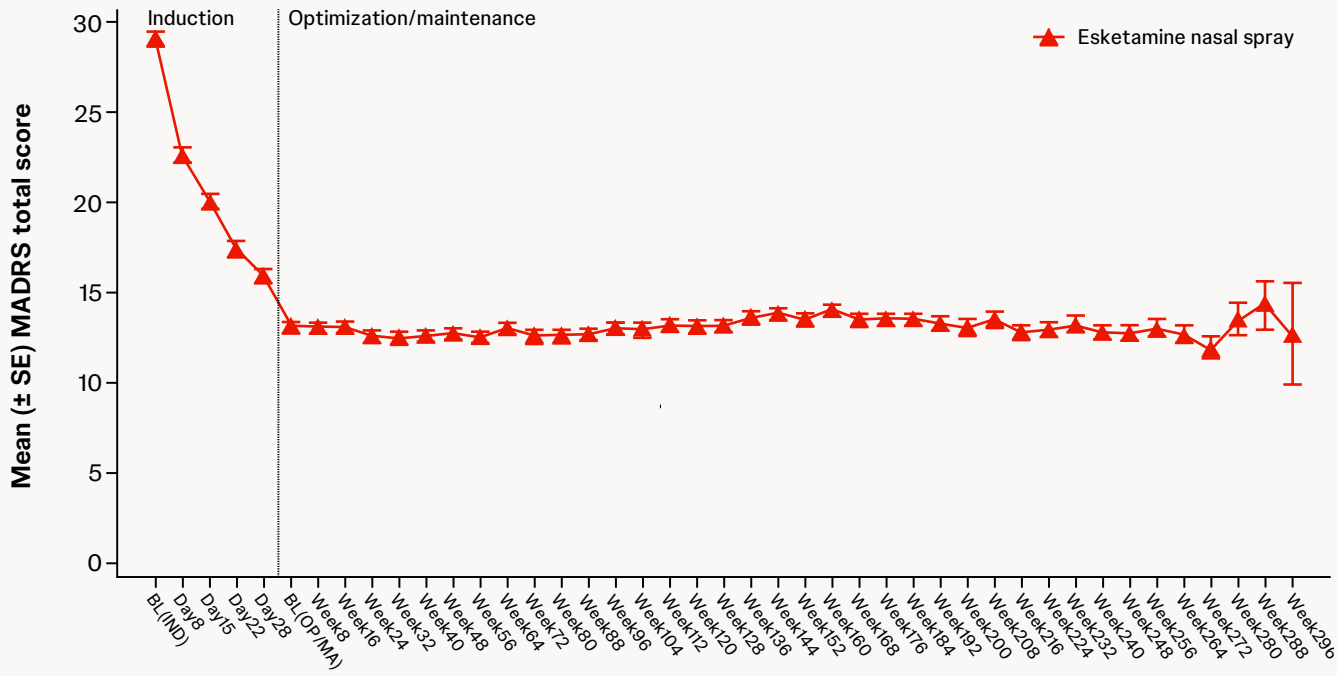
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# Long-term trials in treatment-resistant depression

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- Reduction in the **MADRS total score** was observed during the IND phase and was maintained through OP/M phase (mean [SD] change from BL to the IND phase endpoint, -12.8 [9.73]; to the OP/M phase endpoint, +0.2 [9.93]).[3]

**Mean MADRS total score (observed cases)**




| No. of participants | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Esketamine | 439 | 429 | 1110 | 1018 | 965 | 920 | 882 | 844 | 831 | 788 | 760 | 748 | 708 | 606 | 534 | 476 | 460 | 439 | 352 | 218 | 37 | |
| Nasal spray | 456 | 437 | 443 | 1050 | 968 | 943 | 893 | 864 | 838 | 806 | 785 | 763 | 740 | 682 | 569 | 504 | 466 | 459 | 426 | 282 | 80 | 10 |

Responders from the IND phase of the SUSTAIN-3 study and the parent studies were to enter the OP/M phase.
Poster presented at: Psych Congress; September 6-10, 2023; Nashville, TN.

- During the IND phase, the percentage of **responders** (≥50% reduction in MADRS total score) increased over time from 15.0% (66/439) at day 8 to 49.2% (224/455) at the endpoint of the IND phase.[3]
- **Remission** (MADRS total score ≤12) was reported in 35.6% (162/455) of patients at the IND phase endpoint and in 49.6% (551/1110) at the OP/M phase endpoint.[3]

# SPRAVATO® (esketamine)
# Long-term trials in treatment-resistant depression

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## PHQ-9 score[3]

- A decrease in the PHQ-9 score was observed during the IND phase (mean [SD] change from BL, -5.8 [5.84]), which was maintained during the OP/M phase (mean [SD] change from BL, +0.6 [6.22]).
- The percentage of patients with moderately severe to severe depressive symptoms decreased from a BL value of 56.5% (258/456) to 20.5% (93/454) and 16.2% (180/1110) at IND and OP/M endpoints, respectively.
- The percentage of remitters (PHQ-9 score <5) was 19.8% (90/454) during the IND phase. This increased to 32.2% (253/785) at week 112 and 33.9% (376/1110) at OP/M endpoint.

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## SDS total score[3]

- An improvement in the SDS total score was observed over the course of the IND phase (mean [SD] change from BL, -6.4 [7.13]), which was maintained during the OP/M phase (mean [SD] change from BL, -0.1 [8.35]).
- At IND and OP/M endpoints, the percentage of responders (SDS score ≤4 for each item and total score ≤12) was 44.8% (174/388) and 54.7% (593/1084), respectively.
- At IND and OP/M endpoints, the percentage of remitters (SDS score ≤2 for each item and total score ≤6) was 22.9% (89/388) and 37.0% (401/1084), respectively.

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| | | | |
|---|---|---|---|
| AD | Antidepressant | GGT | Gamma-glutamyl transferase |
| AE | Adverse event | HR | Hazard ratio |
| ALT | Alanine aminotransferase | HVLT-R | Hopkins Verbal Learning Test - Revised |
| AST | Aspartate aminotransferase | IDS-C30 | Inventory of Depressive Symptomatology -Clinician Rated- 30-item |
| BL | Baseline | IND | Induction |
| BP | Blood pressure | MADRS | Montgomery-Åsberg Depression Rating Scale |
| BPIC-SS | Bladder Pain/Interstitial Cystitis Symptom Score | MDD | Major depressive disorder |
| BPRS+ | Brief Psychiatric Rating Scale | MGH-ATRQ | Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire |
| CADSS | Clinician-Assessed Dissociative Symptom Scale | MINI | Mini International Neuropsychiatric Interview |
| CGI-S | Clinical Global Impressions - Severity scale | MOAA/S | Modified Observer's Assessment of Alertness/Sedation |
| CI | Confidence interval | NE | Not estimable |
| COVID-19 | Coronavirus disease 2019 | NNT | Number needed to treat |
| C-SSRS | Columbia - Suicide Severity Rating Scale | OCD | Obsessive compulsive disorder |
| CVD | Cardiovascular disease | OP/M | Optimization/maintenance |
| DBP | Diastolic blood pressure | PHQ-9 | Patient Health Questionnaire 9-Item |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5th Edition | PWC-20 | Physician Withdrawal Checklist, 20-Item |
| ECG | Electrocardiogram | RT | Reaction time |
| ECT | Electroconvulsive therapy | SAE | Serious adverse event |

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| | | | |
|---|---|---|---|
| SBP | Systolic blood pressure | TRD | Treatment-resistant depression |
| SD | Standard deviation | ULN | Upper limit of normal |
| SDS | Sheehan Disability Scale | URTI | Upper respiratory tract infection |
| SE | Standard error | US | United States |
| SNRI | Serotonin-norepinephrine reuptake inhibitor | UTI | Urinary tract infection |
| SSRI | Selective serotonin reuptake inhibitor | XR | Extended release |
| TEAE | Treatment-emergent adverse event | | |

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A literature search of MEDLINE®, BIOSIS®, EMBASE®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 02 March 2026.

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# Long-term trials in treatment-resistant depression

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