Policy Number	**RX501.105**
Policy Effective Date	**5/7/26**

Esketamine Nasal Spray

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association, New England Journal of Medicine, and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

I. Treatment Resistant Depression

Initial Authorization for 3 Months

Esketamine nasal spray (Spravato®) **may be considered medically necessary** when **ALL** of the following conditions are met:

1. Individual is 18 years of age or older; **AND**
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1 in Description) by a structured clinical interview for DSM-5 disorders; **AND**
3. Individual's current depressive episode is moderate or severe depression based on one of the following:
    a. Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 28 (see Policy Guidelines), or
    b. Hamilton Rating Scale for Depression (HAM-D) score ≥ 17 (see Policy Guidelines);
    c. Patient Health Questionnaire 9 (PHQ-9) score ≥ 10 (see Policy Guidelines); or
    d. Quick Inventory of Depressive Symptomatology (QIDS) score ≥ 11 (see Policy Guidelines); **AND**
4. Individual has tried and had an inadequate response to 1 antidepressant agent (i.e., selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, tricyclic antidepressant, bupropion, or mirtazapine). An adequate trial of an antidepressant is defined by the following:

a. The trial length was at least 6 weeks at generally accepted doses, or of sufficient duration as determined by the treating physician at the generally accepted doses; **AND**

5. Individual does not have a current substance use disorder unless in remission (complete abstinence for a month.

Reauthorization

Continuation of treatment with esketamine nasal spray (Spravato) following at least 3 months of use may be reauthorized when **ALL** of the following conditions are met:

1. Individual has had improvement in depression symptoms as evaluated with an appropriate depression rating scale (e.g., MADRS, HAM-D, PHQ-9, QIDS); **AND**
2. Individual does not have a current substance use disorder.

II. Major Depressive Disorder with Acute Suicidal Ideation or Behavior

Esketamine nasal spray **may be considered medically necessary** for a treatment period of 28 days when **ALL** of the following conditions are met:

1. Individual is 18 years of age or older; **AND**
2. Individual with major depressive disorder with acute suicidal ideation or behavior; **AND**
3. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant.

Esketamine nasal spray (Spravato) **is considered experimental, investigational and/or unproven** in all other situations.

Policy Guidelines

1. A treatment session for use of esketamine nasal spray must ensure the following:
   - Treatment is administered under the direct supervision of a healthcare provider.
   - Blood pressure is assessed before and after treatment to ensure safety in accordance with the U.S. Food and Drug Administration label.
   - Individual receiving treatment should be advised to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.
   - Individual receiving treatment should be advised to avoid use of nasal corticosteroid or nasal decongestant 1 hour prior to treatment.
   - Individual is monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the individual is considered clinically stable and ready to leave the healthcare setting.
2. For treatment-resistant depression, the recommended adult dosage of esketamine nasal spray during the induction and maintenance phases are as follows:
   - Induction phase (weeks 1-4): Administer twice per week with day 1 starting dose at 56 mg and subsequent doses at 56 mg or 84 mg. Evidence of therapeutic benefit

should be evaluated at the end of the induction phase to determine need for continued treatment.
    - Maintenance phase (weeks 5-8): Administer once weekly doses at 56 mg or 84 mg. Starting week 9 and after, administer every 2 weeks or once weekly doses at 56 mg or 84 mg. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.
3. For the treatment of adults with major depressive disorder with acute suicidal ideation or behavior, the recommended adult dosage of esketamine nasal spray is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. The use of esketamine nasal spray beyond 4 weeks has not been systematically evaluated.
4. Esketamine nasal spray is contraindicated in individuals with the following conditions:
    - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation.
    - Intracerebral hemorrhage.
    - Hypersensitivity to esketamine, ketamine, or any of the excipients.
5. Esketamine nasal spray has a boxed warning because of 1) risk for sedation and dissociation after administration 2) potential for abuse and misuse. In order to mitigate these risks, it is available only through a restricted program called the Spravato Risk Evaluation and Mitigation Strategy. The essential features of this program include:
    - Esketamine nasal spray is only dispensed and administered to individuals in a medically supervised healthcare setting that monitors these individuals.
    - Pharmacies and healthcare settings that dispense esketamine nasal spray are certified.
    - Ensuring that each individual is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring.
    - Enrollment of all individuals in a registry to further characterize the risks and support safe use.

Montgomery-Asberg Depression Rating Scale

The Montgomery-Asberg Depression Rating Scale is commonly used to evaluate the efficacy of antidepressants by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:

- 0-6: No depression (absence of symptoms)
- 7-19: Mild depression
- 20-34: Moderate depression
- 35-60: Severe depression.

Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression is a 17-item rating scale to determine the severity level of depression in an individual before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal);
- 8-16: Mild depression;
- 17-23: Moderate depression;
- ≥24: Severe depression.

Patient Health Questionnaire 9 (PHQ-9)
PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. (24) There are nine questions, with total scores ranging from 0 to 27, with the score corresponding to the following classifications:
- 0-4: None to minimal depression
- 5-9: Mild depression
- 10-14: Moderate depression
- 15-19: Moderately severe depression
- 20-27: Severe depression

Quick Inventory of Depressive Symptomatology
The 16-item QIDS, derived from the 30-item Inventory of Depressive Symptomatology, is designed to assess the severity of depressive symptoms. (25) Total scores range from 0 to 27, with the score corresponding to the following classifications:
- 0-5: No depression
- 6-10: Mild depression
- 11-15: Moderate depression
- 16-20: Severe depression
- ≥ 21: Very severe depression

Tools for Assessment of Suicidal Ideation/Behavior
There are multiple tools used for assessment of suicidal ideation and behavior. The eligibility criteria in the clinical trials of esketamine required that individuals respond affirmatively to questions B3 (“Think about suicide [killing yourself]?”) and B10 (“Intend to act on thoughts of killing yourself in the past 24 hours?”) on the Mini-International Neuropsychiatric Interview instrument. Other scales that are commonly used to assess suicidal ideation include the Beck Scale for Suicide Ideation and the Columbia-Suicide Severity Rating Scale. SSI is a 19 item clinician-administered scale querying, among other things, the individual's wish to die, wish to live, and the duration and intensity of thoughts of suicide. Each item is rated on a 3-point scale from 0 to 2, with a total score ranging from 0 to 38. The SSI can be administered at initial evaluation and subsequently repeated to assess improvement. C-SSRS characterizes current thoughts of suicide and past suicidal behaviors. It features a clinician-administered initial evaluation form, a “since last visit” version, and a self-report form. It can be used in many settings, including medical, inpatient, and outpatient behavioral health.

Description

Esketamine is the S-isomer of racemic ketamine. Esketamine targets the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor in nerve cells. However, the mechanism by which esketamine exerts its antidepressant effect is unknown. It is currently approved for individuals with treatment-resistant depression as monotherapy or in conjunction with an oral antidepressant or for major depressive disorder with acute suicidal ideation or behavior in conjunction with an oral antidepressant. Treatment-resistant depression is chronic depression that does not improve despite the adequate use of multiple antidepressants. The poor response to multiple antidepressants limits additional treatment options. Individuals with major depressive disorder who have active suicidal ideation with intent constitute a psychiatric emergency as the time between the onset of suicidal ideation and suicide attempt is often very short. While standard antidepressants effectively treat depressive symptomatology, including suicidal ideation, these agents require 4 to 6 weeks to exert their full effect, limiting their utility in crisis situations.

Background

Treatment-Resistant Depression

Patients with either major depressive disorder or bipolar disorder can manifest depressive episodes (Table 1). Patients whose depressive disorder does not respond satisfactorily to adequate treatment have harder-to-treat depression, generally referred to as treatment-resistant depression. (2) Overall, approximately 1 in 3 patients with depression are considered treatment-resistant. (3) While there is no standardized definition of treatment-resistant depression, a generally accepted definition is failure of 2 or more antidepressant treatment attempts with an adequate dose and duration. (4) The majority of systematic reviews and guidelines or consensus statements report that the commonly used definitions were based on treatment of patients whose depression failed to respond (a decrease in depressive severity of at least half) or did not go into remission (complete recovery as measured by a score on a depressive severity instrument below a threshold) following 2 or more treatment attempts of an adequate dose and duration. Experts do not agree on how to define adequate dose and adequate duration, although the minimum duration cited is typically 4 weeks.

Lack of consensus on the definition of treatment-resistant depression limit the ability of systematic reviewers or other experts to synthesize information and generalize treatment-resistant depression findings to the array of patient populations encountered in daily practice. According to the Technology Assessment by the Agency for Healthcare Research and Quality on defining treatment-resistant depression in the Medicare population, the lack of a clear definition for treatment-resistant depression has made translating research findings or systematic reviews into clinical practice guidelines challenging and inconsistent. As a result, guideline definitions of treatment-resistant depression differ, agreement on what constitutes prior treatment adequacy is lacking, and recommended “next step” interventions can diverge. (4)

According to the AHRQ Report, there are no validated, standard diagnostic tools for treatment-resistant depression. Diagnosis of a major depressive episode or bipolar disorder can be made through a standard clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders, International Classification of Diseases, or through a structured clinical assessment tool. Subsequently, treatment history may be elicited by a clinical interview (e.g., the number of prior pharmacologic attempts of adequate dose and duration that did not produce remission) or administering a structured, staging tool (Antidepressant Treatment Response Questionnaire, Thase Rush Staging Model, Massachusetts General Hospital Staging Model, or the Maudsley Staging Model) to confirm treatment resistance. No preferred approach exists and careful history has not been compared directly with a structured tool. (4)

Table 1. Diagnostic Criteria for a Major Depressive Episode

	Criteria (Meet A through E)
A	Five or more symptoms for 2 weeks (1 of which must be either depressed mood or anhedonia): 1. Depressed mood most of the day nearly every day. 2. Anhedonia most of the day nearly every day. 3. Significant weight loss or gain. 4. Insomnia or hypersomnia. 5. Psychomotor agitation or retardation. 6. Fatigue or loss of energy. 7. Feelings of worthlessness or excessive guilt. 8. Diminished ability to think or concentrate; indecisiveness. 9. Recurrent thoughts of death; suicidal ideation or attempt.
B	Symptoms cause clinically significant distress or functional impairment.
C	The episode is not attributable to the physiological effects of a substance or another medical condition.
D	The episode is not better explained by a psychotic illness.
E	There has never been a manic or hypomanic episode.

Adapted from Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatry Association, 2013. (5)

Major Depressive Disorder and Suicidal Ideation/Behavior

In a community survey conducted in 21 countries with over 100,000 individuals by the World Health Organization, the 12-month prevalence of suicidal ideation (thoughts) was approximately 2%, (6) and the lifetime prevalence was 9%. (7) Approximately 12.8 million US adults have had serious thoughts of suicide in the past year. (8) Psychiatric illness is strongly associated with risk of suicide, (9) and major depressive disorder is the psychiatric diagnosis most commonly associated with suicide. (10) The reported prevalence of suicidal ideation in adult patients with major depressive disorder is as high as 60%, and the lifetime

incidence of attempted suicide in this population ranges between 10% and 20%. (11, 12) Further, the lifetime risk of completed suicide has been estimated to be 3.4% in this population. (13)

Patients with major depressive disorder who have active suicidal ideation with intent constitute a psychiatric emergency as the time between the onset of suicidal ideation and suicide attempt is often very short. (14) These patients are often hospitalized to protect them from self-harm, although the benefits of hospitalization are often temporary. Moreover, while standard antidepressants effectively treat depressive symptomatology, including suicidal ideation, (15) they require 4 to 6 weeks to exert their full effect, (16, 17) limiting their utility in crisis situations.

Current Treatment

Prior to the approval of esketamine, olanzapine-fluoxetine combination was the only U.S. Food and Drug Administration (FDA)-approved drug for treatment-resistant depression. The strategy for managing treatment-resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics). (18, 3) Modification strategies include use of higher doses, switching to a new antidepressant, or adding on to an existing therapy. The adequate duration of antidepressant therapy is usually a minimum of 6 weeks. An additional 4 to 6 weeks may be required for patients who show a partial response. (19)

Patients with long-standing treatment-resistant depression who do not benefit from treatment modification or augmentation strategies are referred to as having refractory depression. For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, or vagus nerve stimulation techniques have been used with limited success. (20, 21) Depression-focused psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy for refractory depression. Off-label treatments include: drugs from multiple classes (antipsychotics, lithium, thyroid hormone, ketamine), often in combination with antidepressants.

Regulatory Status

On March 6, 2019, esketamine (Spravato) nasal spray was approved by the FDA for the treatment of treatment-resistant depression in adults in conjunction with an oral antidepressant.

On July 31, 2020, esketamine (Spravato) nasal spray received an approval for a supplemental indication for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior in conjunction with an oral antidepressant.

In January 2025, esketamine (Spravato) nasal spray received expanded FDA approval as monotherapy for treatment-resistant depression in adults.

Rationale

This policy is based on the U.S. Food and Drug Administration labeled indications for Esketamine (Spravato) and a review of relevant professional guidelines and position statements.

Esketamine (Spravato) (1)

Treatment-Resistant Depression

Short-Term Study

Spravato was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), Phase 3 study (Study 1; NCT02418585) in adult patients 18 to <65 years old with treatment-resistant depression. Patients in Study 1 met DSM-5 criteria for major depressive disorder and in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients in Study 1 were randomized to receive twice weekly doses of intranasal Spravato (flexible dose; 56 mg or 84 mg) or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (duloxetine, escitalopram, sertraline, or extended-release venlafaxine as determined by the investigator based on patient's prior treatment history). Spravato could be titrated up to 84 mg starting with the second dose based on investigator discretion.

The demographic and baseline disease characteristics of patients in Study 1 were similar for the Spravato and placebo nasal spray groups. Patients had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. The newly initiated oral AD was an SSRI in 32% of patients and an SNRI in 68% of patients.

In Study 1, the primary efficacy measure was change from baseline in the Montgomery-Åsberg Depression Rating Scale total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. Spravato plus a newly initiated oral AD demonstrated statistical superiority
on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral AD (see Table 2).

Table 2. Primary Efficacy Results for Change from Baseline in MADRS Total Score at Week 4 in Patients with TRD in Study 1

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from	LS Mean Difference (95% CI)[a]

			Baseline to end of Week 4	
Spravato (56 mg or 84 mg) + Oral AD[b]	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	-

AD: antidepressant; CI: confidence interval; LS Mean: least-squares mean; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation; SE: standard error; TRD: treatment resistant depression.

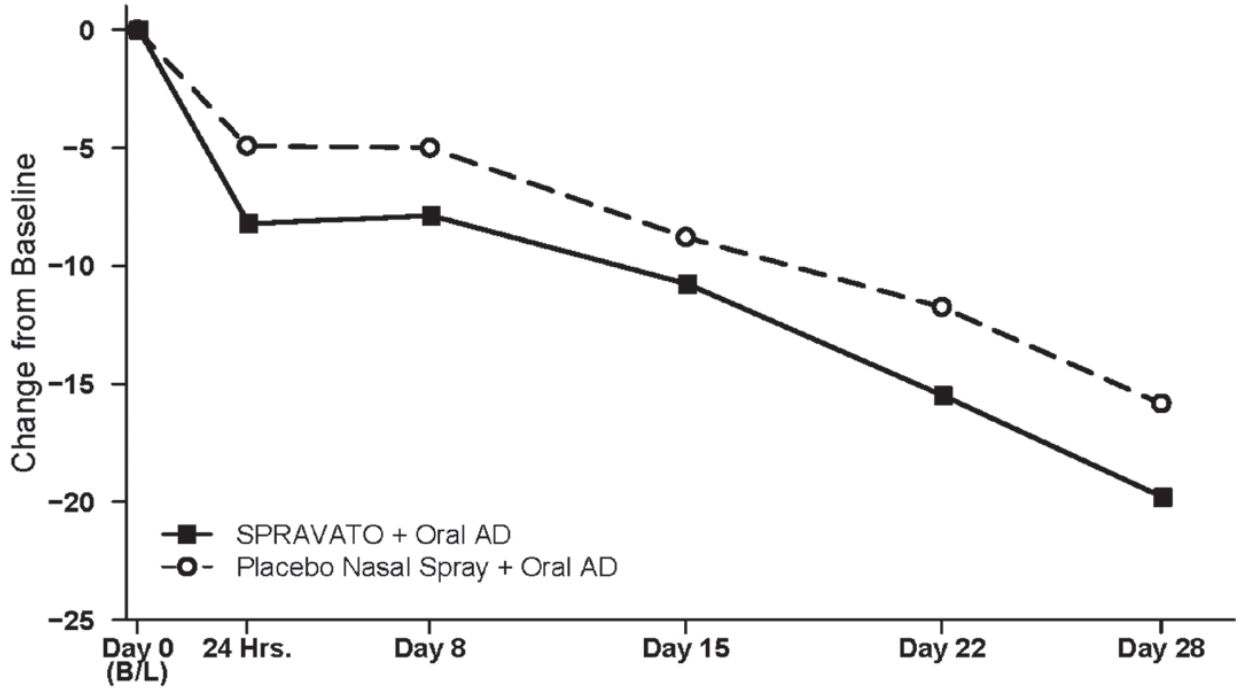
[a] Difference (Spravato + oral AD minus placebo nasal spray + oral AD) in least-squares mean change from baseline.

[b] Spravato + oral AD was statistically significantly superior to placebo nasal spray + oral AD.

Time Course of Treatment Response

Figure 1 shows the time course of response for the primary efficacy measure in Study 1. Most of Spravato's treatment difference compared to placebo was observed at 24 hours. Between 24 hours and Day 28, both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 28. At Day 28, 67% of the patients randomized to Spravato were receiving 84 mg twice weekly.

Figure 1. Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1[a] (Full Analysis Set)



[a] 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.

Treatment-Resistant Depression: Long-term Study

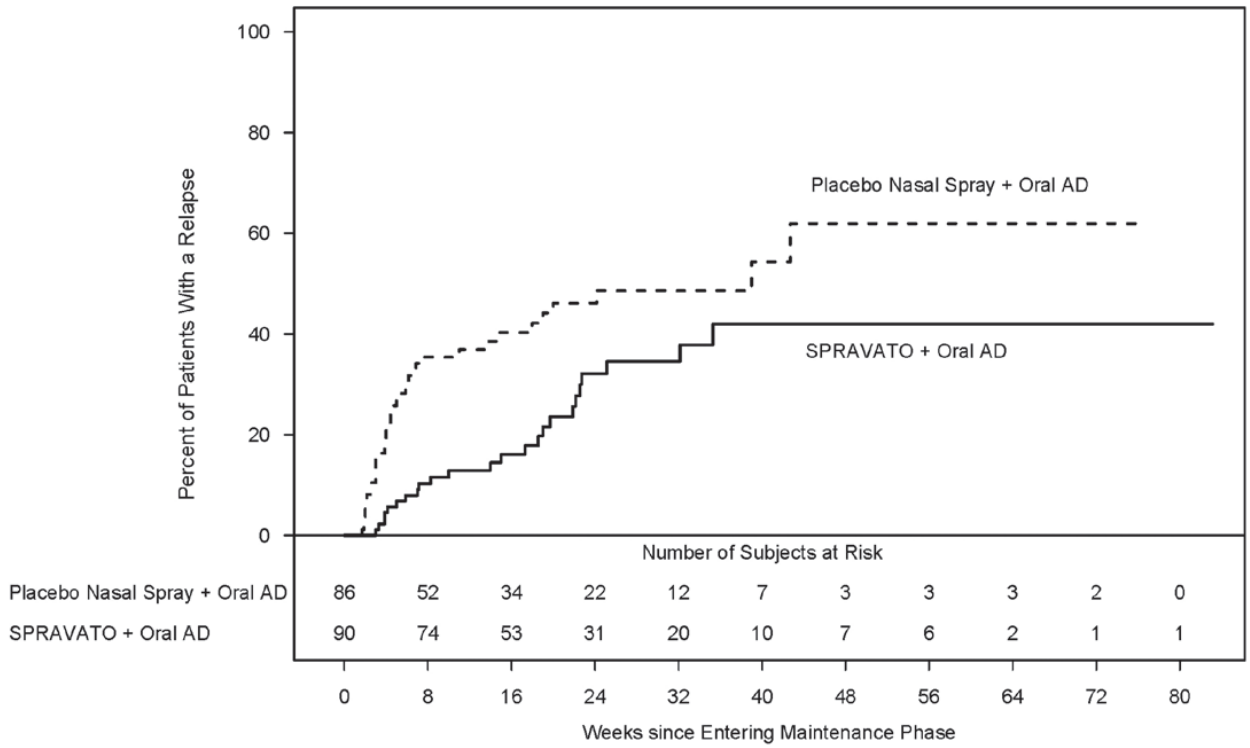
Study 2 (NCT02493868) was a long-term randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to Spravato. Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly-dosed Spravato (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase.

Stable remission was defined as a MADRS total score ≤ 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction ≥ 50% for the last 2 weeks of optimization and not in remission. After at least 16 initial weeks of treatment with Spravato and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with Spravato or switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

The demographic and baseline disease characteristics of the two groups were similar. Patients had a median age of 48 years (range 19 to 64 years) and were 66% female, 90% Caucasian, and 4% Black.

Patients in stable remission who continued treatment with Spravato plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (see Figure 2).

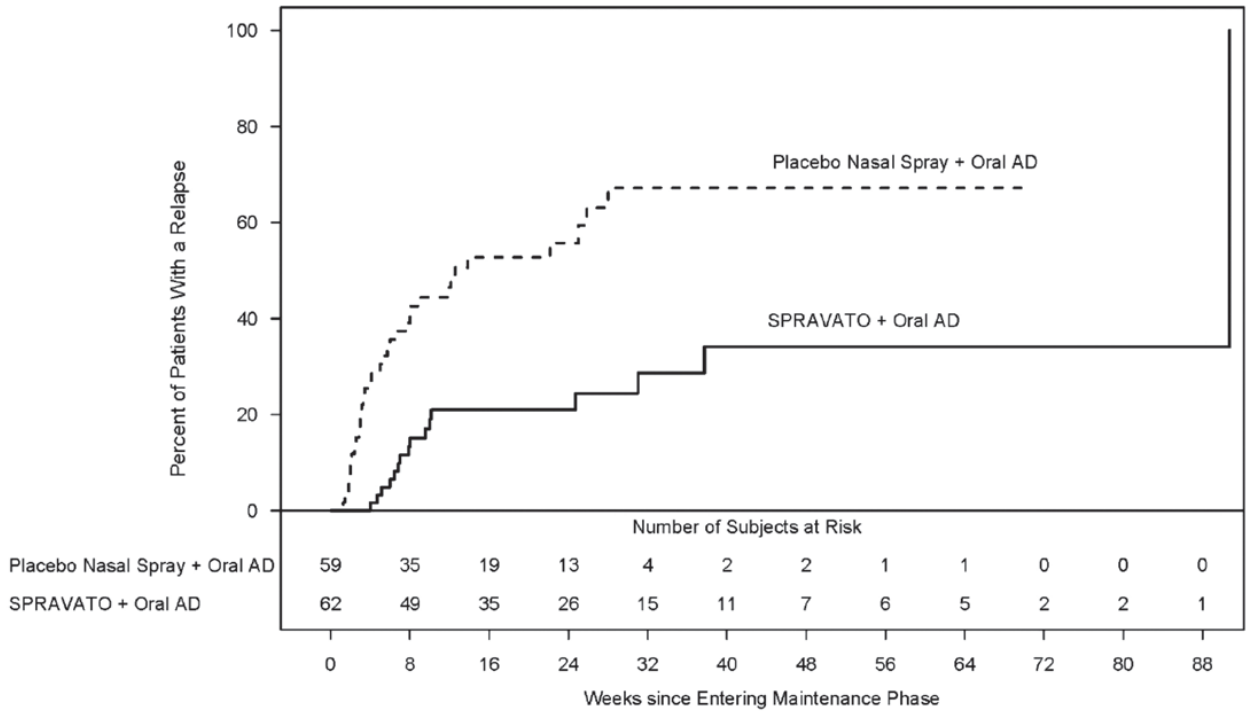
Figure 2. Time to Relapse in Patients with TRD in Stable Remission in Study 2[a] (Full Analysis Set)



[a] Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on weighted estimates was 0.49 (95% CI: 0.29, 0.84). However, the hazard ratio did not appear constant throughout the trial.

Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time to relapse of depressive symptoms than patients on placebo nasal spray plus oral AD (see Figure 3).

Figure 3. Time to Relapse in Patients in Stable Response in Patients with TRD in Study 2[a] (Full Analysis Set)



[a] Note: The estimated hazard ratio (95% CI) of Spravato + Oral AD relative to Placebo nasal spray + Oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55).

In Study 2, based on depressive symptomatology, the majority of stable remitters (69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remitters received weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to Spravato, 39% received the 56 mg dose and 61% received the 84 mg dose.

Monotherapy Study

Spravato was evaluated in a randomized, double-blind, placebo-controlled, multicenter study (Study 3; NCT04599855) in adult patients with treatment resistant depression (TRD) to evaluate the efficacy, safety, and tolerability of Spravato nasal spray, 56 mg and 84 mg, administered as monotherapy. Patients in Study 3 met DSM-5 criteria for major depressive disorder (MDD) and in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments if applicable, patients in Study 3 were randomized in a 1:1:2 ratio to receive twice weekly doses of intranasal Spravato 56 mg or 84 mg or intranasal placebo for four weeks.

The demographic and baseline disease characteristics of patients in Study 3 were similar for the Spravato and placebo nasal spray groups. Patients had a median age of 46 years (range 19 to 76 years) and were 61% female, 87% Caucasian, and 7% Black.

In Study 3, the primary efficacy measure was change from baseline in the total score at Day 28. Spravato 56 mg and 84 mg monotherapy demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray (see Table 3).

Table 3. Primary Efficacy Results for Change From Baseline in MADRS Total Score at Day 28 in Patients with TRD in Study 3

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from Baseline at Day 28	LS Mean Difference (95% CI)[a]
Spravato (56 mg)[b]	86	37.5 (5.2)	-11.4 (1.2)	-5.1 (-7.9; -2.3)
Spravato (84 mg)[b]	95	36.6 (4.5)	-13.0 (1.2)	-6.8 (-9.5; -4.1)
Placebo nasal spray	197	37.5 (4.9)	-6.3 (0.8)	-

CI: confidence interval; LS Mean: least-squares mean; SD: standard deviation; SE: standard error; MADRS: Montgomery-Åsberg Depression Rating Scale; TRD: treatment-resistant depression.

[a] Difference (SPRAVATO minus Placebo nasal spray) in least-squares mean change from baseline.

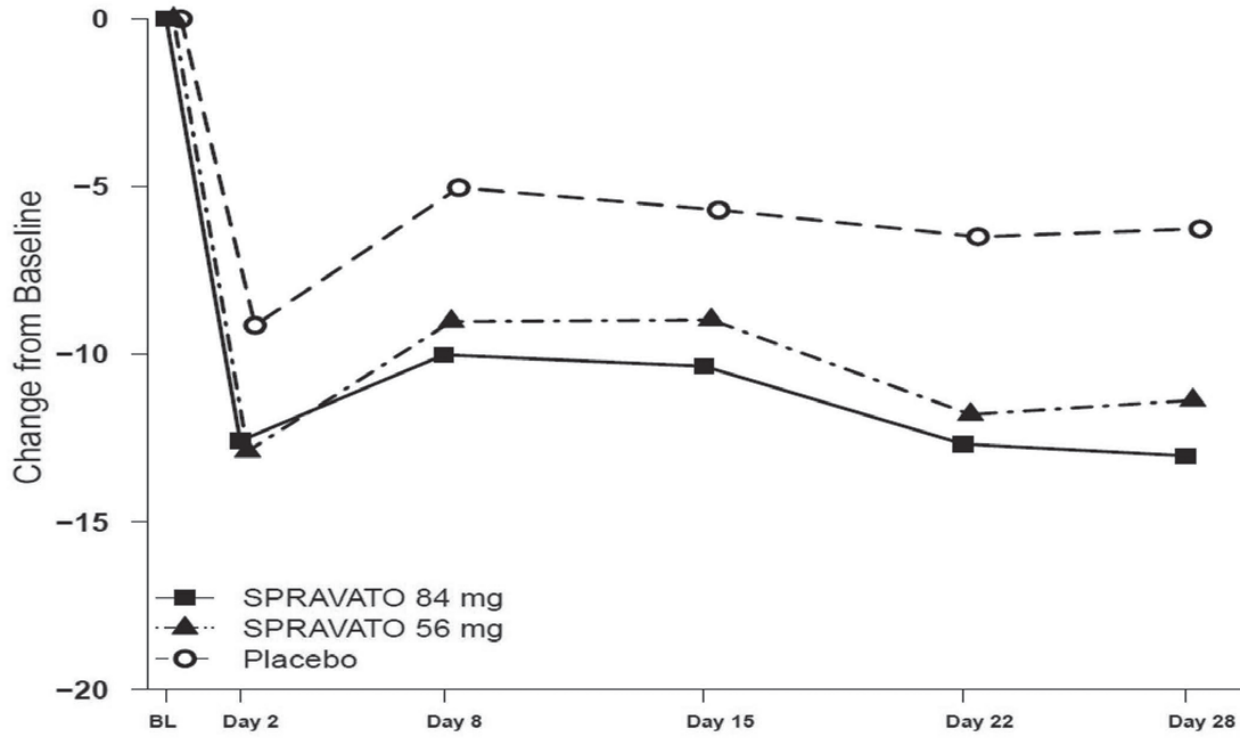
[b] SPRAVATO monotherapy is statistically significantly superior to placebo nasal spray.

In Study 3 the key secondary endpoint was change from baseline to Day 2 (approximately 24 hours) in the MADRS total score. The improvement at Day 2 by Spravato 56 mg and 84 mg monotherapy demonstrated statistical superiority when compared to placebo nasal spray.

Time Course of Treatment Response

Figure 4 shows the time course of response for the primary efficacy measure in Study 3. The effect of Spravato (56 mg and 84 mg) was observed at Day 2 (approximately 24 hours) and remained through Day 28.

Figure 4. Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 3 (Full Analysis Set)



Depressive Symptoms in Patients with Major Depressive Disorder with Acute Suicidal Ideation or Behavior

Spravato was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Study 4 (NCT03039192) and Study 5 (NCT03097133), in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, patients received treatment with Spravato 84 mg or placebo nasal spray twice-weekly for 4 weeks. After the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD) (AD monotherapy or AD plus augmentation therapy) as determined by the investigator. After completion of the 4-week treatment period with Spravato/ placebo, study follow-up continued through Day 90.

The baseline demographic and disease characteristics of patients in Study 4 and Study 5 were similar between the Spravato plus standard of care or placebo nasal spray plus standard of care treatment groups. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation therapy, and 6% received both AD monotherapy/AD plus augmentation therapy.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In Study 4 and Study 5, Spravato plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care (see Table 4).

Table 4. Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies 4 and 5)

Study No.	Treatment Group[a]	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline to 24 hr Post First Dose (SE)	LS Mean Difference (95% CI)[b]
Study 4	Spravato 84 mg + SOC[c]	111	41.5 (5.87)	-15.9 (1.04)	-3.8 (-6.56; -1.09)
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.0 (1.02)	-
Study 5	Spravato 84 mg + SOC[c]	113	39.4 (5.21)	-16.0 (1.02)	-3.9 (-6.60; -1.11)
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.2 (1.05)	-

CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation; SE: standard error; SOC: standard of care.

[a] SOC treatment included an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (antidepressant monotherapy or antidepressant monotherapy plus augmentation therapy).

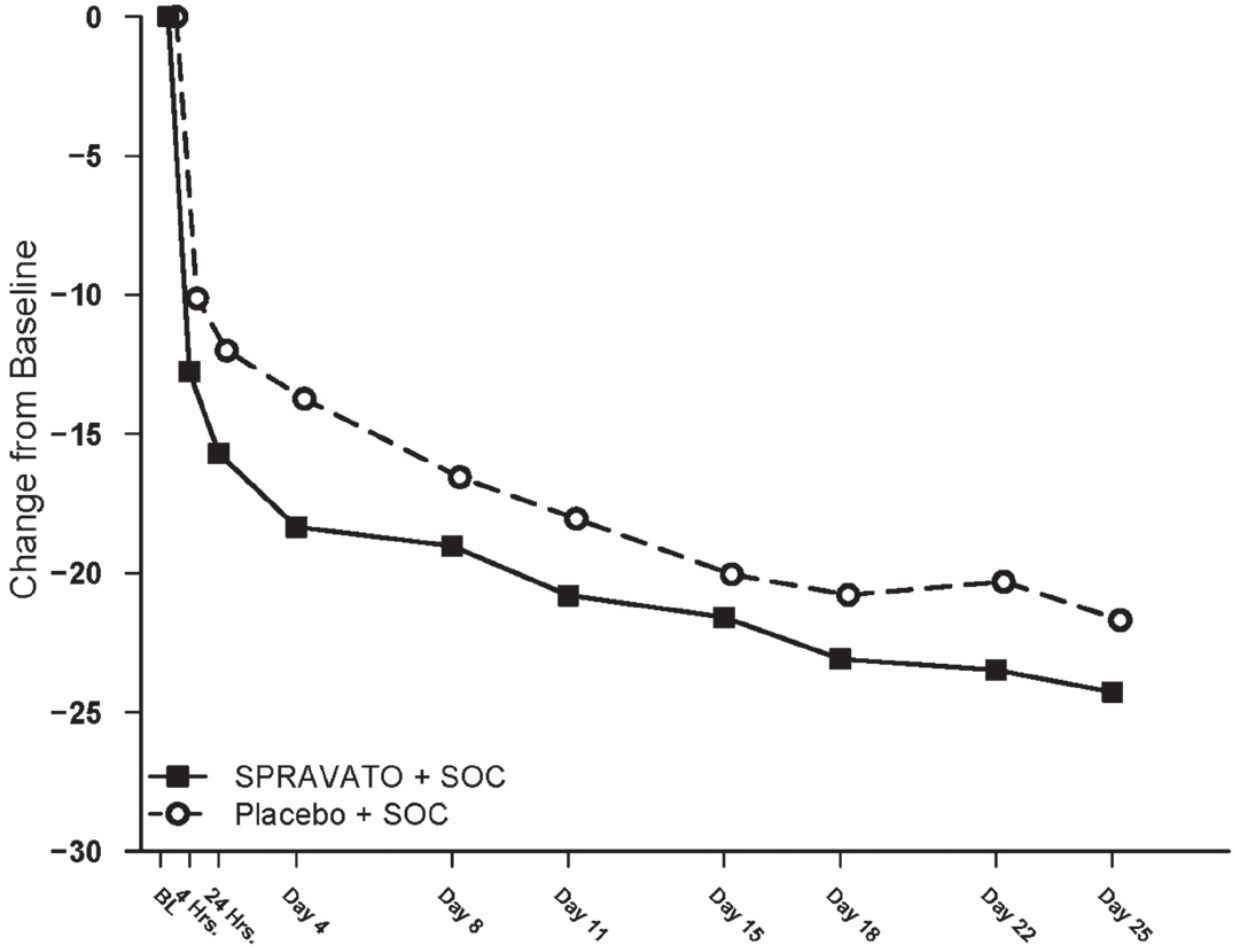
[b] Difference (Spravato + SOC minus placebo nasal spray + SOC) in least-squares mean change from baseline.

[c] Spravato + SOC were statistically significantly superior to placebo nasal spray + SOC.

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). The CGI-SS-r is a one-item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior. In Study 4 and Study 5, Spravato plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r.

Time Course of Treatment Response
In both Study 4 and Study 5, Spravato's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25. Figure 5 depicts time course of the primary efficacy measure of change in MADRS total score from Study 4.

Figure 5. Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study 4[a] (Full Analysis Set)



[a] Note: In Study 4, after the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose. Approximately 19% of patients had reduction in Spravato dosage from 84 mg to 56 mg twice weekly.

Special Safety Studies
Effects on Driving
Two studies were conducted to assess the effects of Spravato on driving skills; one study in adult patients with major depressive disorder (Study 6) and one study in healthy subjects (Study 7). On-road driving performance was assessed by the mean standard deviation of the lateral position, a measure of driving impairment.

A single-blind, placebo-controlled study in 25 adult patients with major depressive disorder evaluated the effects of a single 84 mg dose of intranasal Spravato on next day driving and the effect of repeated administration of 84 mg of intranasal Spravato on same-day driving performance (Study 6). For the single dose treatment phase, an ethanol-containing beverage was used as a positive control. The SDLP after administration of single 84 mg dose of Spravato nasal spray was similar to placebo 18 hours post-dose. For the multiple dose treatment phase, the SDLP after repeated administration of 84 mg intranasal Spravato was similar to placebo 6 hours post-dose on Day 11, Day 18, and Day 25.

A randomized, double-blind, cross-over, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84-mg dose of esketamine nasal spray on driving (Study 7). Mirtazapine (30 mg) was used as a positive control. Driving performance was assessed at 8 hours after Spravato or mirtazapine administration. The SDLP 8 hours after Spravato nasal spray administration was similar to placebo. Two subjects discontinued the driving test after receiving Spravato because of a perceived inability to drive after experiencing post-dose adverse reactions; one subject reported pressure behind the eyes and paresthesia of the hands and feet, the other reported headache with light sensitivity and anxiety.

Practice Guidelines and Position Statements

American College of Physicians

The American College of Physicians published a living clinical guideline for the acute phase of major depressive disorder in 2023, which was most recently updated in August 2025. (22) They recommend either cognitive behavioral therapy or a second-generation antidepressant or both for patients with acute moderate or severe major depressive disorder. There are no recommendations relevant to esketamine.

American Psychiatric Association

The American Psychiatric Association issued clinical practice guidelines for major depressive disorder in 2010 with no subsequent updates. (23) These are considered legacy practice guidelines and can no longer be assumed to be current.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final Report on the comparative clinical effectiveness and value of esketamine for treatment-resistant depression on June 20, 2019. (3) The Report concludes the following on the strength of evidence that esketamine improves outcomes in patients with treatment-resistant depression- “Evidence provides moderate certainty that the addition of esketamine to a newly initiated antidepressant has comparable or better net health benefit, with a small (but non-zero) chance of net harm, compared with newly initiated antidepressant alone. There was insufficient evidence to judge the net health benefit of esketamine versus ketamine or other therapies for treatment-resistant depression.”

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 5.

Table 5. Summary of Key Clinical Studies

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT05973851	A Randomised, Controlled Trial to Investigate the Effect of a Four Week Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment	418	Jun 2026
NCT04829318	Open-label Long-Term Extension Study for Participants with Treatment-resistant Major Depressive Disorder Who Are Continuing Esketamine Nasal Spray Treatment from Study 54135419TRD3013	183	Jul 2024
NCT03185819	Study to evaluate the efficacy and safety of 3 fixed doses of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric participants assessed to be at imminent risk for suicide	147 (actual)	Mar 2023

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	G2082, G2083, J3490, J0013

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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U.S. Food and Drug Administration Label:

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Other:

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Centers for Medicare & Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare & Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/26	New medical document. Treatment Resistant Depression: Esketamine nasal spray may be considered medically necessary in adults ages 18 years or older for an initial authorization period of 3 months, who meet all of the following criteria: member meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive disorder; the current depressive episode is moderate or severe based on one of the following a Montgomery-Asberg Depression Rating Scale (MADRS) ≥28 or a Hamilton Rating Scale for Depression (HAM-D) score ≥17; or a Patient Health Questionnaire 9 (PHQ-9) score ≥ 10; or a Quick Inventory of Depressive Symptomatology (QIDS) score ≥ 11 and has tried and had an inadequate response to one antidepressant agent (i.e. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine). An adequate trial of an antidepressant is defined by the following: The trial length was at least 6 weeks at generally accepted doses or of sufficient duration as determined by the treating physician at the generally accepted doses; and individual does not have a current substance use disorder unless in remission (complete abstinence for a month. Continuation of treatment with esketamine nasal spray following at least 3 months of use may be reauthorized when all of the following conditions are met; there has been improvement in depression symptoms as evaluated with an appropriate depression rating scale (e.g. MADRS, HAM-D, PHQ-9, QIDS); individual does not have a current substance use disorder. Major Depressive Disorder with Acute Suicidal Ideation or Behavior: Esketamine nasal spray may be considered

	medically necessary for a treatment period of 28 days when ALL of the following conditions are met: Individual is 18 years of age or older; AND Individual with major depressive disorder with acute suicidal ideation or behavior; AND Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant. Esketamine nasal spray is considered experimental, investigational and/or unproven in all other situations.