Medical Policy

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Title: Esketamine Nasal Spray for Depression

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Populations	Interventions	Comparators	Outcomes
Individuals: Who are adults and diagnosed with treatment-resistant depression	**Interventions of interest are:** Esketamine	**Comparators of interest are:** Standard medical management (pharmacotherapy, psychotherapy and/or somatic therapy)	**Relevant outcomes include:** Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity

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Individuals: Who are adults and diagnosed with major depressive disorder with acute suicidal ideation or behavior	**Interventions of interest are:** Esketamine	**Comparators of interest are:** Standard medical management (pharmacotherapy, psychotherapy and/or somatic therapy)	**Relevant outcomes include:** Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity

DESCRIPTION

Esketamine is the S-isomer of racemic ketamine. Esketamine targets the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor in nerve cells.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with esketamine improves the net health outcome in patients with treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior.

BACKGROUND

Treatment-Resistant Depression

Patients with either major depressive disorder or bipolar disorder can manifest depressive episodes (See 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.[1,] Overall, approximately 1 in 3 patients with depression are considered treatment-resistant.[2,] While there is no standardized definition of treatment-resistant depression, generally accepted definition is failure of 2 or more antidepressant treatment attempts with an adequate dose and duration.[3,]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 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 Agency for Healthcare Research and Quality (AHRQ) on defining treatment-resistant depression in the Medicare population, lack of clear definition for treatment-resistant depression have 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.[3,]

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 Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), 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.[3,]

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.[4,]

Major Depressive Disorder and Suicidal Ideation/Behavior

In a community survey conducted in 21 countries with over 100,000 individuals by World Health Organization, 12-month prevalence of suicidal ideation (thoughts) was approximately 2 percent[5,], and that the lifetime prevalence was 9 percent.[6,] Reported annual prevalence of suicidal ideation in US adults is 4 percent [7,]. Psychiatric illness is strongly associated with risk of suicide[8,] and major depressive disorder is the psychiatric diagnosis most commonly associated with suicide.[9,] The reported prevalence of suicidal ideation in adult patients with MDD is as high as

60%, and the lifetime incidence of attempted suicide in this population ranges between 10% and 20%.[10,11,] Further, the lifetime risk of completed suicide has been estimated to be 3.4% in this population.[12,]

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.[13,] 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,[14,] they require 4–6 weeks to exert their full effect,[15,16,] limiting their utility in crisis situations. Currently, there is no approved medication for emergency treatment of patients with depression who have active suicidal ideation with intent.[17,]

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. Strategy for managing treatment resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics).[18,2,] Modification strategies include use of higher dose, switching to a new antidepressant, or adding on to an existing therapy. The adequate duration of antidepressant therapy is usually minimum of 6 weeks. Additional 4 to 6 weeks may be required for patients who show partial response.[19,]

For patients with long-standing treatment-resistant depression who do not benefit from treatment modification or augmentation strategies are referred to as refractory depression. For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, 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.

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

POLICY

A. Esketamine nasal spray may be considered **medically necessary** if all of the following conditions are met:

Initial Authorization for 28 Days

1. Individual is 18 years of age or older
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders.
3. Individual current depressive episode is moderate or severe based on either 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)
4. Individual has tried and had an inadequate response to 2 antidepressant agents from 2 different antidepressant classes (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 BOTH of 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
    b. Individual was ≥80% adherent to the agent during the trial
5. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant.
6. Individual does not have current substance use disorder unless in remission (complete abstinence for a month)
7. Individual does NOT have any U.S. Food and Drug Administration (FDA) labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label (see policy guidelines) including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements (see policy guidelines).
8. The prescriber is a specialist in the area of the patient's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis.

Reauthorization for UP TO 1 Year

B. Esketamine nasal spray may be reauthorized for up to 1 year if 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. Patient Health Questionnaire -9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D).
2. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant.
3. Individual does not have current substance use disorder

4. Individual does NOT develop any FDA labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label (see policy guidelines) including meeting Spravato REMS program requirements (see policy guidelines).

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

C. Esketamine nasal spray may be considered **medically necessary** for a treatment period of 28 days if all of the following conditions are met:
   1. Individual is 18 years of age or older
   2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders.
   3. Individual current depressive episode is moderate or severe based on either of the following scales:
      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)
   4. Individual is currently hospitalized and is at a imminent risk for suicide as documented by:
      a. Individual response to a structured assessment for suicidal ideation indicative of imminent risk of suicide (see policy guidelines) AND
      b. Confirmation of imminent risk of suicide by clinical assessment by a mental health professional/psychiatrist (see policy guidelines)
   5. Individual is to receive esketamine nasal spray in conjunction with standard-of-care treatment based on clinical judgment and practice guidelines that may be comprised of oral antidepressant(s), an atypical antipsychotic, or a mood stabilizer.
   6. Individual does NOT have any U.S. Food and Drug Administration (FDA) labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label (see policy guidelines) including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements (see policy guidelines).
   7. The prescriber is a specialist in the area of the patient's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis.

D. Esketamine nasal spray is considered **experimental/ investigational** in all other situations.

POLICY GUIDELINES

A. A treatment session for use of esketamine nasal spray must ensure the following:
   1. Treatment is administered under the direct supervision of a healthcare provider.
   2. Blood pressure is assessed before and after treatment to ensure safety in accordance with the U.S. Food and Drug Administration label.

3. 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.
4. Individual receiving treatment should be advised to avoid use of nasal corticosteroid or nasal decongestant 1 hour prior to treatment.
5. Individual is monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

B. For treatment-resistant depression, the recommended adult dosage of esketamine nasal spray during the induction and maintenance phases are as follows:
    1. 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.
    2. 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.

C. 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.

D. Esketamine nasal spray is contraindicated in patients with following conditions:
    1. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
    2. Intracerebral hemorrhage.
    3. Hypersensitivity to esketamine, ketamine, or any of the excipients.

E. Esketamine nasal spray has a black box 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 REMS. The essential features of this program include
    1. Esketamine nasal spray is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients.
    2. Pharmacies and healthcare settings that dispense esketamine nasal spray are certified.
    3. Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring.

4. Enrollment of all patients in a registry to further characterize the risks and support safe use

Montgomery–Asberg Depression Rating Scale (MADRS)
MADRS is commonly used to evaluate the efficacy of antidepressant 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 (HAM-D)
HAM-D is a 17-item rating scale to determine the severity level of depression in a patient 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

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 the patients 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 (SSI) and the Columbia-Suicide Severity Rating Scale (C-SSRS). SSI is a 19 item clinician-administered scale querying, among other things, the patient'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.

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RATIONALE

This evidence review was created in August 2019 and with a search of the PubMed database. The most recent literature update was performed through September 3, 2020.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Esketamine

Clinical Context and Therapy Purpose

The purpose of esketamine in adult patients who have treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior is to provide a treatment option that is an improvement on or an alternative to existing therapies. Potential benefits of this therapy may include the following:

- A fast-acting treatment to "jump start" recovery
- A durable treatment that keeps them well over time
- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many patients for whom other available treatments have failed.

The question addressed in this evidence review is: Does treatment with esketamine improve the net health outcome in individuals with treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with a diagnosis of treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior. In this context,

- Treatment-resistant depression is defined as failure of 2 or more antidepressants treatment attempts with adequate dose and duration.
- Major depressive disorder is defined as individual meeting DSM-5 diagnostic criteria (See Table 1) without psychotic features.

- Current suicidal ideation with intent defined by a confirmed "Yes" response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (ie, about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the he Mini-International Neuropsychiatric Interview. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours.
-

Interventions

The therapy being considered is esketamine, which is a non-selective, non-competitive N-Methyl-D-aspartate receptor antagonist. The exact mechanism by which esketamine exerts antidepressant effect is unknown. Esketamine is administered as a nasal spray in a medically-supervised setting because of the risk of sedation and dissociation.

Comparators

The relevant comparators are standard medical management (pharmacotherapy, psychotherapy, and/or somatic therapy). Available treatments have significant adverse reactions: weight gain and extrapyramidal symptoms (combination olanzapine and fluoxetine); risks of general anesthesia and memory loss (electroconvulsive therapy); surgical intervention and infection (vagus nerve stimulator). Transcranial magnetic stimulation has fewer risks relative to these other interventions, but may be less effective.

Outcomes

The general outcomes of interest are change in disease status, functional outcomes, quality of life, treatment-related mortality and treatment-related morbidity. See Table 2 for the description and relevance of MADRS and HAM-D. While pivotal trials to establish short-term efficacy for other U.S. Food and Drug Administration (FDA) approved antidepressants typically lasted at least 6 weeks, the acute term esketamine trials were designed for only 4 weeks with the objective to demonstrate treatment effects in a shorter period of time. Event driven randomized withdrawal trials are required to demonstrate durability of effect in maintenance treatment.

Table 2. Health Outcome Measures Relevant to Treatment-Resistant Depression, Major Depressive Disorder, Suicidal Ideation and Suicidal Behavior

Outcome	Description	Scale	Clinically Meaningful Difference
MADRS	Physician scored: Rates presence and severity of depression Symptom domains include sadness; pessimism; inability to feel; suicidality	Contains 10 items (scored from 0 to 6) with higher scores indicating more severe depression No validated cut-off score but generally 0 to 6 normal (no depression); 7 to 19 mild depression; 20 to 34 moderate depression; 35 to 59 severe depression; 60 or greater very severe depression[22,]	No consensus to define remission. Thresholds for remission have ranged from 6 to 12 in trials. One literature review reported that the mean weighted MADRS score for remission was 4.0 (95% CI: 3.5-4.5) based on 10 studies.[23,] The definition of

Outcome	Description	Scale	Clinically Meaningful Difference
			remission was a complete absence of clinically significant symptoms of depression. As per FDA, for drugs that have been approved to treat MDD as monotherapy or adjunctive treatment, treatment differences were typically closer to 3 or 4 points in MADRS scores. The observed treatment differences in esketamine studies were in that range.[24,]
HAM-D	Physician scored Rates presence and severity of depression Used in a number of registration studies of approved oral antidepressants. Symptom domains include sadness; pessimism; inability to feel; suicidality	There are 2 versions: 17 or 25 items; 17 items is more common Each item scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. Scores range from 0 to 48 Scores as low as 17 are associated with moderate depression and those at or above 24 are associated with severe depression.[25,]	Remission is defined as total score of 7 or less. But 2 or less has been suggested as optimal. Response to treatment is defined as 50% reduction from baseline scores.
SIBAT	Contains both patient- and clinician-reported modules and can be assessed by patient or rated by the physician Includes assessments of Severity of Suicidality (CGI-SS-r) Imminent Suicide Risk (CGI-SR-I) Frequency of Suicidal Thinking (FoST)[26,]	CGI-SS-r: rated from 0 [normal, not at all suicidal] to 6 [among the most extremely suicidal patients]) CGI-SR-I: rates best clinical judgment of participant's imminent risk for suicide within the next 7 days. Scale indicates: 0 (No imminent suicide risk), 1 (Minimal imminent), 2 (Mild imminent), 3 (Moderate imminent),	No literature was identified for a consensus definition for a clinically meaningful change in scores

Outcome	Description	Scale	Clinically Meaningful Difference
		4 (Marked imminent), 5 (Severely imminent), 6 (Extreme imminent). FoST: describes the clinician determined estimate of the frequency of the participant's suicidal thinking. Scored on a 6-point Likert scale 0 (Never), 1 (Rarely), 2 (Sometimes) 3 (Often), 4 (Most of the time), 5 (All of the time).[26,]	

MADRS: Montgomery-Asberg Depression Rating Scale, CGI-SS-r: Clinical Global Impression of Severity of Suicidality-Revised, CGI-SR-I: Clinical Global Impression of Imminent Suicide Risk Scale, FoST: Frequency of Suicidal Thinking, HAM-D: Hamilton Depression rating Scale, MDD: major depressive disorder, SIBAT: Suicide Ideation and Behavior Assessment Tool.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Treatment-Resistant Depression

Esketamine received a breakthrough therapy designation based on preliminary evidence that it could provide an advantage over existing therapy for treatment resistant depression by providing rapid relief of depressive symptoms.[24,] The clinical development program for esketamine is summarized in Table 3. The clinical development program comprises of 3 randomized controlled studies in acute (4-week) setting (TRANSFORM-1, 2 and 3) and 1 randomized withdrawal study in long term (16 week) setting (SUSTAIN-1) and 1 open-label long term (52 week) safety study (SUSTAIN-2). Information summarized here was obtained primarily from FDA documents[22,24,27,28,29,] as well as peer reviewed publications.[30,31,32,]

Table 3. Summary of the Clinical Development Program for Esketamine

	Phase	N	Esketamine Dose	Design & Objective	Rx phase and duration	Outcome
PIVOTAL TRIALS						
TRANSFORM-2 (NCT02418585)[33]	3	223	Flexible dose esketamine 56 or 84 mg	DBRCT (Efficacy and safety in adults (18-64 years)	4-week prospective observation phase + 4-weeks RCT + 24-week follow-up	MADRS change Clinical remission Clinical response
SUSTAIN-1 (NCT02493868)[31]	3	297	Flexible dose esketamine 56 or 84 mg	Open label single arm (Assess relapse prevention in those who attain stable remission or response with esketamine)	16-week open-label induction phase + 48-week (variable) randomized maintenance phase + 2-week follow-up	Relapse
SUPPORTING TRIALS						
TRANSFORM-1 (NCT02417064)[32]	3	342	Fixed dose esketamine 56 or 86 mg	DBRCT (Efficacy and safety in adults (18-64 years))	4-week prospective observation phase + 4-weeks RCT + 24-week follow-up	MADRS change Clinical remission Clinical response
TRANSFORM-3 (NCT02422186)Unpublished	3	137	Flexible dose esketamine 28, 56 or 84 mg	DBRCT (Efficacy and safety in adults 65 years or older)	Same as above	MADRS change Clinical remission Clinical response

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial.

Pivotal Trials

The primary evidence for the approval of esketamine was comprised of a flexible-dose trial in adults younger than 65 years of age (TRANSFORM-2) and the randomized withdrawal study (SUSTAIN-1). The pivotal trial characteristics and results are summarized in Table 4 and 5 respectively. Across studies, demographic and baseline disease characteristics of patients randomized to esketamine and placebo nasal spray groups were similar. Patients in all of these studies had failed trials of at least 2 prior antidepressant drugs and had more severe symptoms on average than patients entering antidepressant studies for previously FDA approved drugs including trials for olanzapine plus fluoxetine for treatment-resistant depression. All patients in phase 3 studies initiated a new daily oral antidepressant (open-label duloxetine, escitalopram, sertraline, or venlafaxine extended-release) at the time of randomization to esketamine or placebo.

In the TRANSFORM-2 trial, the primary endpoint was change in MADRS total score from baseline to week 4. Secondary endpoints were onset of clinical response by day 2 and sustained response through week 4, change in functioning and disability and change in patient-reported depressive symptoms. The trial met the primary endpoint with a 4-point difference (95% CI -7.3 to 0.6) in least square mean difference of MADRS score in favor of esketamine. Assessment of time course of response in MADRS score showed that a treatment difference between esketamine vs placebo was observed at 24 hours (data not shown). The drug-placebo difference in MADRS change from baseline remained consistent through the end of 4 week with no further separation between groups after day 2. At the end of week 4, 67% of the patients randomized to esketamine were receiving 84 mg twice weekly.

In the SUSTAIN-1 trial, the primary objective was to assess durability of treatment effect by assessing how long do patients who received at least 16 initial weeks of treatment with esketamine and achieved remission or stable response were able to delay relapse of depressive symptoms after being randomized to withdrawal or continuation of esketamine. Background antidepressant therapy was continued in both treatment arms. 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. The primary 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. Results showed time to relapse was significantly delayed if patients continued esketamine vs being switched to placebo among stable remitters (not estimable vs 273 days; HR= 0.49) as well as responders (635 days vs 88 days; HR=0.30).

Adverse events were appropriately monitored, with specific assessments for adverse events of special interest that include sedation, dissociation, and increases in blood pressure (data not shown). The time course of these events closely follows the pharmacokinetic profile of esketamine, and their incidence was dose-related. These events are monitorable, and most occurred within the first 2 hours following drug administration.[24,]

The purpose of the study limitations is to display notable limitations identified in each study. While no major limitations in study relevance or study design and conduct were noted, concerns related to possibility of unblinding and limited generalizability of trials results to intended

population of use are noteworthy. Esketamine is known to result in dissociative effects and therefore there were concerns that blinded patients would be able to discern whether they were receiving active treatment or not. To minimize the potential of unblinding, investigators incorporated design elements in the study protocols to enhance blinding. For example, centralized, blinded, remote raters were used in all phase 3 studies. Bittering agent was also added to placebo to enhance the blind. Regarding the generalizability of the results, lack of racial/ethnic diversity and enrollment of patients with less severe depression were the main concerns. More than 90% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities.[34,] While esketamine is likely to be used for patients with chronic, severe depression, who have failed multiple other therapies, only 36 to 40% of studied patients had failed 3 or more therapies in the current depressive episode. Lastly, more robust data are needed to determine how esketamine compares with other therapies for treatment-resistant depression as there no head-to-head trials comparing esketamine with standard of care prior to its approval.

Table 4. Summary of Key Randomized Trials of Esketamine

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
TRANSFORM-2[24,22,33,]	US and global	50	2015-2017	*Inclusion criteria* • Ages 18 to 64 years • Major depressive disorder (DSM-5) • IDS-C30 ≥ 34· Failed 1 to 5 oral antidepressants based on MGH-ATRQ • MADRS ≥ 28 *Patient characteristics* • Current episode duration (yrs.):2.2 • MADRS mean: 37 • Past failures of ≥ 3 ADs: 36%	Esketamine plus oral antidepressant (n= 109)	Placebo + oral antidepressant (n=114)
SUSTAIN-1 Daly et al, 2019[31,]	US and global	160	2015-2018	*Inclusion criteria* • Participants from TRANSFORM-1 and -2 who	Esketamine + oral antidepressant(n=152)	

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
				achieved stable remission or stable response[a] *Patient characteristics* • Current episode duration (yrs.): NR • Stable remitters (59% of enrolled), MADRS mean: 37.5 • Stable responders (41% of enrolled), MADRS mean: 39.5		

[a] Stable remission was defined as achieving MADRS ≤ 12 for at least 3 out of the last 4 weeks of the 12-week optimization phase of receiving esketamine, while stable response was defined as achieving ≥ 50% reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.
DSM: Diagnostic and Statistical Manual of Mental Disorders; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MGH-ATRQ: Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MADRS: Montgomery-Asberg Depression Rating Scale

Table 5. Summary of Key Randomized Trials of Esketamine

Study	**Change in MADRS (SD)**	**Clinical Response**	**Clinical Remission**
TRANSFORM-2[27,29,33,]	**223**	**223**	**223**
Esketamine	-20.8 (-23.3 to -18.4)	69%	53%
Placebo	-16.8 (-19.3 to -14.4)	52%	31%
Difference (95% CI)	- 4.0 (-7.3, -0.6); p=0.010	-	-
	Relapse (%)	**Median Time to Relapse (days)**	
SUSTAIN-1[27,29,31,]	**297**	**297**	
Among stable remitters, n	176	176	
Esketamine	27%	NE	

Study	Change in MADRS (SD)	Clinical Response	Clinical Remission
Placebo	45%	273 (97 to NE)	
HR (95% CI)	-	0.49[a] (0.3 to 0.8); p=0.003[b]	
Among stable responders	**121**	**121**	
Esketamine	26%	Median: 635 (265 to 635)	
Placebo	58%	Median: 88 (46 to 196)	
HR (95% CI)	-	0.30[a] (0.16 to 0.55); p<0.001	

HR: Hazard ratio; NE; not estimable
[a] Compares esketamine arm to placebo arm.
[b] P-value adjusted for interim analysis that included a sample size re-estimation

Supportive Evidence
Supporting trials include TRANSFORM-1 and -2. Trial characteristics and results are summarized in Table 6 and 7 respectively.

TRANSFORM-1 was the fixed-dose study in adults younger than 65 years of age. The study was conducted at 96 sites worldwide with 42 sites in the United States. Subjects were randomized at a 1:1:1 ratio to either 56 mg esketamine, 84 mg esketamine, or placebo. The prespecified analysis plan dictated that efficacy of the 84-mg dose would be evaluated first, followed by evaluation of the 56-mg dose. The primary endpoint of change from baseline to day 28 in mean MADRS total score showed no statistical significant difference between 84 mg esketamine dose vs placebo, the 56 mg dose as well as other secondary endpoints were formally evaluated. TRANSFORM-3 was the flexible-dose study in patient's ≥ 65 years of age. The sample size in the geriatric study was only about half of that in the successful flexible-dose study. The study included flexible doses ranging from 28 to 84 mg; the effect of esketamine in the combined dose group was not statistically superior to placebo. However, the magnitude of the treatment effect (3.6-point improvement on the MADRS) is in the range of effects observed in other antidepressant studies, as well as other phase 3 studies in the esketamine development program. Unlike other studies where separation of clinical response was apparent within 2 days of treatment and treatment effect remained constant throughout, in this trial, the treatment difference with esketamine was only apparent towards the end of the study with no separation of MADRS scores early. The reason for this anomaly remains unexplained.

Table 6. Summary of Supporting Randomized Trials of Esketamine

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
TRANSFORM-1[32,]	US and global	91	2015-2018	*Inclusion criteria* • Ages 18 to 64 years	Esketamine plus oral antidepressants (n=229)	Placebo plus oral antidepressants (n=113)

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
				• Major depressive disorder (DSM-5) • IDS-C30 ≥ 34 • Failed 1 to 5 oral antidepressants based on MGH-ATRQ • MADRS ≥ 28 *Patient characteristics* • Current episode duration (yrs.): 3.9 • MADRS mean: 37.5 • Past failures of ≥ 3 ADs: 40%		
TRANSFORM-3	US and global	70	2015-2017	*Inclusion criteria* • Same as above except age ≥65 *Patient characteristics* • Current episode duration (yrs.): 4.1 • MADRS mean: 35 • Past failures of ≥ 3 ADs: 39%	Esketamine plus oral antidepressant(n=72)	Placebo + oral antidepressant (n=65)

[a] Stable remission was defined as achieving MADRS ≤ 12 for at least 3 out of the last 4 weeks of the 12-week optimization phase of receiving esketamine, while stable response was defined as achieving ≥ 50% reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.
DSM: Diagnostic and Statistical Manual of Mental Disorders; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MGH-ATRQ: Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MADRS: Montgomery-Asberg Depression Rating Scale

Table 7. Summary of Supporting Randomized Trials of Esketamine

Study	Change in MADRS (SD)	Clinical Response	Clinical Remission
TRANSFORM-1	**342**	**342**	**342**
Esketamine 84 mg	-18.2 (-20.9 to -15.6)	53%	39%

Study	Change in MADRS (SD)	Clinical Response	Clinical Remission
Esketamine 56 mg	-18.9 (-21.4 to -16.4)	54%	36%
Placebo	-14.9 (-17.4 to -12.4)	39%	31%
Difference (95% CI) Esketamine 84 mg Esketamine 56 mg	 -3.2 (-6.9, 0.5); p=0.088- 4.1 (-7.7, -0.6); p=0.027	[a]	[a]
TRANSFORM-3	**137**	**123**	**123**
Esketamine	-10.1 (-13.1 to -7.1)	27%	18%
Placebo	-6.5 (-9.4 to -3.6)	13%	7%
Difference (95% CI)	-3.6 (-7.2, 0.07); p=0.059	[a]	[a]

[a] As per U.S. Food and Drug Administration, none of the results on the prespecified key secondary endpoints (only designated in TRANSFORM-1 and TRANSFORM-2) were statistically significant after controlling for type I error based on the prespecified statistical analysis plan.

Section Summary

The evidence for use of esketamine for treatment resistant depression consists of 4 RCTs (TRANSFORM-1, -2 and -3 and SUSTAIN-1) with placebo comparators that enrolled more than 700 patients across studies. Of the 4 RCTs, TRANSFORM-2 and SUSTAIN-1 were the basis for FDA approval. While both trials used the flexible esketamine dosing, the objective of TRANSFORM-2 was to assess short-term (4 week) efficacy of esketamine while SUSTAIN-1 aimed to assess durability of efficacy over the long-term (event-driven study with no fixed duration). Results of TRANSFORM-2 showed that trial met the primary endpoint with a 4 point difference (95% CI -7.3 to 0.6) in least square mean difference of MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in TRANSFORM-2 was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that treatment effect was apparent at 24 hours, remained fairly consistent through end of 4 week with no further separation between groups after day 2. Results of the SUSTAIN trial showed that patients who received at least 16 initial weeks of treatment with esketamine and achieve clinical remission or response were less likely to relapse if they continued esketamine vs being switched to placebo (HR= 0.49 for remitters and HR=0.30 for responders respectively). TRANSFORM-1 (a fixed-dose study) and TRANSFORM-3 (flexible-dose study in patient's ≥ 65 years of age) were negative. While no major limitations in study relevance or study design and conduct were noted, concerns related to possibility of unblinding and limited generalizability of trials results to intended population of use are noteworthy.

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

The clinical development program for esketamine is summarized in Table 8 comprises of 2 identical randomized controlled studies in acute (4-week) setting (ASPIRE-1 and 2). The pivotal trial characteristics and results are summarized in Table 9 and 10 respectively. Across both studies, demographic and baseline disease characteristics of patients randomized to esketamine and placebo nasal spray groups were similar. Patients in the 2 studies enrolled adults with

moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent and were treated with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. A 1 time dose reduction to 56 mg was allowed for patients unable to tolerate the 84 mg dose after the first dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant as determined by the investigator. After completion of the 4-week treatment period with esketamine/placebo, study follow-up continued through day 90.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose. 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. In both studies, esketamine plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo. On an average, difference in LS mean change in total MADRS score from baseline to 24 hrs was 3.8 and 3.9 point improvement in ASPIRE-1 and -2 respectively. Further, between 4 hours after the first dose and day 25, both esketamine and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through day 25 according to the prescribing label. In both studies, treatment with esketamine did not demonstrate superiority compared to placebo nasal spray in improving CGI-SS-r. The CGI-SS-r is a 1 item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Among other endpoints, the proportion of patients who achieved remission was higher among esketamine treated patients versus placebo at 24 hrs after first dose as well as on day 25 (See Table 10). Adverse events were appropriately monitored, with specific assessments for adverse events of special interest that include sedation, dissociation, and increases in blood pressure (data not shown). The time course of these events closely follows the pharmacokinetic profile of esketamine, and their incidence was dose-related. These events are monitorable, and most occurred within the first 2 hours following drug administration.[35.]

The purpose of the study limitations is to display notable limitations identified in each study. While no major limitations in study relevance or study design and conduct were noted, concerns related to possibility of unblinding and limited generalizability of trials results to intended population of use are noteworthy. Esketamine is known to result in dissociative effects and therefore there were concerns that blinded patients would be able to discern whether they were receiving active treatment or not. To minimize the potential of unblinding, investigators incorporated design elements in the study protocols to enhance blinding. For example, efficacy and safety assessments were performed by different raters. Bittering agent was also added to placebo to enhance the blind. Regarding the generalizability of the results, lack of racial/ethnic diversity and enrollment of patients with less severe depression were the main concerns. More than 70% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities.[34.] Lastly, the effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated in ASPIRE-1 and -2 studies. Both studies were not powered to detect a statistical significant difference between suicidal ideation and/or suicides. Patients in both esketamine and placebo group experienced a rapid reduction in the severity of their suicidality, the difference between treatment groups was not statistically significant. This may be due to the substantial impact of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis. Further,

comprehensive standard-of-care was enhanced by twice-weekly study visits with extensive clinical contact and permitted benzodiazepine use, all of which may have contributed to the rapid reduction of suicidality in both treatment groups.

Table 8. Summary of the Clinical Development Program for Esketamine

	Phase	N	Esketamine Dose	Design & Objective	Rx phase and duration	Outcome
PIVOTAL TRIALS						
ASPIRE I (NCT03039192)[36,35,]	3	224	Flexible dose (initiated at 84 mg but could be reduced to 56 mg after 4 weeks)	DBRCT (Efficacy and safety in adults (18-64 years)	• 24- to 48-hr screening period to assess eligibility • 4-week double-blind treatment phase • 9-week post-treatment followup	• MADRS change • SIBAT change
ASPIRE II (NCT03097133)[37,35,]	3	227	Flexible dose (initiated at 84 mg but could be reduced to 56 mg after 4 weeks)	DBRCT (Efficacy and safety in adults (18-64 years)	• Same as above	• Same as above

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial; MADRS: Montgomery-Asberg Depression Rating Scale; SIBAT: Suicide Ideation and Behavior Assessment Tool

Table 9. Summary of Key Randomized Trials of Esketamine

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
ASPIRE I (NCT03039192)[36,35,]	US, Europe Asia and South Africa	50	2017-2018	*Inclusion criteria* • Ages 18 to 64 years • Major depressive disorder (DSM-5) • Patients respond	Esketamine plus standard of care antidepressant (n=112)	Placebo plus standard of care antidepressant (n=112)

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
				affirmatively to MINI questions B3 ("Think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") within 24 hours of randomization • In clinical need of acute psychiatric hospitalization due to imminent suicide risk • MADRS ≥ 28 on predose day 1 *Patient characteristics* • Mean age: 41 years • MADRS total scores, mean: 41 • Prior suicide attempt: 60% • Suicide attempt in the last month: 28%		

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
ASPIRE II (NCT03097133)[37,35,]	US and global (47 sites)	160	2017-2019	*Inclusion criteria* • Same as above *Patient characteristics* • Mean age: 41 years • MADRS total scores, mean: 40 • Prior suicide attempt: 66% • Suicide attempt in the last month: 26%	Esketamine + oral antidepressant(n=114)	Placebo plus standard of care antidepressant (n=113)

[a] Stable remission was defined as achieving MADRS ≤ 12 for at least 3 out of the last 4 weeks of the 12-week optimization phase of receiving esketamine, while stable response was defined as achieving ≥ 50% reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.
DSM: Diagnostic and Statistical Manual of Mental Disorders; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MGH-ATRQ: Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; MADRS: Montgomery-Asberg Depression Rating Scale; MINI: mini-International Neuropsychiatric Interview

Table 10. Summary of Key Randomized Trials of Esketamine

Study	**MADRS Scores (Primary Endpoint)**	**Remission (MADRS Total Score ≤ 12), %**	**CGI-SS-r Score (Primary Secondary Endpoint)[a]**
ASPIRE I (NCT03039192)[36,35,]	N=223	N=223	N=223
Esketamine[b]	Baseline: 41.3 (±5.87[c]) LS mean change 24 hrs post first dose: -15.9 (±1.04[d])	24 hrs post first dose: 19% Day 25, 4 hrs post dose: 54%	Not reported
Placebo[b]	Baseline Score: 41.0 (±6.29[c]) LS mean change 24 hrs post first dose: -12.0±(1.02[d])	24 hrs post first dose: 9% Day 25, 4 hrs post dose: 38%	Not reported
Difference	LS Difference (95% CI): -3.8 (-6.56 to -1.09)	24 hrs post first dose: 9.8% (0.87 to 18.77)	24 hrs post first dose: -0.26 (-0.59 to 0.08)

Study	MADRS Scores (Primary Endpoint)	Remission (MADRS Total Score ≤ 12), %	CGI-SS-r Score (Primary Secondary Endpoint)[a]
		Day 25, 4 hrs post dose: 16.1 (3.20 to 28.94)	
ASPIRE II (NCT03097133)[37,35,]	N=226	N=226	N=223
Esketamine[b]	Baseline Score: 39.4 (±5.21[c]) LS Mean Change: -16.0 (±1.02[d])	24 hrs post first dose: 22% Day 25, 4 hrs post dose: 47%	Not reported
Placebo[b]	Baseline Score: 39.9 (±5.76[c]) LS Mean Change: -12.2 (1±1.05[d])	24 hrs post first dose: 11% Day 25, 4 hrs post dose: 37%	Not reported
Difference	LS Difference (95% CI): -3.9 (-6.60 to -1.11)	24 hrs post first dose: 11.3% (1.83 to 20.80) Day 25, 4 hrs post dose: 10.2% (-2.58 to 22.98)	24 hrs post first dose: -0.14 (-0.48 to 0.19)

CGI-SS-r= Clinical Global Impression–Severity of Suicidality – revised; CI=confidence interval; LS Mean=least-squares mean; MADRS= Montgomery-Asberg Depression Rating Scale; SD=standard deviation; SE=standard error
[a] The CGI-SS-r is a 1 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.
[b] Treatment included an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (antidepressant monotherapy or antidepressant monotherapy plus augmentation therapy).
[c] standard deviation
[d] standard error

Section Summary

The evidence for use of esketamine for treatment of adults with major depressive disorder with acute suicidal ideation or behavior consists of 2 RCTs (ASPIRE-1 and -2) with placebo comparators that enrolled 449 patients across 2 studies. The 2 identical RCTs ASPIRE-1 and -2 enrolled adults with moderate-to-severe major depressive disorder who had active suicidal ideation and intent with the primary objective to assess short-term (24-hour after first dose) efficacy of esketamine. Results showed that both trials met the primary endpoint with approximately a 4 point difference in least square mean difference of MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in trials was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that treatment effect was apparent at 24 hours and remained fairly consistent through day 25 with no further separation between groups after day 2. While no major limitations in study relevance or study design and conduct were noted, concerns related to possibility of unblinding and limited generalizability of trials results to intended population of use are noteworthy.

Summary of Evidence

Treatment-Resistant Depression

For individuals with treatment-resistant depression who receive esketamine, the evidence includes 4 randomized, double-blind, placebo-controlled trials. Relevant outcomes are change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The 4 randomized controlled trials (TRANSFORM-1, -2 and -3 and SUSTAIN-1) with placebo comparators enrolled more than 700 patients across studies. Of the 4 randomized controlled trials, TRANSFORM-2 and SUSTAIN-1 were the basis for regulatory approval in the United States. While both trials used flexible esketamine dosing, the objective of TRANSFORM-2 was to assess short-term (4 week) efficacy of esketamine while SUSTAIN-1 aimed to assess durability of treatment effect over the long-term (event-driven study with no fixed duration). Results of TRANSFORM-2 showed that trial met the primary endpoint with a 4 point difference (95% CI -7.3 to 0.6) in least square mean difference of Montgomery-Asberg Depression Rating Scale (MADRS) total score in favor of esketamine. As per the U.S. Food and Drug Administration, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in TRANSFORM-2 was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that treatment effect was apparent at 24 hours, remained consistent through end of 4 week with no further separation between groups after day 2. Results of the SUSTAIN trial showed that patients who received at least 16 initial weeks of treatment with esketamine and achieved clinical remission or response were less likely to relapse if they continued esketamine vs being switched to placebo (hazard ratio=0.49 for remitters and hazard ratio=0.30 for responders respectively). Results of TRANSFORM-1 (a fixed-dose study) and TRANSFORM-3 (flexible-dose study in patient's ≥ 65 years of age) did not reach statistical significance for the primary endpoint. Limitations included possibility of unblinding due to patients perception of treatment assignment influenced by acute subjective dissociative effects of esketamine that could bias the results. Further, there is limited generalizability of trials results. More than 90% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

For individuals with major depressive disorder with acute suicidal ideation or behavior who receive esketamine, the evidence includes 2 randomized, double-blind, placebo-controlled trials. Relevant outcomes are change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The 2 identical randomized controlled trials (ASPIRE-1 and -2) with placebo comparators enrolled 449 adults patients with moderate-to-severe major depressive disorder who had active suicidal ideation. The primary objective was to assess short-term (24-hour after first dose) efficacy of esketamine. Results showed that both trials met the primary endpoint with approximately a 4 point difference in least square mean difference of MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in trials was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that treatment effect was apparent at 24 hours and remained fairly consistent through day 25 with no

further separation between groups after day 2. Limitations included possibility of unblinding due to patients perception of treatment assignment influenced by acute subjective dissociative effects of esketamine that could bias the results. Further, there is limited generalizability of trials results. More than 90% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Psychiatric Association

The American Psychiatric Association issued clinical practice guidelines for major depressive disorder in 2010 with no subsequent updates.[38,] In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse, these guidelines can no longer be assumed to be current.

Institute for Clinical and Economic review

The Institute for Clinical and Economic Review (ICER) published a final Report on the comparative clinical effectiveness and value of esketamine for treatment-resistant depression on June 20, 2019.[2,] 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 vs ketamine or other therapies for treatment-resistant depression."

U.S. Preventive Services Task Force Recommendations

Not applicable

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Clinical Studies

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03852160	A study of esketamine nasal spray plus a new standard-of-care oral antidepressant or placebo nasal spray plus a new standard-of-care oral antidepressant in adult and elderly participants with treatment-resistant depression (Phase 3 trial in Europe)	580	July 2021
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	145	Feb 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
	reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric participants assessed to be at imminent risk for suicide		
NCT02782104	A Long-term Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression (SUSTAIN-3)	1150	Mar 2022

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

J3490	Unclassified drugs (no specific code)
G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation

ICD-10 Diagnoses

F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.89	Other specified depressive episodes
F32.9	Major depressive disorder, single episode, unspecified

F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.8	Other recurrent depressive disorders
F33.9	Major depressive disorder, recurrent, unspecified

REVISIONS

12-02--2021	Policy added to the bcbsks.com web site.

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