CADTH

CADTH Common Drug Review

# Clinical Review Report

## ESKETAMINE HYDROCHLORIDE (SPRAVATO)

## (Janssen Inc.)

**Indication:** Major Depressive Disorder in Adults


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# Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **ANCOVA** | analysis of covariance |
| **ANOVA** | analysis of variance |
| **BDI** | Beck Depression Inventory |
| **CGI-SR-I** | Clinician Global Impression–Imminent Suicide Risk |
| **CGI-SS-R** | Clinician Global Impression–Severity of Suicidality (Revised) |
| **CI** | confidence interval |
| **CMHA-AB** | Canadian Mental Health Association, Alberta Division |
| **CMHA-National** | Canadian Mental Health Association National |
| **C-SSRS** | Columbia-Suicide Severity Rating Scale |
| ***DSM-5*** | *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* |
| **EQ-5D-5L** | EuroQol 5-Dimensions 5-Levels |
| **EQ VAS** | EuroQol Visual Analogue Scale |
| **ESK** | esketamine |
| **FAS** | full analysis set |
| **HAM-D17** | 17-item Hamilton Depression Rating Scale |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **LS** | least squares |
| **LOCF** | last observation carried forward |
| **MADRS** | Montgomery-Åsberg Depression Rating Scale |
| **MCID** | minimal clinically important difference |
| **MDAO** | Mood Disorders Association of Ontario |
| **MDD** | major depressive disorder |
| **MDE** | major depressive episode |
| **MDSC** | Mood Disorders Society of Canada |
| **MMRM** | mixed-effects model for repeated measures |
| **OC** | observed case |
| **PHQ-9** | Patient Health Questionnaire-9 |

| | |
|---|---|
| **QoL** | quality of life |
| **RCT** | randomized controlled trial |
| **SAE** | serious adverse event |
| **SD** | standard deviation |
| **SDS** | Sheehan Disability Scale |
| **SNRI** | serotonin-norepinephrine reuptake inhibitor |
| **SSRI** | selective serotonin reuptake inhibitor |
| **TEAE** | treatment-emergent adverse event |
| **WDAE** | withdrawal due to adverse event |
| **XR** | extended release |

# Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Esketamine hydrochloride (Spravato), solution for intranasal use; 28 mg single-use device |
| **Indication** | In combination with a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor, for the treatment of major depressive disorder in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode |
| **Reimbursement request** | As per indication |
| **Health Canada approval status** | Approved |
| **Health Canada review pathway** | Priority review |
| **NOC date** | NOD issued July 29, 2019<br>NOC issued May 20, 2020 |
| **Sponsor** | Janssen |

NOC = Notice of Compliance; NOD = Notice of Deficiency.

## Introduction

Major depressive disorder (MDD) is a common debilitating disorder characterized by a depressed mood with markedly diminished interest or pleasure in activities, functional impairment, poor quality of life (QoL), suicidal ideation and attempts, self-injurious behaviour, and a high relapse rate.[1,2] MDD is one of the most prevalent chronic conditions in Canada with an annual prevalence reaching 4.7% and a lifetime prevalence of 11.3% of the population.[3] *Treatment-resistant depression* is used to describe a subpopulation of patients with MDD who have not achieved optimal response with conventional therapy.

Esketamine nasal spray is supplied as a single-use device that delivers a total of 28 mg of esketamine in 2 sprays (1 spray per nostril). It is approved for use in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) for the treatment of MDD in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode.[4] According to the product monograph, the initial dose is 56 mg for adults younger than 65 years.[4] Recommended subsequent doses are 56 mg or 84 mg twice weekly for the first 4 weeks, then weekly for week 5 to 8. For week 9 and onwards, the recommended dose is 56 mg or 84 mg weekly or every 2 weeks, based on the lowest frequency needed to maintain remission or response. Esketamine should be administered in conjunction with an oral SSRI or SNRI antidepressant.[4]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of esketamine nasal solution, available as a 28 mg single-use nasal spray device, in combination with a SSRI or SNRI for the treatment of MDD in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode.

## Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

Four patient groups including the Mood Disorders Society of Canada (MDSC), Canadian Mental Health Association National (CMHA-National), the Alberta Division of CMHA (CMHA-AB), and the Mood Disorders Association of Ontario (MDAO) provided patient input for this summary. The groups gathered information from patients with MDD and their caregivers through social media, online discussions, phone interviews with a total of 6 patients, a focus group discussion with 9 patients, and online surveys conducted by MDSC (119 respondents), CMHA-AB (21 respondents), and MDAO (86 respondents).

Depression has serious impacts for patients and their caregivers that can be long-term, especially for those with treatment-resistant depression. All patient groups emphasized that depression negatively impacts a patient's emotions, QoL, and ability to do normal daily activities. Patients may experience suicidal thoughts, particularly when their depressive symptoms are compounded with life- or work-related stress. Relationships with family, friends, colleagues, and society may be negatively affected, with some experiencing stigma and social isolation due to their mental illness. The financial burden can be profound, as many patients are unable to work and must rely on disability payments or savings, may have limited access to government supports and resources, or have high out-of-pocket treatment costs.

Patients with treatment-resistant depression are desperate for symptom relief and are seeking new treatments that lead to quick recovery and improved QoL that will lower the negative long-term impact on their performance. In addition, they prefer treatments which are less frequently administered, least invasive, and least expensive. Approval of esketamine in Canada will be welcomed by patients with treatment-resistant depression; however, challenges exist with the use of this drug due to the time required for the treatment (esketamine should be administered in a health care provider setting) and difficult access to the drug (limited availability of the drug as well as the high cost). The groups suggested that affordable, equitable, and timely access to a full spectrum of psychological support is critical for individuals when medication alone does not resolve depression.

### Clinician Input

Canadian-context population studies have shown that there is a vast, unmet need for treatment for persons with any form of MDD including treatment-resistant depression. All available antidepressant treatments have significant limitations including the substantial amount of time required to develop their full potential effect. Neither medications nor psychotherapy are effective for all people, and often residual symptoms persist. Continuation of the same treatment does not prevent relapse or recurrence in all individuals. Although many antidepressants are well tolerated, there remains a significant dropout rate due to a range of different adverse effects, and patients' adherence to medication and psychological treatments is imperfect.

The clinical experts consulted by CADTH stated that the safety and adverse effect profile of esketamine will dictate that it is not used as a first-line treatment but will be used later in the

treatment algorithm for most. The optimal time point to add esketamine, however, is not clear. There are multiple strategies used for second, third, and subsequent antidepressant treatment trials, and at present, there is inadequate evidence regarding the effectiveness of esketamine in comparison to other interventions for treatment-resistant depression. Treatment resistance can be considered to vary by degrees, and there is no accepted definition in clinical practice. Based on the existing evidence for esketamine and the STAR*D trial, the clinical experts stated that patients should have exposure to at least 2 prior antidepressants, which were inadequate in achieving patient and provider defined objectives, before initiating esketamine. However, it may be used later in the treatment paradigm, in patients who have failed to respond to multiple treatments as mono- or combination therapy. Clinically meaningful outcomes include reduction in the number, frequency, and severity of depression symptoms; reduction or elimination of thoughts, intents, or plans for suicide; improvement in QoL; return to baseline in functioning in a variety of domains; and prevention of relapse or recurrence of major depressive episode (MDE). There are no routine laboratory tests or other means to identify who will respond to a particular antidepressant (including esketamine). Esketamine must be administered under the supervision of a health care provider, although the setting has yet to be determined.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

#### *Description of Studies*

Three 4-week double-blind randomized controlled trials (RCTs) (TRD3001, TRD3002, and TRD3005), and 1 double-blind, randomized withdrawal study (TRD3003) met the inclusion criteria for the systematic review. These trials enrolled adult patients with moderate-to-severe MDD who had shown nonresponse to at least 2 antidepressant drugs, 1 of which was documented during the screening phase of the trials. In the 4-week induction studies, patients received intranasal esketamine (28 mg to 84 mg fixed or flexible dosing) or placebo twice weekly, plus a newly initiated oral antidepressant (duloxetine, sertraline, escitalopram, or venlafaxine extended release [XR]) and were assessed for the change from baseline using the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at 4 weeks. Other outcomes included the change in health-related QoL (HRQoL) (using the EuroQol 5-Dimensions 5-Levels [EQ-5D-5L] index score and EuroQol Visual Analogue Scale [EQ VAS]), disability (using the Sheehan Disability Scale [SDS]), and patient-reported symptom severity (using the Patient Health Questionnaire-9 [PHQ-9]).

The longer-term relapse prevention study (TRD3003) included adults with moderate-to-severe treatment-resistant depression who underwent 2 treatment phases with intranasal esketamine plus newly initiated oral antidepressant (4-week induction phase and 12-week optimization phase). Those who achieved stable remission (MADRS total score ≤ 12 for at least 3 of the last 4 weeks of the optimization phase) with intranasal esketamine (56 mg or 84 mg weekly or every 2 weeks) were randomized to either continue esketamine plus antidepressant or switch to intranasal placebo plus antidepressant in the maintenance phase. Patients who achieved stable response (≥ 50% decrease in MADRS total score) underwent a separate randomization to esketamine or placebo. The primary outcome was time to relapse for the stable remission population.

The patients enrolled were predominantly female (62% to 71%) and White (77% to 95%), with moderate-to-severe MDD (mean MADRS score at baseline > 34 points). The mean age was approximately 46 years in Study TRD3001, Study TRD3002, and Study TRD3003,

whereas Study TRD3005 enrolled older adults with a mean age of 70.0 years (standard deviation [SD] = 4.5). The number of patients enrolled in the trials ranged from 138 patients in Study TRD3005, to 705 patients in TRD3003, with 59 to 115 patients per randomized treatment group.

*Efficacy Results*

Although HRQoL and suicidality were identified as key efficacy outcomes of interest to patients, none of the included studies were designed or powered to evaluate these outcomes. Other outcomes of interest (i.e., hospitalizations or emergency room visits and withdrawal frequency) were not analyzed as a measure of efficacy in any of the included studies. All trials reported data for the EQ-5D-5L and EQ VAS, with placebo and active treatment groups showing improvement in HRQoL scores. These data, however, were reported descriptively, with no pre-planned between-group comparisons, thus no inferences can be drawn from the results. Suicidality was also reported descriptively using the Columbia-Suicide Severity Rating Scale (C-SSRS) and through reporting of adverse events (AEs). During the trials, suicidal behaviour was infrequent but data on suicidality should be interpreted cautiously considering that all the studies excluded those with suicidal ideation or intent to act prior to enrolment.

Patient input indicated that depression affects many aspects of life including the ability to work, participate in social activities, and perform the tasks of daily life. In the trials, functional impacts were assessed using the SDS, a 30-point scale where patients rate the extent to which their work, social life or leisure activities, and home life or family responsibilities are impaired by symptoms (higher scores indicate more severe disability). The change from baseline to day 28 in the SDS score was a key secondary outcome in 2 induction studies (Table 2). For Study TRD3001, the least squares (LS) mean difference between esketamine and placebo was 2.2 points (95% confidence interval [CI], –4.9 to 0.5) for the 84 mg dose group and –2.5 points (95% CI, –5.3 to 0.2) for the 56 mg dose group, which were not statistically significant. In Study TRD3002, the LS mean difference between groups was –4.0 points (95% CI, –6.3 to –1.6) however due to failure of a prior outcome in the statistical testing hierarchy, these data should be interpreted as inconclusive. The SDS data from Study TRD3001 and Study TRD3002 were also limited by the extent of missing data, with 20% to 25% of patients not reporting day 28 results. The relapse prevention trial (TRD3003) also reported data for SDS during the maintenance phase (Table 3). The LS mean differences favoured esketamine versus placebo in the stable remitter (–2.9 points; 95% CI, –5.5 to –0.4) and the stable responder populations (–4.7 points; 95% CI, –7.3 to –2.1), with 95% CI that excluded the null; however, there was no control for multiple testing and these data should be interpreted in light of the potentially inflated risk of type I error. In addition, the clinical importance of these findings is unclear given the uncertain validity of the SDS and the lack of a minimal clinically important difference (MCID).

Depression symptom severity was measured using a patient-reported instrument (PHQ-9) and a clinician-reported instrument (MADRS). The PHQ-9 includes 9 symptom domains and is scored from 0 to 27 points with higher scores indicating greater severity of depressive symptoms. The change from baseline to day 28 in the PHQ-9 score, which was a key secondary outcome in 2 of the induction studies, were inconclusive due to failure of a prior outcome in the serial gatekeeping procedures to control the type I error. In Study TRD3001, the difference in the LS means for esketamine 56 mg versus placebo was –2.3 points (95% CI, –4.3 to –0.3) and for esketamine 86 mg was –2.2 points (95% CI, –4.3 to –0.2). In Study TRD3002, the LS mean difference between esketamine and placebo was –2.4 points (95% CI, –4.2 to –0.7). In the relapse prevention study, the mean PHQ-9 scores

increased from baseline to the last time point measured in both the esketamine and placebo groups. The difference between groups favoured esketamine over placebo with a LS mean difference of –2.4 points (95% CI, –4.2 to –0.7) for the stable remitter population, and –3.0 points (95% CI, –4.9 to –1.2) for the stable responder population. However, the interpretation of these data should take into consideration that there was no control for type I error for secondary outcomes in Study TRD3003. The MCID for the PHQ-9 is not known.

The change from baseline to day 28 in the MADRS total score was the primary outcome in all 3 induction studies. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. It is scored from 0 to 60 with higher scores indicating more severe symptoms. Both the esketamine and placebo groups showed a reduction in MADRS scores over time (Table 2). In Study TRD3002, the LS mean difference between esketamine and placebo was –4.0 points (95% CI, –7.3 to –0.6), which was statistically significant (1-sided P = 0.010). In Study TRD3001, the LS mean difference of –3.2 points (95% CI, –6.9 to 0.5) between esketamine 84 mg and placebo did not reach statistical significance, and according to the statistical analysis plan, testing of the 56 mg dosage group was to stop. The study reported an LS mean difference for esketamine 56 mg versus placebo of –4.1 points (95% CI, –7.7 to –0.5). In Study TRD3005 that enrolled patients 65 years or older, the LS mean difference between esketamine and placebo for the change from baseline in MADRS score was –3.6 points (95% CI, –7.2 to 0.07), which was not statistically significant with the 1-sided P value of 0.029.

Time to relapse was the primary outcome of Study TRD3003. Relapse was defined as a MADRS total score of 22 points or more for 2 consecutive assessments or hospitalization for worsening depression or any other clinically relevant event that was suggestive of a relapse of depressive illness (for example, suicide attempt, completed suicide, or hospitalization for prevention of suicide). Among patients who achieved stable remission at the end of the optimization period, 24 patients (27%) relapsed in the esketamine group and 39 patients (45%) relapsed in the placebo group (Table 3). Relapse was delayed in the esketamine group relative to placebo with a hazard ratio (HR) of 0.49 (95% CI, 0.29 to 0.84; P = 0.003). Among patients in the stable responder population, relapse was delayed in the esketamine versus placebo group with a HR of 0.30 (95% CI, 0.16 to 0.55; P < 0.001).

*Harms Results*

In the induction studies, the proportion of patients who reported AEs was higher among those who received esketamine (71% to 89%) than placebo (60% to 68%) (Table 2). The most commonly reported AEs in the esketamine groups were dissociation (13% to 28%), dizziness (21% to 28%), vertigo (11% to 26%), nausea (18% to 32%), dysgeusia (6% to 24%), and somnolence (1% to 21%).

In the relapse prevention study (TRD3003), 74% to 82% of patients who received esketamine experienced 1 or more AEs, compared with 46% of patients who received placebo in the maintenance phase (Table 3). Similar to the induction studies, the most commonly reported events in the esketamine group were dissociation, dizziness, vertigo, nausea, dysgeusia, and somnolence, which were reported by 11% to 27% of patients.

The percentage of patients who stopped intranasal study drug treatment due to AEs ranged from 1% to 7% of patients who received esketamine and 1% to 3% who received placebo. Serious adverse events (SAEs) were reported by 0% to 4% of patients in the esketamine groups, and from 0% to 3% of patients in the placebo groups during the 4 RCTs. Worsening

depression, anxiety, suicidal ideation, increased blood pressure, hypertensive crisis, cerebral hemorrhage, dizziness, vertigo, and sedation were among the SAEs reported. There was 1 death reported in the esketamine group of Study TRD3002. No other deaths were reported in the RCTs.

The sponsor reported 3 completed suicides among patients treated with esketamine during the phase II and phase III trials in treatment-resistant depression (2.9 events per 1,000 patient-years). No suicides were reported among those who received placebo (per 100 patient-years). The frequency of treatment-emergent suicidality in patients who received esketamine ranged from 0% to 4.0% in the treatment and follow-up phases of the RCTs, and 2 longer-term uncontrolled studies. In comparison, the frequency of treatment-emergent suicidality in placebo-treated patients ranged from 0% to 2.5%, although it should be noted that the total follow-up time for the placebo groups was limited.

The trials reported groupings of AEs related to abuse potential, dizziness, and increased blood pressure, which were all reported more frequently among patients who received esketamine than placebo (Table 2 and Table 3). The group labelled “drug abuse, dependence, and withdrawal” in included terms for dissociation, dizziness, somnolence, euphoria, hallucination, feeling drunk, feeling relaxation, and mental impairment, as well as terms related to substance use disorder.

## Table 2: Summary of Key Results From Induction Studies

| Outcomes | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Change from baseline to day 28 in SDS total score (MMRM OC)[a]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 88 (77) | 87 (76) | 90 (80) | 86 (75) | 85 (78) | NR | NR |
| Baseline, mean (SD) | 24.0 (4.1) | 24.7 (4.6) | 24.4 (3.9) | 24.0 (4.1) | 24.2 (4.4) | NR | NR |
| End point, mean (SD) | 13.4 (9.8) | 13.5 (10.1) | 16.0 (9.8) | 10.1 (7.7) | 14.8 (9.1) | NR | NR |
| Change from baseline, mean (SD) | –11.0 (9.3) | –11.1 (10.0) | –8.4 (9.7) | –13.6 (8.3) | –9.4 (8.4) | NR | NR |
| Difference of LS means versus placebo (95% CI) | –2.5 (–5.3 to 0.2)[b] | –2.2 (–4.9 to 0.5)[b] | Ref | –4.0 (–6.3 to –1.6) | Ref | NR | NR |
| P value (1-sided) | NS[b,c] | NS[b,c] | NA | NS[c] | NA | NR | NR |
| **Change from baseline to day 28 in MADRS total score (MMRM OC)[a]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 111 (97) | 98 (86) | 108 (96) | 101 (89) | 100 (92) | 63 (88) | 60 (92) |
| Baseline, mean (SD) | 37.4 (4.8) | 37.8 (5.6) | 37.5 (6.2) | 37.0 (5.7) | 37.3 (5.7) | 35.5 (5.9) | 34.8 (6.4) |
| Day 28, mean (SD) | 18.5 (13.3) | 19.4 (13.9) | 22.8 (13.7) | 15.5 (10.7) | 20.6 (12.7) | 25.4 (12.7) | 28.7 (10.1) |
| Change from baseline, mean (SD) | –19.0 (13.9) | –18.8 (14.1) | –14.8 (15.1) | –21.4 (12.3) | –17.0 (13.9) | –10.0 (12.7) | –6.3 (8.9) |

| Outcomes | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| Difference of LS means versus placebo (95% CI) | –4.1 (–7.7 to –0.5) [b] | –3.2 (–6.9 to 0.5) [b] | Ref | –4.0 (–7.3 to 0.6) | Ref | 3.6 (–7.2 to 0.07)[b] | Ref |
| P value (1-sided) | NS[b,c] | 0.044 NS[b] | NA | 0.010 | NA | 0.029 NS[b] | NA |
| **Harms, n (%) (safety set)** | **N = 115** | **N = 116** | **N = 113** | **N = 115** | **N = 109** | **N = 72** | **N = 65** |
| Patients with ≥ 1 adverse event | 100 (87) | 103 (89) | 77 (68) | 98 (85) | 66 (61) | 51 (71) | 39 (60) |
| Patients who stopped intranasal treatment due to adverse events | 1 (1) | 7 (6) | 2 (2) | 8 (7) | 1 (1) | 4 (6) | 2 (3) |
| Patients with ≥ 1 SAE | 2 (2) | 0 | 0 | 1 (1) | 1 (1) | 3 (4) | 2 (3) |
| Deaths | 0 | 0 | 0 | 1 (1) | 0 | 0 | 0 |
| **Notable harms, n (%)** | | | | | | | |
| TEAE suggestive of abuse | 65 (57) | 60 (52) | 20 (18) | 58 (50) | 14 (13) | 21 (29) | 9 (14) |
| Dizziness or vertigo | 52 (45) | 50 (43) | 13 (12) | 59 (51) | 9 (8) | 20 (28) | 7 (11) |
| Suicidality | 1 (1) | 2 (2) | 1 (1) | 0 | 1 (1) | 1 (1) | 0 |
| Increased blood pressure | 9 (8) | 14 (12) | 5 (4) | 12 (10) | 1 (1) | 10 (14) | 4 (6) |

CI = confidence interval; ESK = esketamine; FAS = full analysis set; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; NR = not reported; NS = not statistically significant; OC = observed case; ref = reference; SAE = serious adverse event; SD = standard deviation, SDS = Sheehan Disability Scale; TEAE = treatment-emergent adverse event.

[a] MMRM model with treatment, day, country or region, class of oral antidepressant (serotonin-norepinephrine reuptake inhibitor or selective serotonin reuptake inhibitor), treatment-by-day interaction, and baseline value as covariates for the FAS OC population (no imputation for missing data). Negative differences favour ESK.

[b] Difference from placebo was based on the median unbiased estimate for the weighted combination of the LS means for stage 1 (patients enrolled prior to the interim analysis) and stage 2 (patients enrolled after the interim analysis) versus placebo.

[c] Not statistically significant. Statistical testing stopped due to failure of a prior outcome in the statistical testing hierarchy.

[d] Safety set.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 3: Summary of Key Results From Relapse Prevention Study

| Outcomes | Stable remitters (FAS) | | Stable responders (FAS) | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Time to relapse** | | | | |
| Number of patients contributing to the analysis (% of total N) | 90 (100) | 86 (100) | 62 (100) | 59 (100) |
| Number of relapses, n (%) | 24 (26.7) | 39 (45.3) | 16 (26) | 34 (58) |
| 25th percentile time to relapse (95% CI) | 153 (105 to 225) | 33 (22 to 48) | 217 (56 to 635) | 24 (17 to 46) |
| Median time to relapse, days (95% CI) | NE | 273 (97 to NE) | 635 (264 to 635)[a] | 88 (46 to 196) |
| HR (95% CI) | 0.49 (0.29 to 0.84)[b] | Ref | 0.30 (0.16 to 0.55)[c] | Ref |
| P value (2-sided) | 0.003[d] | NA | < 0.001[e] | NA |

| | Stable remitters (FAS) | | Stable responders (FAS) | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Change from baseline to end point in SDS total score** | | | | |
| Number of patients contributing to the analysis (% of total N) | 82 (91) | 77 (90) | 58 (94) | 53 (90) |
| Baseline, mean (SD) | 2.6 (4.6) | 3.6 (5.7) | 6.7 (5.8) | 7.0 (6.7) |
| End point, mean (SD) | 6.6 (7.5) | 10.3 (9.0) | 8.9 (7.0) | 12.8 (8.3) |
| Change from baseline, mean (SD) | 4.7 (7.3) | 7.2 (10.4) | 2.2 (6.6) | 6.8 (7.6) |
| Difference of LS means versus placebo (95% CI) | –2.9 (–5.5 to –0.4)[f] | Ref | –4.7 (–7.3 to –2.1)[f] | Ref |
| P value (2-sided) | 0.025[g] | NA | < 0.001[g] | NA |
| | **Induction phase** | **Optimization phase** | **Maintenance phase** | |
| | **ESK N = 437** | **ESK N = 455** | **ESK N = 152** | **Placebo N = 145** |
| **Harms, n (%) (safety set)** | | | | |
| Patients with ≥ 1 adverse event | 336 (77) | 335 (74) | 125 (82) | 66 (46) |
| Patients who stopped intranasal treatment due to adverse events | 22 (5) | 5 (1) | 4 (3) | 3 (2) |
| Patients with ≥ 1 SAE | 13 (3) | 11 (2) | 4 (3) | 1 (1) |
| Deaths | 0 | 0 | 0 | 0 |
| **Notable harms, n (%)** | | | | |
| TEAE suggestive of abuse | 205 (47) | 170 (37) | 75 (49) | 9 (6) |
| Dizziness or vertigo | 214 (49) | 161 (35) | 66 (43) | 17 (12) |
| Suicidality | 5 (1.1) | 1 (0.2) | 3 (2.0) | 1 (0.7) |
| Increased blood pressure | 40 (9) | 30 (7) | 13 (9) | 5 (3) |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; FAS = full analysis set; HR = hazard ratio; LOCF = last observation carried forward; LS = least squares; NE = not estimable; ref = reference; SAE = serious adverse event; SD = standard deviation; SDS = Sheehan Disability Scale; TEAE = treatment-emergent adverse event.

[a] Influence by 1 patient who had a long time to relapse (635 days).

[b] HR and 95% CI calculated based on weighted estimates as per Wassmer (2006).[8]

[c] Based on Cox proportional hazards model with treatment as a factor.

[d] Based on weighted combination of the log-rank test. Two-sided significance level of 0.046 to control type I error due to interim analysis.

[e] Based on log-rank test.

[f] ANCOVA model with treatment, country, and baseline value as covariates for the FAS-remitters or FAS-responders population and LOCF for missing data. Negative differences favour esketamine.

[g] No adjustment to control the type I error.

Source: Clinical Study Report for Study TRD3003.[9]

### *Critical Appraisal*

All studies were multi-centre, double-blind RCTs that used accepted methods to randomize and allocate patients to treatments. The baseline characteristics of patients appear to be balanced between groups within studies; however, there were differential losses to follow-up in the induction studies, with more patients withdrawing from the esketamine groups

than the placebo groups. As a result, the mixed-effects model for repeated measures (MMRM) analysis may inflate the treatment effects of esketamine relative to placebo, as those who remained in the trial until day 28 likely reflect those who would show a positive outcome (i.e., missing not at random). Although all trials took steps to blind patients and study site personnel to treatment allocation, there was potential for unblinding due to the frequency of acute adverse effects (e.g., sedation, dissociation, nausea, and cardiovascular changes) that are known to be associated with esketamine. Given the subjective nature of the outcome measures, it is possible that reporting of efficacy outcomes or harms may have been influenced by expectations of treatment, and although sensitivity analyses were conducted to explore the impacts of unblinding, the possibility of bias cannot be ruled out. Study TRD3003 and Study TRD3005 did not control the type I error for secondary outcomes, and thus any statistically significant results should be interpreted in light of the potentially inflated risk of type I error.

The patients enrolled reflect an enriched population, as only those who were adherent to treatments entered the induction phase of all trials, and only those responsive to esketamine were randomized in the relapse prevention study (TRD3003). This is particularly important for the interpretation of the relapse prevention trial, in which patients underwent 2 rounds of enrichment during the induction and optimization phases. Thus, the findings of this longer-term trial may have limited generalizability to the broader population of patients with treatment-resistant depression. The trials also excluded patients with comorbid psychiatric disorders, substance use disorder, or recent suicidality, thus the generalizability to these populations may be limited.

There is no direct evidence available comparing esketamine to other therapeutic options for treatment-resistant MDD.

## Indirect Comparisons

No indirect treatment comparisons of adequate methodological quality were identified.

## Other Relevant Evidence

This report also includes a summary of 4 trials that did not meet the inclusion criteria for the systematic review but provide supplementary data on esketamine. These studies include 2 open-label, uncontrolled trials in patients with treatment-resistant depression (TRD3004 and TRD3008) and 2 double-blind RCTs in patients at imminent risk of suicide (ASPIRE 1, ASPIRE 2).

### *Description of Uncontrolled Studies*

The objective of Study TRD3004 and Study TRD3008 was to assess the long-term safety and tolerability of intranasal esketamine plus an oral antidepressant in patients with treatment-resistant depression. Study TRD3004 was a 1-year open-label, uncontrolled phase III clinical trial in 802 patients with MDD who had shown inadequate response to 2 antidepressant drugs. Study TRD3008 is an ongoing open-label extension study for patients who participated in Study TRD3001, Study TRD3002, Study TRD3005, Study TRD3003, Study TRD3004, and Study TRD3006 (an ongoing RCT). The interim analysis reported data from 1,140 patients who had received intranasal esketamine. In both studies, patients had to show response to esketamine after a 4-week induction period in order to continue in the maintenance phase of these trials. In the maintenance phase, patients self-administered esketamine (28 mg, 56 mg, or 84 mg), as a flexible dose regimen on a

weekly, biweekly, or every 4 weeks dosing regimen with adjustments based on efficacy and tolerability.

### *Efficacy Results*

In Study TRD3004, MADRS, PHQ-9, SDS, and EQ-5D-5L outcome scores were lower than baseline and appeared to remain constant during the maintenance phase among patients who remained in the study. No efficacy data were reported for the interim analysis of Study TRD3008.

### *Harms Results*

Most patients in Study TRD3004 and Study TRD3008 experienced 1 or more adverse effects (90% and 89%), with dizziness, dissociation, headache, and nausea reported by more than 20% of patients in each trial. SAEs were reported in 7% and 8%, and suicidality was reported in 5% and 3% of patients in Study TRD3004 and Study TRD3008, respectively. In both trials, 13% of patients reported increased blood pressure. There was a total of 5 deaths reported, including 2 completed suicides. No new safety signals were identified in the uncontrolled trials that had a median treatment duration of 23 weeks in Study TRD3004 and 15 months in Study TRD3008.

### *Critical Appraisal*

These trials are limited by their open-label study design and lack of randomization or control groups. Both trials included enrichment strategies and allowed only those who had demonstrated response to esketamine to continue treatment in the longer-term maintenance period. Moreover, efficacy data based on observed case (OC) data may inflate the treatment response as patients with poor outcomes tend to drop out. Considering the potential selection and attrition biases, these data likely overestimate effects that may be observed in clinical practice. While these trials provide longer-term safety outcomes, which is of interest to decision-makers, these data cannot be used to draw conclusions on the comparative safety of esketamine.

### *Description of Studies in Patients at Risk of Suicide*

The primary objective of the ASPIRE 1 and ASPIRE 2 studies was to evaluate the efficacy of intranasal esketamine 84 mg twice weekly compared with intranasal placebo (as add-on to standard of care antidepressant therapy) in reducing the symptoms of MDD including suicidal ideation, in patients who were assessed to be at imminent risk for suicide. Patients received intranasal esketamine or placebo for 25 days, followed by a 65-day follow-up period. The primary and key secondary efficacy end points were the change from baseline to 24 hours after the first dose (day 2) in the MADRS total score and in the Clinician Global Impression–Severity of Suicidality (Revised) (CGI-SS-R) for the double-blind treatment phase.

### *Efficacy Results*

In both trials, patients in the esketamine group had statistically significantly lower MADRS total scores compared to the placebo group 24 hours after the first dose. The MADRS score in the ASPIRE 1 study was –3.8 points (95% CI, –6.6 to –1.1; P = 0.006) and in the ASPIRE 2 study was –3.9 points (95% CI, –6.6 to –1.1; P = 0.006). The between-group differences were considered clinically relevant, according to the clinical experts consulted for this review. Results of the key secondary outcome showed that in both trials at day 2,

there were no statistically significant differences in the CGI-SS-R score between the esketamine group and the placebo group (P = 0.107 in ASPIRE 1; P = 0.379 in ASPIRE 2).

*Harms Results*

Most patients in the ASPIRE studies experienced 1 or more AEs: ASPIRE 1, 89% with esketamine versus 74% with placebo; ASPIRE 2, 91% with esketamine versus 77% with placebo. Dizziness, dissociation, and nausea were reported by more than 20% of patients treated with esketamine in each trial.

SAEs were reported in 4.4% of patients in the ASPIRE 1 study and 4.8% in the ASPIRE 2 study. Withdrawal due to adverse events (WDAEs) were reported in 4.4% of patients in the ASPIRE 1 study and 5.3% in the ASPIRE 2 study. There were no deaths during the double-blind treatment phase in either study, while in the ASPIRE 1 study, 1 completed suicide occurred in the esketamine group during the follow-up phase. Compared to placebo, more patients treated with esketamine experienced treatment-emergent adverse events (TEAEs) suggestive of abuse.

*Critical Appraisal*

Although the ASPIRE studies were multi-centre, randomized, double-blind studies, these studies enrolled a different target population than the current CADTH review. According to the sponsor, study participants' past treatment history was not captured in the ASPIRE 1 and ASPIRE 2 studies, therefore it is unclear what proportion of patients in the ASPIRE studies would meet the criteria for treatment-resistant depression. Generalizability of the results of these 2 trials to patients with treatment-resistant depression is limited. In addition, due to the short duration of the ASPIRE studies (up to 90 days), the long-term efficacy and safety of esketamine in the study population is uncertain.

## Conclusions

Among adult patients with MDD who had an inadequate response to at least 2 prior antidepressant therapies, esketamine nasal spray plus a newly initiated oral antidepressant was associated with short-term improvement in depression symptom severity scores relative to placebo plus new oral antidepressant therapy. Statistical differences between esketamine and placebo, however, were not consistently observed across trials, and while the point estimates for the change from baseline in MADRS scores suggest the differences may be clinically meaningful, the 95% CI includes values of minimal clinical importance.

In patients who had achieved remission with esketamine plus an oral antidepressant, relapse was delayed among those who remained on esketamine compared with patients switched to placebo. However, due to the selection of an enriched population that had maintained a favourable response and tolerability to esketamine over 4 months, the generalizability of these findings to patients with MDD in Canada may be limited.

In all trials, the possibility of reporting bias cannot be ruled out due to the challenges in maintaining blinding with a drug that has frequent acute adverse effects. No inferences can be drawn from the SDS data due to the extent of missing data, or statistical issues related to lack of control of type I error, or failure of a prior outcome in the statistical testing procedure. Thus, the impact of esketamine on disability is unclear. No conclusions can be drawn regarding the effect of esketamine on HRQoL, suicidality, hospitalization, or emergency department visits, as the trials were not designed or powered to evaluate these outcomes.

Esketamine was associated with increased frequency of AEs compared with placebo; notably, dissociation, dizziness, vertigo, nausea, somnolence, and increased blood pressure. Longer-term safety of esketamine is uncertain. Due to the hemodynamic and cognitive adverse effects, and the abuse potential of esketamine, the drug will be available through a controlled distribution program, but the details have not yet been determined.

# Introduction

## Disease Background

MDD is a common debilitating disorder characterized by a depressed mood with markedly diminished interest or pleasure in activities, functional impairment, poor QoL, suicidal ideation and attempts, self-injurious behaviour, and a high relapse rate.[1,2] MDD is one of the most prevalent chronic conditions in Canada with an annual prevalence reaching 4.7% and a lifetime prevalence of 11.3% of the population.[3] Globally, depressive disorders are the leading cause of nonfatal health loss.[10]

Approximately one-third of patients experience a remission of a MDE with the first selected antidepressant medication, and with each subsequent treatment trial the likelihood of remission diminishes.[11], Poorer longer-term outcomes, including higher relapse rates, were associated with those who required more treatment steps in the STAR*D trial.[11] treatment-resistant depression is used to describe a subpopulation of patients with MDD who have not achieved optimal response with conventional therapy. There is, however, no consensus on the definition of treatment resistance or what constitutes an adequate trial of therapy in terms of dose, duration, or outcome measures.[12]

## Standards of Therapy

The following information is based on input from clinicians consulted by CADTH for the purpose of this review.

The most common and important treatments for MDD include antidepressant medication and psychotherapy. Access to evidence-based psychotherapies is imperfect in most jurisdictions due to a variety of factors including access to appropriate providers and lack of adequate public or insurance funding. Other significant treatments include transcranial magnetic stimulation and electroconvulsive therapy. Transcranial magnetic stimulation is not funded or not available in many jurisdictions, limiting its applicability. Electroconvulsive therapy is an important treatment of very severe forms of depression and/or very treatment refractory depressive disorders but is administered to a minority of people with MDD, many of whom are hospitalized. The clinical experts reported that ketamine is used in Canada as an off-label treatment for patients with MDD that have not responded to other treatments.

Evidence-based psychotherapies and antidepressant medications are similar in effectiveness for mild depressive disorders. More severe and psychotic forms of depression are much more likely to require biological treatments like antidepressant medications. However, only a minority of patients experience a remission of a MDE with the first selected antidepressant medication — approximately 30%. This means that the majority of people following a single trial of an antidepressant medication will either be nonresponsive, or partly responsive with very significant remaining symptoms. When treatment has been given with a single antidepressant agent at an adequate dose, and for an adequate duration, there are several possibilities for next steps.[13] In general, “dose optimization” is routinely recommended as a first step. “Dose optimization” typically means increasing the dose into the higher end of the dosing range and allowing a further period to re-evaluate effectiveness. This may or may not be acceptable to patients, depending on their ability to tolerate adverse effects which typically increase with dose increments. Following dose optimization, subsequent strategies include switching to an alternative antidepressant or combining the initial antidepressant with another medication to improve effectiveness. For

example, a second-generation antipsychotic drug (e.g., aripiprazole, quetiapine, risperidone, or olanzapine) could be added to an ongoing SSRI or SNRI or another antidepressant could be given simultaneously (e.g., adding bupropion or mirtazapine). Other add-on options include lithium carbonate, liothyronine, buspirone, and stimulant medications. With each successive antidepressant medication trial, the likelihood of having symptomatic remission decreases in comparison to the first trial of antidepressant medication. As such, there are a very significant number of patients who continue to have clinically important symptoms following 2 or more trials of current antidepressant treatments. The quality of evidence comparing different "step 2" or "step 3" treatments is not very robust. So, clinicians are currently left with a list of multiple possible options, from which they choose their next steps based on a combination of (likely) tolerability, key target symptoms, past experience, convenience, and affordability.

The goals of treatment in MDD include reduction of depression symptoms (or ideally, elimination of symptoms), provision of positive mental health (rather than symptom resolution exclusively), return to baseline in functional ability, reduction in suicide and thoughts of suicide, improvement in QoL, and after acute treatment is complete, prevention of relapse or recurrence of depressive episodes and suicide. All of the potential benefits of antidepressant medication need to be considered in balance with the nature and extent of medication adverse effects since maintenance medication is routinely offered for a minimum period of 6 to 12 months after acute treatment, and for people with long-lasting, treatment-resistant, or frequently recurring episodes, maintenance medication may be prescribed for much longer or even indefinitely. Ideally treatments for MDD would also have positive effects on other mental health conditions, such as panic disorder, generalized anxiety disorder, or social anxiety disorder, that frequently co-exist in patients with depression.

## Drug

Esketamine is the S-enantiomer of ketamine, a nonselective, non-competitive antagonist of the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor (Table 4).[4] The mechanism of action for depression is not fully understood. Esketamine was granted priority review status in 2018, was issued a Notice of Deficiency on July 29, 2019, and was granted a Notice of Compliance by Health Canada on May 20, 2020. It is approved for use in combination with a SSRI or SNRI, for the treatment of MDD in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode.[4] The sponsor is seeking reimbursement as per the indication.

Esketamine nasal spray is supplied as a single-use device that delivers a total of 28 mg of esketamine in 2 sprays (1 spray per nostril). It is intended for administration by the patient under the supervision of a health professional, using 1 device (for a 28 mg dose), 2 devices (for a 56 mg dose), or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.[4] According to the product monograph, the initial dose is 56 mg for adults younger than 65 years of age.[4] Recommended subsequent doses are 56 mg or 84 mg twice weekly for the first 4 weeks, then weekly for week 5 to 8. For week 9 and onwards, the recommended dose is 56 mg or 84 mg weekly or every 2 weeks, based on the lowest frequency needed to maintain remission or response. Patients should be monitored by a health care professional after administration of each dose for at least 2 hours until the patient is stable. Esketamine will be available through a controlled distribution program

(JANSSEN JOURNEY; www.JanssenJourneyHCP.ca), however no details are available at this time.[4]

In 2019, esketamine was approved in the US, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults.[14] esketamine was also approved by the European Medicines Agency in combination with an SSRI or SNRI, for adults with treatment-resistant MDD, who have not responded to at least 2 different treatments with antidepressants in the current moderate-to-severe depressive episode.[15] esketamine was granted breakthrough designation and is currently under review in the US for the reduction of depressive symptoms in adults with MDD who have active suicidal ideation with intent.[16]

## Table 4: Key Characteristics of Esketamine

| | Esketamine |
|---|---|
| **Mechanism of action** | S-enantiomer of ketamine; antagonist of the N-methyl-D-aspartate receptor |
| **Indication[a]** | In combination with a SSRI or SNRI, for the treatment of MDD in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode |
| **Route of administration** | Intranasal |
| **Recommended dose** | 56 mg or 84 mg twice weekly (first 4 weeks), then weekly for 4 weeks, then weekly or biweekly based on efficacy and tolerability[b] |
| **Serious adverse effects or safety issues** | Contraindications: patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage, recent [within 6 weeks] major cardiovascular event)<br>Warnings: Use with caution in patients with clinically significant or unstable cardiovascular, cerebrovascular, or respiratory conditions, such as poorly controlled hypertension, prior cardiovascular event (e.g., MI) or stroke, valvular heart disease, uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability, or NYHA class III or IV heart failure; for these patients, esketamine should be administered in a setting with resuscitation equipment and health care professionals with training in cardiopulmonary resuscitation<br>Use with caution in patients with higher risk of substance abuse, hyperthyroidism, psychosis, or conditions associated with increased intracranial pressure<br>Patients should be monitored for suicidal ideation or other indicators of suicidal behaviour<br>Patients to avoid driving or operating machinery until the day after dosing due to impacts on attention, judgment, thinking, reaction speed, and motor skills |
| **Other** | Will be available through a controlled distribution program with only select pharmacies able to dispense the product (JANSSEN JOURNEY; www.JanssenJourneyHCP.ca).<br>Drug administration must be supervised by a health care professional, and patients monitored for at least 2 hours until clinically stable; medical support to manage adverse reactions such as increased blood pressure, dissociation, sedation, and anxiety, should be available |

MDD = major depressive disorder; MI = myocardial infarction; NYHA = New York Heart Association; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] Health Canada approved indication.

[b] The initial dose for patients with Japanese ancestry and patients 65 years or older is 28 mg. The product monograph states that efficacy was not established in patients 65 years or older and esketamine is not recommended in these patients.

Source: Esketamine product monograph.[4]

# Stakeholder Engagement

## Patient Group Input

*This section was prepared by CADTH staff based on the input provided by patient groups.*

### About the Patient Groups and Information Gathered

Four patient groups, including the MDSC, CMHA-National, CMHA-AB, and MDAO, provided patient input for this summary. The MDSC is a mental health consumer-led organization which was incorporated in 2001. Its objective is to provide people with mood disorders, their families, and caregivers with a strong, cohesive voice at the national level to improve access to treatment, shape program development and treatment innovations, inform research, influence government policies, help with better understanding mood disorders, and ensure that the voices of consumers, family members, and caregivers are accurately communicated and heard on issues of national importance . The CMHA-National is a nationwide community mental health organization founded in 1918 . Supported by its volunteers and staff across every province and 1 territory in Canada, the CMHA-National provides advocacy and resources that help to prevent mental health problems and illnesses, support recovery and resilience, and enable all Canadians to flourish and thrive. CMHA-AB has a focus on recovery and support for Albertans impacted by mental illness . The MDAO is a community-based mental health services provider with a 30-year history. It supports Ontarians who experience mood disorders, early psychosis, and mental health or addictions issues, and their caregivers, through peer support, clinical services, and counselling programs . CMHA-National, CMHA-AB, and MDAO prepared a joint patient input submission for this review.

The MDSC reported that they had no help from outside their group to collect and analyze data, or to complete the submission. Janssen (one of the funders for CMHA-National and MDAO) assisted CMHA-National and MDAO by providing patient contacts and reference material to the drug during the preparation of their submission. CMHA-AB declared receiving help from individuals and EXEP Consulting Inc. to collect and analyze data in the preparation of this submission.

Each organization provided the source(s) of information contained in their submissions. The MDSC gathered perspectives of patients diagnosed with MDD, their family members, and caregivers via social media, website visits, fundraising campaigns, and online discussion. In addition, an online survey was conducted in March 2018, where 119 respondents provided input on treatment-resistant depression. Among them, 51% experienced more than 10 acute depression episodes. CMHA-National gathered patient perspectives by conducting phone interviews with 3 American patients (2 males and 1 female, aged 40 to 70 years) who had long-term treatment-resistant depression and were participating in a study of esketamine nasal spray at the time of interview. CMHA-AB conducted a survey (16 individuals completed and 5 partially completed the survey) and follow-up focus groups (N = 9) with Albertan adults with depression and who had experience with at least 2 antidepressant agents but had continuous or unresolved depressive symptoms. From April to July 2019, the MDAO collected the personal experiences of patients with MDD or their caregivers using an online survey or phone interviews. Eighty-six responses were received from the survey: 75 were collected from patients with depression (the vast majority of them resided in Ontario; mean age of 53 years; 76% female, 23% male, and 1% other) and 11 were from caregivers. Individual phone interviews were conducted with 3 patients with

depression who were treated with nasal ketamine in a clinical trial setting (2 females and 1 male, aged 43 and 60 years) in the US.

## Disease Experience

The impacts from depression are serious and could be long-term, or sometimes permanent, especially for treatment-resistant depression. The MDSC survey reported that 69% of the respondents had been treating their MDD for more than 11 years. All patient groups emphasized that depression negatively impacts a patient's emotions, QoL, and ability to do normal daily activities. Specifically, survey respondents indicated that depression affected sleep, appetite, mood, relationships, exercise, work, and the ability to do the activities they used to enjoy, as well as the tasks of daily life such as getting out of bed, getting ready, preparing meals, or tidying the house. Respondents also reported feeling apathetic and always felt "darkness," feeling tired or having little energy, little interest or pleasure in doing things, feeling down or hopeless, difficulty concentrating, and feeling bad about themselves. "Negative coping" strategies such as self-harm and alcohol or drug abuse were reported. Respondents' depression was also accompanied by suicidal thoughts, particularly when their depressive symptoms were compounded with life- and/or work-related stress. Their relationships with family, friends, colleagues, and society were negatively affected as well, with some reporting experiencing stigma and social isolation due to their mental illness. Many feel the need to hide their condition from family or co-workers. The financial burden can be profound, as many patients are unable to work and must rely on disability payments or savings, may have limited access to government supports and resources, or have high out-of-pocket treatment costs. In the submission by CMHA-National, CMHA-AB, and MDAO, 87% of the respondents reported experiencing financial difficulties since the diagnosis of depression. Furthermore, the caregivers' responses showed a high burden of care that negatively impacted their physical, mental, and financial health, given the limited availability of supports in the health care system.

Some examples of quotes from patients include:

- "When things are bad, I'm extremely unmotivated and uninterested, and, you know, I can't get off the couch, so to speak. […] It severely impacts my ability to work, and enjoy my life, and all that"
- "If I went to sleep tonight and never woke up that wouldn't be terrible news"
- "Some days are better than others, some months are better than others, but, I try not to let it impact, especially my daughter. My poor husband gets the brunt of it. I try not to let it impact him, but it does."

## Experience With Treatment

All patient respondents in the patient groups have tried some medications for depression. Various antidepressant drugs are available, such as Wellbutrin, Effexor/Effexor XR, Celexa, Prozac, Cipralex, Paxil, Cymbalta, and Luvox. Patients also reported receiving supplemental medications including antipsychotic drugs and anticonvulsants. The respondents had tried multiple treatment options in hopes of managing their disorder, sometimes trying several treatments simultaneously. Patients responded differently to the available antidepressants. Some respondents reported that the treatments did have a positive impact on their QoL and the level of satisfaction, as long as the experienced side effects were transient. For some respondents, the medications had no impact. The MDSC survey reported that 49% of the respondents did not respond well to the treatment. Common adverse effects related to these antidepressants included weight gain, memory

loss, decreased sexual functioning, and a worsening of complications of other conditions that they had. Consequently, medication-related side effects had an impact on patient's overall QoL and willingness and ability to seek new treatments.

In the joint patient input submitted by CMHA-National, CMHA-AB, and MDAO, 6 patients in the US were being treated with intranasal esketamine in controlled clinical trial settings. All of them consistently experienced relatively instantaneous improvement in their depressive symptoms and cognitive functioning in comparison to their previous treatments, while temporary adverse effects such as unpleasant taste, short-term dissociation, headache, and dizziness were reported as well. One patient said:

> So I've had counselling all along, and what's changed is the esketamine has really reduced the symptoms of depression. And as the depression has gotten better, it's also really kind of made me realize (a) how bad it was, and (b) that I could actually expect some additional improvements that were, that I didn't realize, were related to the depression.

Study participants in the esketamine clinical trials were also concerned about the cost beyond their participation in the trial. The MDSC pointed out that there were no Canadian clinical trials on esketamine at the time of their submission, therefore Canadians diagnosed with depression have no direct experience of this drug. The group said that the potential approval of esketamine in Canada will be welcomed by patients with treatment-resistant depression who are desperate for symptom relief; however, challenges exist in the use of this drug due to the time required for the treatment (esketamine should be administered in a health care provider setting) and difficult access to the drug (limited availability of the drug as well as the high cost).

Besides antidepressants, patients also received psychotherapy or other treatments (e.g., electroconvulsive therapy). Some patients stated that these treatments lacked effectiveness. The MDSC submission indicated that although psychotherapy is recommended to be used along with medication for maximized outcomes, it is usually not covered by public funding.

The patient groups identified the barriers to accessing appropriate, professional mental health care in the public health care system, which included wait times, appointment scheduling, service locations, provider or system availability, and a lack of interprofessional communication.

### Improved Outcomes

Patients expressed that they are willing to continue to try new medications in the hopes of finding one that works. The joint input from the groups of CMHA-National, CMHA-AB, and MDAO emphasized that a new treatment should have a more rapid treatment response compared to the current treatments, especially for patients with suicidal ideation and MDD. In addition, a new treatment which is less frequently administered, least invasive, and least expensive is desired. There are limited treatment options available for patients with treatment-resistant depression in the public health care system. CMHA-AB stated that expanding the publicly funded treatment options may reduce the out-of-pocket expense and improve patients' supports. Furthermore, the groups suggested that affordable, equitable, and timely access to a full spectrum of reasonably priced psychological support is critical for individuals when medication alone does not resolve depression. The MDSC echoed that coverage for new mental illness medications leads to significant benefits for the employer

when the employees have quick recovery and lower negative long-term impact on their performance.

## Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the esketamine review, a panel of clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy for the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented as follows.

### Unmet Needs

Canadian-context population studies have shown that there is a vast, unmet need for treatment of persons with any form of MDD including treatment-resistant depression. All available antidepressant treatments have significant limitations. Antidepressant treatments take a substantial amount of time to develop their full potential effect and typically 6 to 8 weeks is required for maximal symptom reduction to occur. This prolonged latency to effect is an important clinical concern for patients, caregivers, and physicians. Neither medications nor psychotherapy are effective in all people, and even when treatments are “effective” they often do not result in complete resolution of symptoms. Even if a treatment is effective in the acute phase, continuation of the same treatment does not prevent relapse or recurrence in all individuals. Residual symptoms (for example, cognitive complaints, fatigue, insomnia, and anxiety) are common, and such residual symptoms are associated with continuing distress or impairment. Adherence to medication and psychological treatments is imperfect. Although most first-line antidepressant medications are relatively well tolerated, there remains a significant dropout rate due to a range of different adverse effects including but not limited to the common sexual side effects that occur with SSRIs and SNRIs. Electroconvulsive therapy may not be an acceptable treatment option for some patients for reasons including religious, family or personal objections, and comorbid conditions that would not allow for this therapy. There is a significant number of persons who fail to respond to currently available, approved, and clinically utilized pharmacological strategies, and for whom treatment options are limited.

### Place in Therapy

Esketamine has a mechanism of action that differs from all other currently available antidepressant and psychotropic medications. By virtue of its unique mechanism of action, it has a more rapid onset of antidepressant effects, although it is not clear that esketamine comes closer than any other current antidepressant treatments in addressing the “underlying disease process” — it still has to be considered a symptomatic treatment.

The safety and adverse effect profile of esketamine will dictate that it is not used as a first-line treatment but will be used later in the treatment algorithm for most. Based on existing

evidence, esketamine will be used in combination with other pharmacotherapies. There is potential for esketamine to create a shift or partial shift in treatment paradigms for depression, at least for treatment-resistant depression. However, treatment resistance can be considered to vary by degrees, and it is not clear what the optimal time point to resort to esketamine might be. There are multiple strategies used for second, third, and subsequent antidepressant treatment trials. At present, there is inadequate evidence regarding the effectiveness of esketamine in comparison to other interventions for treatment-resistant depression. Intranasal esketamine has also not been compared (head-to-head) with intravenous ketamine (racemic ketamine is not an approved treatment of depression, but evidence for a rapid antidepressant effect of ketamine was the impetus for developing esketamine for this indication). Given the abuse liability known to be associated with ketamine, and the clinical adverse effects including sedation and temporary impairment of judgment and thought, there are unique risks with esketamine and strategies to mitigate these risks are important. Also, as many patients will require life-long pharmacological treatment, the long-term safety of esketamine will need to be monitored. Due to practical access and resource utilization factors, it may become a step before electroconvulsive therapy.

## Patient Population

Trials of standard antidepressant medication should be offered before esketamine is tried. Based on the existing evidence for esketamine and the STAR*D trial, patients should have exposure to at least 2 prior antidepressants, which were inadequate in achieving patient and provider defined objectives. In addition, patients should have no significant cardiovascular, cerebrovascular, or known neuropsychiatric risks. It may be used for those with a clear need for rapid relief of symptoms in the treatment-resistant depression setting.

Esketamine would not be suitable for patients who previously failed to respond to esketamine or racemic ketamine or those with hypersensitivity to the drug or components of the product. Individuals who have had significant adverse reactions to either ketamine or esketamine would also be a concern. Patients with dementia or psychotic features may not be suitable for esketamine. There may be concerns about treating patients who have a personal or family history of drug abuse or dependence, as such individuals who might be more vulnerable to abuse of esketamine, but it is not clear that this is an absolute contraindication. As with most clinical trial evidence, many of the people about whom clinicians would have concerns tend to have been excluded from systematic trials.

The selection of patients for treatment with esketamine would be primarily based on clinical examination and judgment. Standard physician clinical practice identifies many persons with MDD and a proper history and longitudinal care should readily reveal those with treatment-resistant depression suitable for a trial of augmentation with esketamine and a new antidepressant. However, there may be issues with mislabelling patients as treatment resistant in cases where patients have not had a sufficient and adequate antidepressant trial. There are no routinely clinically useful laboratory tests or other means to identify who will respond to a particular antidepressant (including esketamine). There is a significant need for improved methods of identifying and characterizing MDD and treatment-resistant depression, particularly for consistent biological markers that vary with illness severity and change with appropriate treatment.

## Assessing Response to Treatment

There is a general alignment between clinical practice and clinical trials in the way response to treatment is determined, in that both practice and trials rely on questions to determine how much change has occurred in key depression symptoms (e.g., depressed mood, loss of interests, fatigue, insomnia, impaired concentration, suicidal thoughts, loss of appetite). Clinical practice evaluates symptomatic change less formally without reliance on standardized rating scales. The use of standardized scales to evaluate mental health outcomes in routine clinical practice has been widely advocated, but not consistently or routinely adopted. In contrast, all clinical trials incorporate standardized measurement of depression, usually using a variety of observer-rated scales (most commonly the Hamilton Depression Rating Scale or MADRS) plus or minus additional patient-rated scales.

Clinically meaningful outcomes include reduction in the number, frequency, and severity of depression symptoms; reduction or elimination of thoughts, intents, or plans for suicide; improvement in QoL; and return to baseline functioning in a variety of domains (e.g., work, school, interpersonal, and recreational). In the maintenance phase, prevention of relapse or recurrence of depressive episodes is the key outcome. It is probable that different clinicians will have somewhat different outcomes with their patients owing to a variety of factors including the frequency and duration of follow-up care, the support, empathy, and guidance that they provide to patients, and their diligence in addressing patient concerns.

The frequency of monitoring varies depending on the patient's current state, their tolerability of the treatment, and practical factors, such as setting of treatment and distance to treatment. Ideally during the acute phase, treatment response should be assessed frequently (e.g., every 1 to 2 weeks), and periodically during maintenance treatment. The more severe the MDD episode, and the more risk associated with it, the more frequent assessment should be.

## Discontinuing Treatment

All adverse effects need to be assessed to determine how frequent and severe the problems are and to determine how well the patient tolerates them. Lack of effectiveness is another important reason for discontinuation (although partial responders may be prescribed a higher dose or an additional augmenting agent rather than stopping). Lack of effectiveness may also emerge as "secondary treatment resistance" meaning that symptoms have reoccurred despite maintenance treatment. Lastly, a scheduled discontinuation may occur when the recommended maintenance treatment interval is complete. Patient preference and cost may also be factors in decisions to stop therapy.

## Prescribing Conditions

Esketamine would mostly be prescribed by psychiatrists, though there may be an impetus for this to change over time, particularly in consideration of challenges with access to psychiatrists in many jurisdictions. A specialist is not required to make a diagnosis or to administer the treatment.

The clinical experts had different opinions on the setting in which esketamine could be administered. One expert stated this treatment should only be given in either a hospital or a specialized clinic that has pharmacy co-localization, expertise in the provision in advanced cardiac life support, and nursing support for the necessary safety monitoring. Another expert stated that inpatient or outpatient settings may be appropriate, although it would

most likely be in specialty clinics rather than general practice (at least initially). One expert stated that esketamine could be administered in a community pharmacy, family medicine clinic, outpatient community clinics, some private physician offices, hospital clinics, inpatient settings, or in the emergency department.

# Clinical Evidence

The clinical evidence included in the review of intranasal esketamine is presented in 3 sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

## Systematic Review (Pivotal and Protocol Selected Studies)

### Objectives

To perform a systematic review of the beneficial and harmful effects of esketamine nasal solution, available as a 28 mg single-use nasal spray device, in combination with a SSRI or SNRI, for the treatment of MDD in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode.

### Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to the CADTH Common Drug Review and Health Canada, as well as those meeting the selection criteria presented in Table 5.

**Table 5: Inclusion Criteria for the Systematic Review**

| | |
|---|---|
| **Patient population** | Adults with MDD who have not responded adequately to at least 2 different antidepressants of adequate dose and duration in the current moderate-to-severe depressive episode |
| **Intervention** | Esketamine nasal solution at Health Canada-recommended dosages, in conjunction with an oral antidepressant[a]<br><br>Induction phase (week 1 to 4):<br>• Initial dose of 28 mg in adults ≥ 65 years and 56 mg in those < 65 years<br>• Subsequent doses of 56 mg or 84 mg twice weekly<br><br>Maintenance phase:<br>• Week 5 to 8: 56 mg or 84 mg weekly<br>• Week 9 and onwards: 56 mg or 84 mg every 2 weeks or once weekly |
| **Comparators** | • Antidepressant(s) alone or in combination (e.g., SNRIs, SSRIs, NRIs, NDRIs, TCAs, MAOIs, mirtazapine, trazodone, vilazodone)[a]<br>• Augmentation therapy with oral antidepressant plus second-generation antipsychotic drugs (e.g., aripiprazole, brexpiprazole, quetiapine, risperidone), lithium, modafinil, triiodothyronine, stimulants (e.g., methylphenidate), or ketamine[a]<br>• Placebo[a] |
| **Outcomes** | **Efficacy outcomes:**<br>• HRQoL (e.g., SF-36, EQ-5D or disease specific instrument)[b]<br>• Function/disability (e.g., SDS)[b]<br>• Suicidality (e.g., C-SSRS)[b]<br>• Remission<br>• Response<br>• Hospitalizations or emergency room visits for depression |

| | |
|---|---|
| | • Symptom severity score rated by patients (e.g., BDI, PHQ-9, IDS-SR)[b]<br>• Symptom severity score rated by physician (e.g., HAM-D, MADRS)<br>• Relapse<br>• Withdrawals or discontinuation of treatment (all-cause or due to lack of efficacy)<br><br>**Harms outcomes:**<br>• Mortality (all-cause and suicide)<br>• Serious adverse events<br>• Withdrawals or discontinuation of treatment due to adverse events<br>• Adverse events<br>• Notable adverse events: withdrawal or rebound symptoms, dependence or abuse potential, cognitive effects (i.e., sedation or dissociation), elevated blood pressure, cystitis |
| **Study design** | Published and unpublished phase III and IV RCTs |

BDI = Beck Depression Inventory; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; HAM-D = Hamilton Depression Rating Scale; HRQoL = health-related quality of life; IDS-SR = Inventory of Depressive Symptomatology–Self-Rated; MADRS = Montgomery-Åsberg Depression Rating Scale; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NDRI = norepinephrine and dopamine reuptake inhibitor; NRI = norepinephrine reuptake inhibitor; PHQ-9 = Patient Health Questionnaire-9; RCT = randomized controlled trial; SDS = Sheehan Disability Scale; SF-36 = Short Form (36) Health Survey; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

[a] May be used in combination with psychotherapy (e.g., cognitive behavioural therapy, mindfulness, or interpersonal therapy).

[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[17]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were esketamine and depression. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 2, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on June 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[18]

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews

- clinical trials registries
- databases (free).

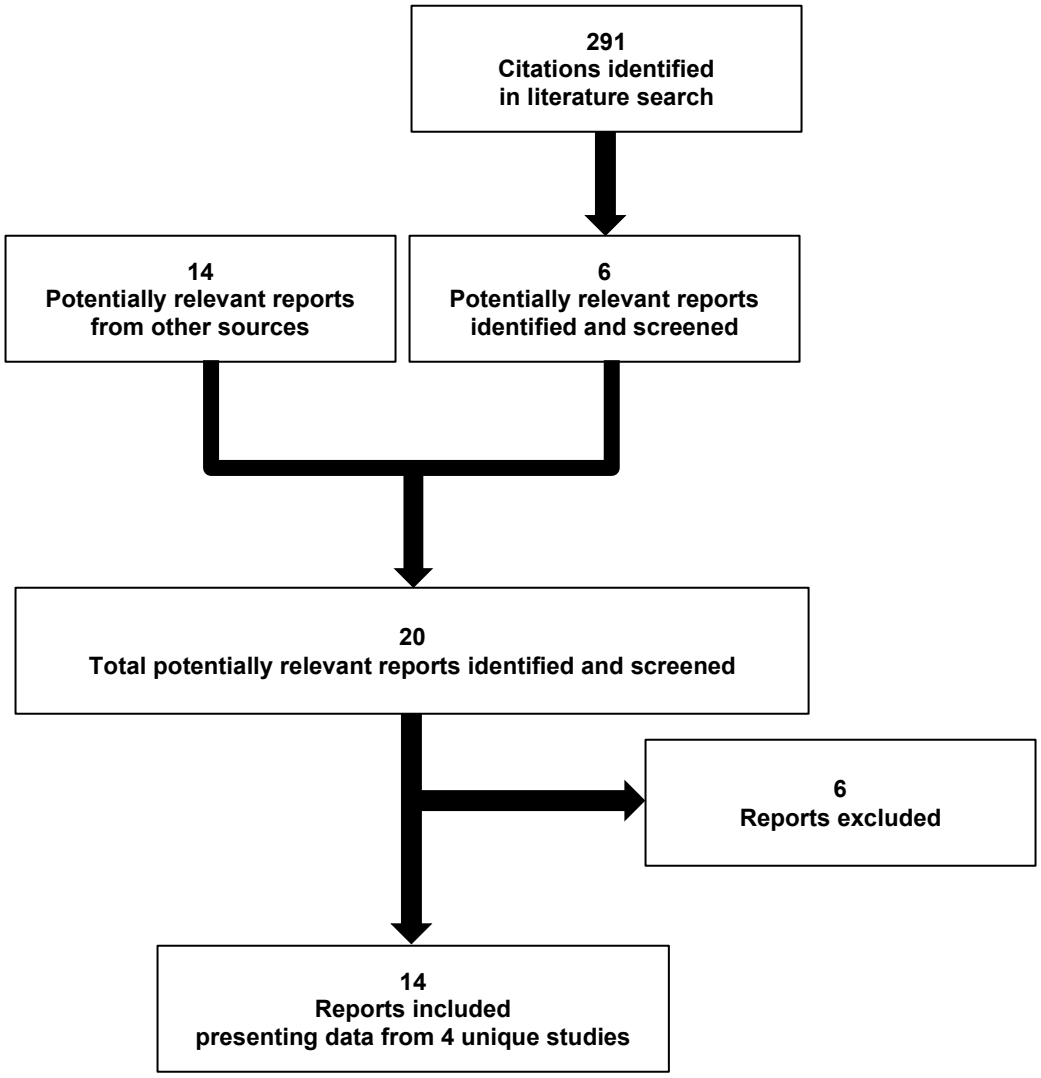
Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

## Findings From the Literature

A total of 4 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

## Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



## Table 6: Details of Included Induction Studies

| | Study characteristic | TRD3001 (TRANSFORM-1) | TRD3002 (TRANSFORM-2) | TRD3005 (TRANSFORM-3) |
|---|---|---|---|---|
| Designs and Populations | **Study design** | Double-blind RCT | Double-blind RCT (pivotal) | Double-blind RCT |
| | **Locations** | Europe, US, Canada, Mexico, Brazil | US, Europe | Europe, US, South Africa, Brazil |
| | **Randomized (N)** | 346 | 227 | 138 |
| | **Inclusion criteria** | • Age 18 to 64 years who met *DSM-5* diagnostic criteria for recurrent MDD or single-episode MDD (with duration ≥ 2 years) without psychotic features<br>• Nonresponse to ≥ 1 and ≤ 5 oral antidepressant drugs in the current MDE and administered a different antidepressant for at least 2 weeks at the start of screening period and continued during the 4-week screening period<br>• IDS-C30 score ≥ 34 points (moderate-to-severe depression) at start of screening period<br>• At the end of the screening period, patients who were nonresponders to the current antidepressant (≤ 25% improvement in MADRS score and MADRS ≥ 28 points) were eligible to be randomized to the double-blind induction period | | • Aged 65 or older who met *DSM-5* diagnostic criteria for recurrent MDD, or single-episode MDD (with duration ≥ 2 years), without psychotic features<br>• Nonresponse to ≥ 1 and ≤ 8 oral antidepressant drugs in the current MDE and administered a different antidepressant for at least 2 weeks at the start of screening period and continued during the 4-week screening period<br>• At screening:<br>○ MMSE score ≥ 25 points (or ≥ 22 if less than high school education) and IDS-C30 score ≥ 31 (moderate-to-severe depression)<br>○ At the end of the screening period, patients who were nonresponders to the current antidepressant (≤ 25% improvement in MADRS score and MADRS ≥ 24 points) were eligible to be randomized to the double-blind induction period |
| | **Exclusion criteria** | • Homicidal ideation or suicidal ideation or intent to act within prior 6 months based on C-SSRS or investigator's judgment<br>• History of moderate-to-severe substance or alcohol use disorder according to *DSM-5* criteria<br>• Prior nonresponse to ketamine or esketamine, all 4 of the active control antidepressant drugs, or ≥ 7 ECT treatments in the current MDE<br>• Had received vagal nerve stimulation or deep brain stimulation in current MDE<br>• *DSM-5* diagnosis of psychotic disorder or MDD with psychotic features, bipolar or obsessive-compulsive disorder, intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder<br>• Cardiovascular conditions including stroke, aneurysmal vascular disease, coronary artery disease, valvular heart disease, NYHA class III or IV heart failure, uncontrolled hypertension, pulmonary insufficiency, clinically significant ECG abnormalities, cirrhosis, uncontrolled diabetes, or conditions associated with increased intracranial pressure or increased intraocular pressure<br>• Study TRD3005 only: neurodegenerative disorder (e.g., Alzheimer disease, vascular dementia, Parkinson disease, cognitive impairment) | | |
| Drugs | **Intervention** | Esketamine 56 mg nasal spray, twice weekly<br>or | Esketamine 56 mg or 84 mg (flexible dosing) nasal spray, twice weekly<br>Plus newly initiated OL oral antidepressant (duloxetine, | Esketamine 28 mg, 56 mg, or 84 mg (flexible dosing) nasal spray, twice weekly<br>Plus newly initiated OL oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) |

| | Study characteristic | TRD3001 (TRANSFORM-1) | TRD3002 (TRANSFORM-2) | TRD3005 (TRANSFORM-3) |
|---|---|---|---|---|
| | | Esketamine 84 mg nasal spray, twice weekly<br>Plus newly initiated OL oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) | escitalopram, sertraline, or venlafaxine XR) | |
| | **Comparator(s)** | Placebo nasal spray twice weekly<br>Plus newly initiated OL oral antidepressant | Placebo nasal spray twice weekly<br>Plus newly initiated OL oral antidepressant | Placebo nasal spray twice weekly<br>Plus newly initiated OL oral antidepressant |
| DURATION | **Phase** | | | |
| | Screening | 4 weeks[a] | 4 weeks[a] | 4 weeks[a] |
| | Induction | 4 weeks | 4 weeks | 4 weeks |
| | Follow-up | Up to 24 weeks | Up to 24 weeks | 2 weeks |
| OUTCOMES | **Primary end point** | Change from baseline to week 4 in MADRS total score | Change from baseline to week 4 in MADRS total score | Change from baseline to week 4 in MADRS total score |
| | **Secondary and exploratory end points** | • Onset of clinical response by day 2<br>• Change from baseline in SDS<br>• Change from baseline in PHQ-9<br>• Proportion of responders<br>• Proportion of patients in remission<br>• Onset of clinical response by day 8<br>• Change from baseline in CGI-S<br>• Change from baseline in GAD-7<br>• Change from baseline in EQ-5D-5L<br>• C-SSRS<br>• Harms | | • Proportion of responders<br>• Proportion of patients in remission<br>• Change from baseline in CGI-S<br>• Change from baseline in EQ-5D-5L<br>• C-SSRS<br>• Harms |
| NOTES | **Publications** | Fedgchin et al. (2019)[19] | Popova et al. (2019)[20] | Ochs-Ross et al. (2020)[21] |

CGI-S = Clinician Global Impression–Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ECG = electrocardiogram; ECT = electroconvulsive therapy; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; GAD-7 = Generalized Anxiety Disorder 7-item; IDS-C30 = Inventory of Depressive Symptomatology–Clinician-Rated, 30-items; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; MMSE = Mini Mental State Exam; NYHA = New York Heart Association; OL = open label; PHQ-9 = Patient Health Questionnaire-9; RCT = randomized controlled trial; SDS = Sheehan Disability Scale; XR = extended release.

Note: Six additional reports were included (FDA Medical and Statistical Reviews,[22,23] Health Canada Notice of Deficiency, [24] Janssen Response to Notice of Deficiency,[25] European Public Assessment Report,[26] and CADTH Common Drug Review Submission.[27])

[a] Optional 3-week period to taper the current antidepressant medication or optimize medical management.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 7: Details of Included Relapse Prevention Study

| | Study characteristic | TRD3003 (SUSTAIN-1) | |
|---|---|---|---|
| Designs and Populations | **Study design** | Double-blind, randomized, withdrawal design (pivotal) | |
| | **Locations** | US, Canada, Mexico, Europe, Brazil | |
| | **Randomized/ enrolled (N)** | Enrolled: 705<br>Randomized: 300 | |
| | **Inclusion criteria** | Direct-entry patients:<br>• Age 18 to 64 years who met *DSM-5* diagnostic criteria for recurrent MDD, or single-episode MDD (with duration ≥ years) without psychotic features<br>• IDS-C30 score ≥ points (moderate-to-severe depression) at start of screening period<br>• Nonresponse to ≥ 1 and ≤ 5 oral antidepressant drugs in the current MDE and administered a different antidepressant for at least 2 weeks prior to study start and continued during the 4-week screening period<br>• At the end of the screening period, patients who were nonresponders to the current antidepressant (≤ 2 5% improvement in MADRS score and MADRS ≥ 28 points) were eligible to enter the induction phase and receive open-label esketamine plus a newly initiated oral antidepressant<br>• Patients with demonstrated treatment response (≥ 50% improvement in MADRS) at the end of the induction phase were eligible for the optimization phase | Patients transferred from TRD3001 or TRD3002: Eligible to enter optimization phase if they had completed the double-blind induction study and had demonstrated treatment response (≥ 50% improvement in MADRS) |
| | | Optimization phase: Patients continued intranasal esketamine plus oral antidepressant for 12 weeks<br>Maintenance phase: Patients who met criteria for stable remission or stable response at the end of the optimization period were randomized to intranasal esketamine or placebo, plus oral antidepressant | |
| | **Exclusion criteria** | • Homicidal ideation or suicidal ideation or intent to act within prior 6 months based on C-SSRS or investigator's judgment<br>• History of moderate-to-severe substance or alcohol use disorder according to *DSM-5* criteria<br>• Prior nonresponse to ketamine or esketamine, all 4 of the active control antidepressant drugs, or ≥ 7 ECT treatment in the current MDE<br>• Had received vagal nerve stimulation or deep brain stimulation in current MDE<br>• *DSM-5* diagnosis of psychotic disorder or MDD with psychotic features, bipolar or obsessive-compulsive disorder, intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder<br>• Cardiovascular conditions including stroke, aneurysmal vascular disease, coronary artery disease, valvular heart disease, NYHA class III or IV heart failure, uncontrolled hypertension, pulmonary insufficiency, clinically significant ECG abnormalities, cirrhosis, uncontrolled diabetes, or conditions associated with increased intracranial pressure or increased intraocular pressure | |
| Drugs | **Intervention** | Induction phase: esketamine 56 mg or 84 mg intranasally (flexible dose) twice weekly<br>Optimization and maintenance phase: esketamine 56 mg or 84 mg intranasally every week for first 4 weeks then weekly or every 2 weeks<br>Plus open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) | |
| | **Comparator(s)** | Placebo nasal spray | |

| | Study characteristic | TRD3003 (SUSTAIN-1) |
|---|---|---|
| | | Plus open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) |
| Duration | **Phase** | |
| | Screening/ observation | 4 weeks[a] (direct-entry patients only) |
| | Induction | 4 weeks (direct-entry patients only) |
| | Optimization | 12 weeks (direct-entry and transferred patients) |
| | Maintenance | Variable (event-driven trial) |
| | Follow-up | 2 weeks |
| Outcomes | **Primary end point** | Time to relapse among those who achieved stable remission at the end of optimization phase |
| | **Secondary and exploratory end points** | • Time to relapse among those who achieved stable response at the end of the optimization phase<br>• Change from baseline in MADRS score, SDS, PHQ-9, GAD-7, CGI-S, EQ-5D-5L<br>• C-SSRS<br>• Harms |
| Notes | **Publications** | Daly et al. (2019)[28] |

CGI-S = Clinician Global Impression–Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ECT = electroconvulsive therapy; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; GAD-7 = Generalized Anxiety Disorder 7-item; IDS-C30 = Inventory of Depressive Symptomatology–Clinician-Rated, 30-items; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; NYHA = New York Heart Association; PHQ-9 = Patient Health Questionnaire-9; SDS = Sheehan Disability Scale; XR = extended release.

Note: 6 additional reports were included (FDA Medical and Statistical Reviews,[22,23] Health Canada Notice of Deficiency, [24] Janssen Response to Notice of Deficiency,[25] European Public Assessment Report,[26] CADTH Common Drug Review Submission[27]).

[a] Optional 3-week period to taper the current antidepressant medication or optimize medical management.

Source: Clinical Study Report for Study TRD3003.[9]

## Description of Studies

### *Induction Studies*

There were 3 double-blind, randomized, controlled induction studies that evaluated the safety and efficacy of intranasal esketamine plus oral antidepressant versus intranasal placebo plus oral antidepressant, in patients with MDD who had shown inadequate response to at least 2 prior antidepressant therapies of adequate dose and duration. The primary outcome in all 3 trials was the change from baseline to week 4 in physician-assessed depression symptom severity measured using the MADRS. The trials (TRD3001, TRD3002, and TRD3005) used a similar study design that included a 4-week screening period, a 4-week double-blind induction period, and up to a 24-week follow-up period (Figure 2). During the screening period, patients continued current antidepressant medications, and those who were adherent and had documented nonresponse (≤ 25% improvement in MADRS total score) were eligible for randomization to receive intranasal esketamine or placebo plus a newly initiated open-label SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine XR) administered daily. In all 3 trials, patients were allocated to treatments through an interactive web response system and the computer-generated randomization code was stratified by country and class of antidepressant (SSRI or SNRI), with permuted blocks of 4 (TRD3002 and TRD3003) or 6 (TRD3001).

In Study TRD3001, 346 adults who were 18 to 64 years of age were randomized 1:1:1 to intranasal esketamine 56 mg, esketamine 84 mg, or placebo administered twice weekly, in addition to a newly initiated open-label oral antidepressant.

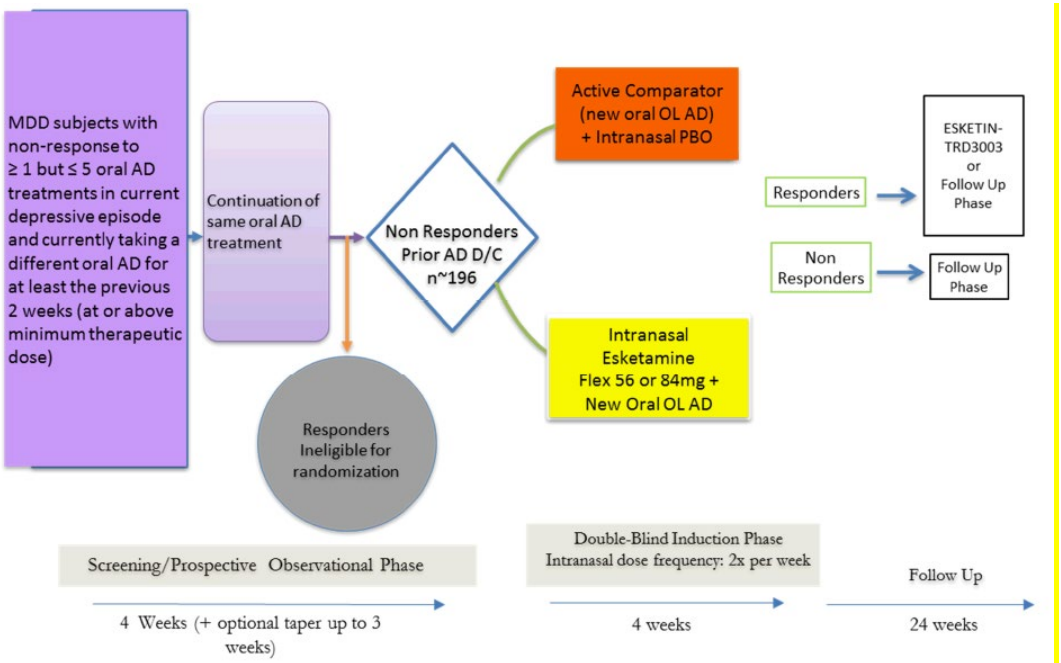
Study TRD3002 enrolled 227 adults (18 to 64 years of age) who were randomized 1:1 to intranasal esketamine (flexible dose: 56 mg or 84 mg) or placebo twice weekly, plus a newly initiated open-label oral antidepressant.

In Study TRD3005, 137 patients 65 years of age or older were randomized 1:1 to intranasal esketamine 28 mg, 56 mg, or 84 mg (flexible dosing) or intranasal placebo twice weekly plus a newly initiated open-label SSRI or SNRI antidepressant.

Only Study TRD3001 included patients from Canada; however, the number of Canadian study sites was not reported. No Canadian sites were included in Study TRD3002 or Study TRD3005.

Patients who met treatment response criteria at the end of Study TRD3001 and Study TRD3002 were eligible to be enrolled in the relapse prevention study (TRD3003). At the end of Study TRD3005, patients could participate in the open-label extension study, TRD3004. Patients who withdrew early from Study TRD3001, Study TRD3002, or Study TRD3005 entered the follow-up phase.

## Figure 2: Study Design of Study TRD3002 (TRANSFORM-2)




2x = twice; AD = antidepressant; D/C = discontinue; Flex = flexible dosing; MDD = major depressive disorder; OL = open label; PBO = placebo.

Source: Reproduced from the Clinical Study Report for Study TRD3002.[6]

*Relapse Prevention Study*

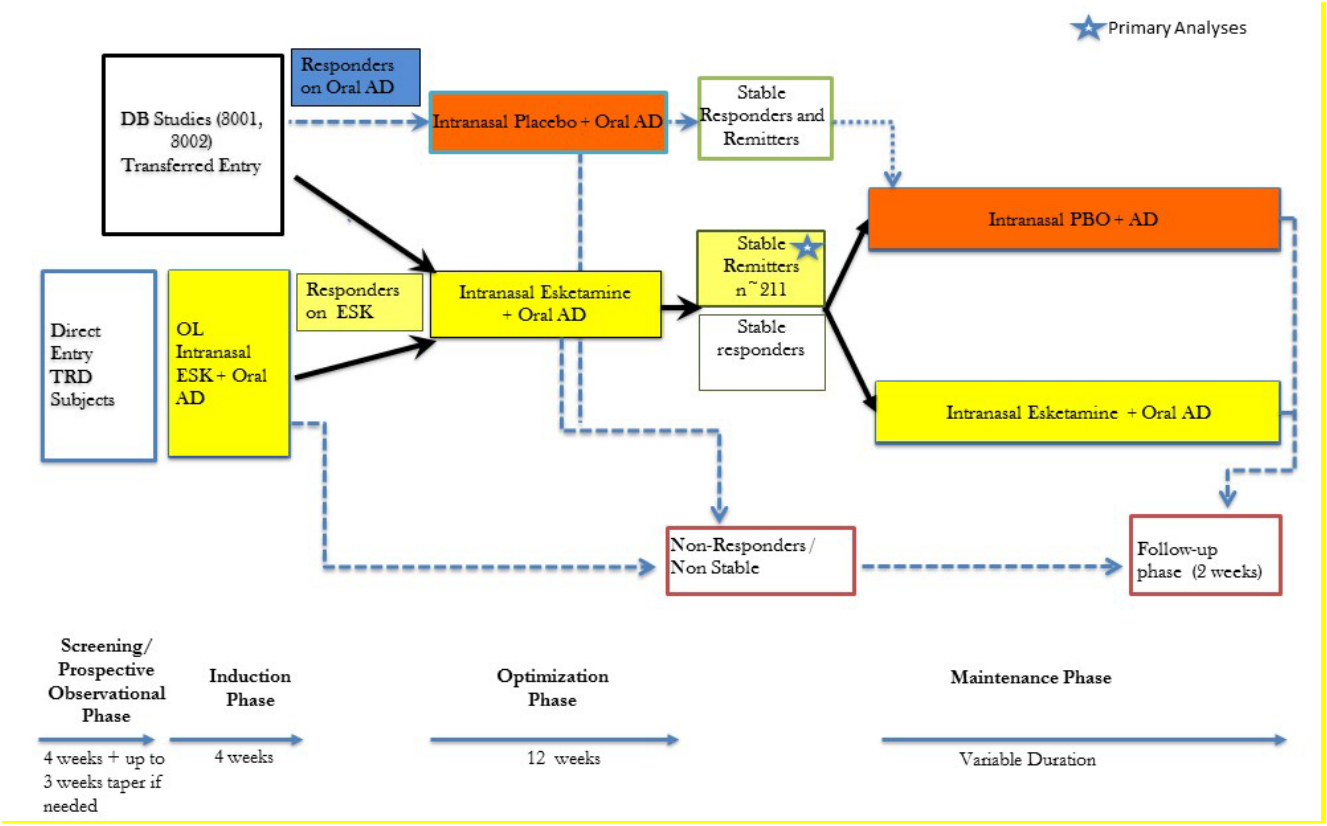
The objective of Study TRD3003 was to evaluate the efficacy of intranasal esketamine plus oral antidepressant compared with intranasal placebo plus oral antidepressant in delaying relapse of depressive symptoms in patients with treatment-resistant depression who were in stable remission or had stable response after an induction and optimization treatment course with esketamine and an antidepressant (enriched population). The study used a double-blind, randomized withdrawal design that included patients transferred from Study TRD3001 and Study TRD3002 as well as patients enrolled directly into the trial.

Study TRD3003 included 5 stages: screening (4 weeks); induction (4 weeks); optimization (12 weeks); maintenance (variable duration); and follow-up (2 weeks) (Figure 3). Patients who were enrolled directly into the trial started with the screening stage and underwent a similar process as in the 3 induction studies. During the 4-week screening phase, patients' current antidepressant therapies were continued and those with demonstrated nonresponse (≤ 25% improvement in MADRS score and MADRS score ≥ 28 points at week 2 and 4) entered the induction phase. Patients then received open-label intranasal esketamine 56 mg or 84 mg twice weekly (flexible dosing) plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR). Patients who met treatment response criteria at the end of the induction phase were eligible to enter the optimization phase. The responders who entered the optimization phase included those who had completed the induction phase of Study TRD3003 (i.e., direct entry), as well as patients transferred from induction Study TRD3001 and Study TRD3002 (i.e., transferred entry). During the optimization phase, patients continued the same dose of intranasal study drug (esketamine 56 mg or 84 mg) but reduced the frequency to once weekly for the first 4 weeks, and then the frequency was individualized based on the MADRS score to either weekly or every 2 weeks. Patients' response to treatment was assessed at the end of the optimization phase to determine their eligibility for entry into the randomized double-blind maintenance phase. Two separate randomizations were conducted. In 1 randomization, patients who met the criteria for stable remission at the end of the optimization phase were randomized 1:1 to either continue intranasal esketamine or switch to intranasal placebo (primary outcome population). Patients who met stable response criteria at the end of the optimization phase underwent a separate randomization to either esketamine or placebo (1:1). All patients continued oral antidepressant therapy during the optimization and maintenance phases. Randomization was conducted centrally through an interactive web response system and the computer-generated randomization codes were stratified by country, with permuted blocks of 4. Study TRD3003 was an event-driven trial and planned to end when 59 relapses had occurred among patients with stable remission.

Transfer-entry patients from Study TRD3001 and Study TRD3002 who received intranasal placebo and met treatment response criteria in the induction studies, were eligible to enter the optimization phase of Study TRD3003. However, these patients were not included in the randomization process at the end of the optimization phase. Patients continued to receive intranasal placebo plus oral antidepressant and were included in the safety analysis only.

Of the 705 patients who entered the study, 297 were randomized in the double-blind maintenance stage. Study TRD3003 included patients from Canada, although the number of sites was not reported.

## Figure 3: Study Design of Study TRD3003 (SUSTAIN-1)




AD = antidepressant; DB = double blind; ESK = esketamine; OL = open label; PBO = placebo; TRD = treatment-resistant depression.

Source: Reproduced from the Clinical Study Report for Study TRD3003.[9]

## Populations

### *Inclusion Criteria*

**Induction Studies**

Study TRD3001 and Study TRD3002 enrolled adults (18 to 64 years of age) who met the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) criteria for single-episode (≥ 2 years in duration) or recurrent MDD without psychotic features that was confirmed by the Mini International Neuropsychiatric Interview. In addition, the severity of the MDE was moderate-to-severe, based on the Inventory of Depressive Symptomatology–Clinician-Rated, 30-items, with a total score of 34 or greater.

To be eligible for Study TRD3001 and Study TRD3002, patients had to have documented nonresponse to at least 1 but no more than 5 antidepressants for the current MDE and receiving a different oral antidepressant for at least 2 weeks prior to screening. Assessment of nonresponse was based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire and confirmed by documented records. The patients' current antidepressant therapy was continued during the 4-week screening phase, with dose adjustments allowed as long as the dose remained above the minimum therapeutic dose as per the Massachusetts General Hospital Antidepressant Treatment Response

Questionnaire. At the end of the screening phase, patients were assessed by independent remote raters and those who were nonresponders were eligible for randomization to the double-blind phase. At screening week 4, nonresponse was defined as an improvement in MADRS score from week 1 to week 4 of 25% or less, and a MADRS total score of 28 points or greater on week 2 and week 4. Thus by the end of the screening period, patients had to meet the criteria for treatment-resistant depression, which the sponsor defined as "a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration (at least 6 weeks) in the current episode of depression."[5]

The inclusion criteria of Study TRD3005 was the same as Study TRD3001 and Study TRD3002 except for the following: eligible patients were 65 years of age or older; at screening patients had shown nonresponse to at least 1 but no more than 8 antidepressants; patients had moderate-to-severe MDD defined by the Inventory of Depressive Symptomatology–Clinician-Rated, 30-items, with a total score of 31 or greater.

**Relapse Prevention Study**

Study TRD3003 enrolled adults (18 to 64 years of age) who met the *DSM-5* criteria for single-episode (≥ 2 years in duration) or recurrent MDD without psychotic features, and by the end of the screening phase, had documented nonresponse to at least 2 antidepressant drugs of adequate dose and duration. Patients underwent induction therapy and received intranasal esketamine at a dose of 56 mg or 84 mg twice weekly plus a newly initiated oral SSRI or SNRI antidepressant. All patients who completed the induction phase of either Study TRD3003 (direct-entry patients), Study TRD3001, or Study TRD3002 and had documented response (≥ 50% improvement in MADRS total score from baseline to week 4) were eligible to enter the 12-week optimization phase. At the end of the optimization phase patients who met the criteria for stable remission or stable response were eligible to be randomized in the double-blind maintenance phase.

Stable remission was defined as MADRS total score of 12 or less for at least 3 of the last 4 weeks of the optimization phase (i.e., week 13 to 16), with 1 excursion of a MADRS total score of greater than 12 or 1 missing MADRS assessment permitted at week 13 or 14 only; MADRS total score at weeks 15 and 16 must be 12 or less.

Stable response was defined as patient with a 50% or greater reduction in the MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but who do not meet criteria for stable remission.

### *Exclusion Criteria*

All 4 trials excluded patients with comorbid psychiatric conditions, substance use disorder, or recent suicidal ideation or behaviour. They also excluded patients with cardiovascular or cerebrovascular conditions, uncontrolled hypertension, clinically significant abnormalities on electrocardiogram, pulmonary insufficiency, cirrhosis, uncontrolled diabetes, or conditions associated with increased intracranial pressure or increased intraocular pressure.

### *Baseline Characteristics*

The baseline characteristics of the patients enrolled appear to be balanced between groups within trials (Table 8 and Table 9). The patients were predominantly female (58% to 72%) and White (75% to 99%) with a mean age per group ranging from 44.9 years (SD = 12.60) to 47.2 years (SD = 11.0) in Study TRD3001, Study TRD3002, and Study TRD3003; Study

TRD3005 had a mean age of 69.4 years (SD = 4.2) and 70.6 years (SD = 4.8). The mean baseline MADRS score ranged from 34.8 points (SD = 6.4) to 40.1 points (SD = 5.6) per group, and in the 6 months prior to enrolment 16% to 50% of patients had reported suicidal ideation. In the current MDE, 41% to 68% of patients had inadequate response to 2 antidepressants, and [redacted] had failed 3 prior antidepressants at the start of the screening phase. There were fewer patients who had only shown nonresponse to 1 antidepressant [redacted] or 4 or more antidepressants [redacted] prior to entering the trials. Most patients had experienced more than 1 prior MDE and the current MDE was protracted for some patients with a median duration of 48 weeks to 115.5 weeks per group (range 6 to 2,288 weeks).

At the start of the screening phase in the induction studies, most patients were receiving antidepressant monotherapy ([redacted] per treatment group), with [redacted] on a combination of 2 antidepressants and [redacted] receiving augmentation therapy (antidepressant plus a drug from another class) (Table 8). No patients were receiving cognitive behaviour therapy in the screening phase in the induction studies, and 0.9%, 1.8% ,and 3.1% in Study TRD3001, Study TRD3002, and Study TRD3005, respectively, were receiving other forms of psychotherapy. Few patients had received electroconvulsive therapy (0% to 2.2%) or repetitive transcranial stimulation (0% to 0.9%) in the past.

In the screening phase of Study TRD3003, [redacted] received antidepressant monotherapy, [redacted] received antidepressant combination therapy and [redacted] received augmentation therapy per treatment group in the stable remitter and stable responder populations (Table 9). Few patients were receiving cognitive behaviour therapy or other forms of psychotherapy (0% to 2.3%) and none had received electroconvulsive therapy or repetitive transcranial stimulation.

## Table 8: Summary of Baseline Characteristics of Induction Studies

| Characteristics | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 to 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| Age, years, mean (SD) | 46.4 (11.2) | 45.7 (11.1) | 46.8 (11.4) | 44.9 (12.6) | 46.4 (11.1) | 70.6 (4.8) | 69.4 (4.2) |
| Female, n (%) | 81 (70) | 79 (69) | 81 (72) | 75 (66) | 63 (58) | 45 (63) | 40 (62) |
| Race, n (%) | | | | | | | |
| White | 91 (79) | 85 (75) | 86 (76) | 106 (93) | 102 (94) | 66 (92) | 64 (99) |
| Black | 7 (6) | 7 (6) | 5 (4) | 6 (5) | 5 (5) | NR | NR |
| Asian | 2 (2) | 1 (1) | 2 (2) | 1 (1) | 1 (1) | NR | NR |
| Other or unknown | 15 (13) | 21 (18) | 20 (18) | 1 (1) | 1 (1) | 6 (8) | 1 (2) |
| BMI kg/m$^2$, mean (SD) | 28.8 (6.7) | 28.4 (5.9) | 29.2 (6.7) | 27.5 (5.8) | 28.6 (6.2) | 28.6 (5.2) | 29.3 (6.1) |
| Employment status, n (%) | | | | | | | |
| Any type of employment | 60 (52) | 67 (59) | 67 (59) | 68 (60) | 63 (58) | 11 (15) | 13 (20) |
| Any type of unemployment | 41 (36) | 41 (36) | 36 (32) | 34 (30) | 35 (32) | 2 (3) | 6 (9) |
| Other | 14 (12) | 6 (5) | 10 (9) | 12 (11) | 11 (10) | 59 (82) | 46 (71) |
| MADRS score, mean (SD) | 37.4 (4.8) | 37.8 (5.6) | 37.5 (6.2) | 37.0 (5.7) | 37.3 (5.7) | 35.5 (5.9) | 34.8 (6.4) |
| Suicidal ideation in past 6 months, n (%)[b] | 53 (46) | 53 (47) | 56 (50) | 37 (32) | 34 (31) | 28 (39) | 20 (31) |

| Characteristics | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 to 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| Suicidal behaviour in past 12 months, n (%)[b] | 0 | 0 | 0 | 0 | 1 (1) | 0 | 1 (2) |
| Duration of current MDE, weeks, median (range) | 99 (12 to 1,525) | 115.5 (12 to 2,288) | 104 (6 to 1,720) | 63.5 (9 to 649) | 52 (8 to 1,196) | 83.5 (8 to 1,700) | 104 (8 to 2,184) |
| Number of MDE,[c] n (%) | | | | | | | |
| 1 | 15 (13) | 25 (22) | 28 (25) | 15 (13) | 14 (13) | 8 (11) | 10 (15) |
| 2 to 5 | 75 (66) | 69 (61) | 56 (50) | 81 (71) | 78 (72) | 45 (63) | 41 (63) |
| ≥ 6 | 24 (21) | 20 (18) | 29 (26) | 18 (16) | 17 (16) | 19 (26) | 14 (22) |
| Number of prior AD, n (%) | | | | | | | |
| 1 | [redacted] | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| ≥ 4 | | | | | | | |
| Therapy received at the start of the screening phase, n (%) | | | | | | | |
| AD monotherapy | [redacted] | | | | | | |
| Combination of 2 AD | | | | | | | |
| AD plus drug from another class | | | | | | | |

AD = antidepressant; BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ESK = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; NR = not reported; SD = standard deviation.

[a] Full analysis set population.

[b] Based on screening C-SSRS.

[c] Including current episode.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7] Additional data supplied by sponsor.[29]

## Table 9: Summary of Baseline Characteristics of Relapse Prevention Study (TRD3003)

| TRD3003 | All enrolled | Stable remitters | | Stable responders | |
|---|---|---|---|---|---|
| | N = 705 | ESK 56 or 84 mg N = 90 | Placebo N = 86 | ESK 56 or 84 mg N = 62 | Placebo N = 59 |
| Age, years, mean (SD) | 46.1 (11.1) | 45.4 (12.1) | 46.2 (11.2) | 47.2 (11.0) | 46.7 (9.8) |
| Female, n (%) | 457 (65) | 58 (64) | 59 (69) | 38 (61) | 42 (71) |
| Race, n (%) | | | | | |
| White | 635 (90) | 80 (89) | 76 (88) | 57 (92) | 55 (93) |
| Black | 31 (4) | 4 (4) | 6 (7) | 2 (3) | 1 (2) |
| Asian | 3 (< 1) | NR | NR | 0 | 1 (2) |
| Other or not reported | 36 (5) | 6 (7) | 4 (5) | 3 (5) | 2 (3) |
| BMI kg/m$^2$, mean (SD) | 28.6 (6.2) | 28.9 (5.8) | 29.5 (6.3) | 28.8 (6.4) | 28.5 (6.6) |
| Employment status, n (%) | | | | | |
| Any type of employment | 448 (64) | 57 (63) | 54 (63) | 43 (69) | 40 (68) |

| TRD3003 | All enrolled | Stable remitters | | Stable responders | |
|---|---|---|---|---|---|
| | N = 705 | ESK 56 or 84 mg N = 90 | Placebo N = 86 | ESK 56 or 84 mg N = 62 | Placebo N = 59 |
| Any type of unemployment | 180 (26) | 23 (26) | 19 (22) | 13 (21) | 14 (24) |
| Other | 77 (11) | 10 (11) | 13 (15) | 6 (10) | 5 (9) |
| MADRS score, mean (SD) | 37.9 (5.5) | 37.4 (5.2) | 37.6 (4.7) | 40.1 (5.6) | 38.9 (4.9) |
| Suicidal ideation in past 6 months, n (%)[a] | 205 (29) | 18 (20) | 14 (16) | 20 (32) | 14 (24) |
| Suicidal behaviour in past 12 months, n (%)[a] | 1 (<1) | 0 | 0 | 0 | 0 |
| Duration of current MDE, weeks, median (range) | 64 (4 to 2,288) | 51.5 (12 to 1,040) | 58 (9 to 884) | 48 (13 to 1,080) | 60 (9 to 1,248) |
| Number of MDE,[b] n (%) | | | | | |
| 1 | 83 (12) | 10 (11) | 9 (11) | 7 (11) | 6 (10) |
| 2 to 5 | 454 (65) | 62 (69) | 60 (70) | 41 (66) | 42 (71) |
| ≥ 6 | 167 (24) | 18 (20) | 17 (20) | 14 (23) | 11 (19) |
| Number of prior AD, n (%) | | | | | |
| 1 | [redacted] | | | | |
| 2 | | | | | |
| 3 | | | | | |
| ≥ 4 | | | | | |
| Therapy received at the start of the screening phase, n (%) | | | | | |
| AD monotherapy | [redacted] | | | | |
| Combination of 2 AD | | | | | |
| AD plus drug from another class | | | | | |

AD = antidepressant; BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ESK = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; NR = not reported; SD = standard deviation.

[a] Based on screening C-SSRS.

[b] Including current episode.

Source: Clinical Study Report for Study TRD3003.[9] Additional data supplied by sponsor.[29]

## Interventions

### *Description of Intranasal Study Drugs*

Esketamine was supplied as a 28 mg nasal spray device that delivered one 14 mg spray to each nostril, thus 2 devices were required for the 56 mg dose and 3 devices were required for the 84 mg dose. The placebo spray contained water for injection, with a bittering agent (denatonium benzoate) to simulate the taste of esketamine, in a matching nasal spray device that delivered 2 sprays.

Nasal sprays were administered by the patient at the study site and were supervised by the investigator or designee. Study sites had supportive ventilation and resuscitation equipment present, and patients were monitored by personnel with training in cardiopulmonary resuscitation. Guidance on blood pressure monitoring was provided to site personnel due to the potential for treatment-emergent increases in systolic and diastolic blood pressure. Patients were to abstain from alcohol for 24 hours prior to intranasal dose, from food for 2

hours, and fluids for 30 minutes. Also, patients were not permitted to drive or operate machinery for 24 hours after the intranasal treatment.

*Description of Oral Antidepressants*

All patients continued their current oral antidepressant therapies during the screening phase of the trials. Prior to entering the induction phase patients stopped all drugs for MDD, including adjunctive or augmentation therapy. Therapies could be stopped abruptly or could be tapered off over an optional 3-week period.

At the start of the induction phase of all 4 trials, patients started a new oral antidepressant that was selected by the investigator, based on the patient's treatment history (i.e., no history of nonresponse to the new antidepressant). The oral antidepressant options available included duloxetine, escitalopram, sertraline, and venlafaxine XR tablets or capsules. The oral antidepressants were supplied open label by the sponsor, and dosing was titrated according to a schedule outlined in each study's protocol and could not exceed the maximum daily dose specified in the US product label. Dose reductions were allowed if higher doses were not tolerated; however, the dose at the end of the induction phase was not to fall below minimum therapeutic dosages. In Study TRD3001, Study TRD3002, and Study TRD3003 the minimum daily dosage was sertraline 50 mg, venlafaxine XR 150 mg, escitalopram 10 mg, and duloxetine 60 mg, whereas in the trial in elderly patients (TRD3005), the minimum daily dosage was sertraline 25 mg, venlafaxine XR 75 mg, escitalopram 5 mg, and duloxetine 30 mg.

The proportion of patients who received duloxetine (35% to 56%), escitalopram (14% to 39%), sertraline (14% to 22%), and venlafaxine XR (10% to 23%) during the trials is summarized in Appendix 3 (Table 49 and Table 50).

*Induction Studies*

In Study TRD3001, patients were randomized 1:1:1 to intranasal esketamine 56 mg, esketamine 84 mg, or placebo administered twice weekly. For patients in the 84 mg dosage group, the initial dose was 56 mg and all subsequent doses were 84 mg, with no further dose adjustments. In Study TRD3002, patients received intranasal esketamine or placebo twice weekly for 4 weeks. The initial dose of esketamine was 56 mg, with subsequent doses titrated as described in Table 10. To maintain blinding to dose of intranasal study drug in Study TRD3001 and Study TRD3002, all patients administered a total of 6 sprays (3 per nostril) from 3 placebo devices (placebo group), 2 esketamine and 1 placebo device (esketamine 56 mg dose), or 3 esketamine devices (84 mg dose).

In Study TRD3005, the initial dose of esketamine was 28 mg and on subsequent days dosages were titrated based on efficacy and tolerability as per the schedule described in Table 10. Patients in the placebo group also had dosages increased or decreased at the investigator's discretion. Patients who were assigned a 28 mg dose of esketamine or placebo administered 2 sprays from a single esketamine or placebo device, and those to receive 56 mg or 84 mg doses of esketamine or placebo used 2 or 3 devices, respectively, at each study visit.

After the end of the induction phase, no further intranasal study drug was supplied but patients continued on oral antidepressants for at least 2 weeks, unless the investigator determined it was not clinically appropriate.

## Table 10: Esketamine Dose Titration Schedule for Studies TRD3002 and TRD3005

| TRD3002 | Titration guidance |
|---|---|
| **Induction phase** | |
| Day 1 | All patients randomized to esketamine received a 56 mg dose |
| Day 4 | Dose could remain at 56 mg or be increased to 84 mg at investigator's discretion based on efficacy or tolerability |
| Day 8 and 11 | Dose could remain the same, be increased from 56 mg to 84 mg, or decreased from 84 mg to 56 mg at investigator's discretion based on efficacy or tolerability |
| Day 15 | Dose could be decreased from 84 mg to 56 mg at investigator's discretion if required for tolerability; no dose increase was permitted |
| Day 18, 22, and 25 | The dose was to remain unchanged; if there was no treatment session on day 15, a dose reduction from 84 mg to 56 mg was permitted on day 18 if required for tolerability; no dose increase was permitted |
| **TRD3005** | |
| **Induction phase** | |
| Day 1 | All patients randomized to esketamine received a 28 mg dose |
| Day 4 | Dose could remain at 28 mg or be increased to 56 mg at investigator's discretion based on efficacy or tolerability |
| Day 8, 11, and 15 | Dose could remain the same or be increased or decreased by 28 mg at investigator's discretion based on efficacy or tolerability; no dose increases were permitted after day 15 |
| Day 18, 22, and 25 | No dose increases were permitted; the dose could be reduced by 28 mg if needed for tolerability |

Source: Clinical Study Reports for Study TRD3002[6] and Study TRD3005.[7]

*Relapse Prevention Study*

In Study TRD3003 direct-entry patients underwent the screening and induction phases as described for the short-term studies. During the induction phase, patients received open-label intranasal esketamine titrated according to the dosing schedule in Table 11, plus a newly initiated oral antidepressant. Responders to intranasal esketamine (direct entry or transferred from TRD3001 or TRD3002) who entered the optimization phase continued on the same dose of esketamine but the dosing frequency was changed to weekly for the first 4 weeks, and then was altered from weekly to biweekly based on MADRS score (< 12 or ≥ 12 points at week 8 or week 12, Table 11). Stable responders and stable remitters who were randomized in the maintenance phase received double-blind intranasal placebo or esketamine (previous dose administered weekly or biweekly as described in Table 11). To maintain blinding, all patients administered a total of 6 sprays (3 per nostril) from 3 placebo devices (placebo group), 2 esketamine and 1 placebo device (esketamine 56 mg dose), or 3 esketamine devices (84 mg dose).

Patients who missed more than 20 days of oral antidepressant doses during the optimization phase were not allowed to continue into the maintenance phase.

*Concomitant Treatments*

In all trials, patients who were taking benzodiazepines (up to 6 mg per day of lorazepam or equivalent), or other sleep medications (e.g., zolpidem or zaleplon) were allowed to continue treatment during the study at the same dose. Benzodiazepines and other sleep medications were not permitted within 12 hours prior to each intranasal treatment or cognitive testing. Patients receiving psychotherapy could continue therapy during the trials, however cognitive behaviour therapy had to have been ongoing for the 3 months prior to the start of the screening period. Initiation of cognitive behaviour therapy was not allowed during the trials, but other forms of psychotherapy could be started. Overall, 1.2%, 0.4%, 2.2%, and 1.7% of patients received some form of psychotherapy during the double-blind phase of Study TRD3001, Study TRD3002, Study TRD3005, and Study TRD3003, respectively.[29]

Patients were not allowed to receive electroconvulsive therapy, deep brain stimulation, transcranial magnetic stimulation, or vagal nerve stimulation. Patients could receive rescue medication if they experienced adverse effects after intranasal treatments. These included midazolam or other short-acting benzodiazepine for anxiety or agitation, and ondansetron, metoclopramide, or dimenhydrinate for nausea. No rescue medication was recommended for transient increases in blood pressure.

## Table 11: Esketamine Dose Titration Schedule for Study TRD3003

| | Titration guidance |
|---|---|
| **Induction phase**[a] | **Direct-entry patients only** |
| Day 1 | All patients received a 56 mg dose. |
| Day 4 | The dose could remain at 56 mg or be increased to 84 mg at investigator's discretion based on efficacy or tolerability. |
| Day 8, 11, 15, and 22 | The dose could remain the same, be increased from 56 mg to 84 mg, or decreased from 84 mg to 56 mg at investigator's discretion based on efficacy or tolerability |
| Day 25 | A dose reduction from 84 mg to 56 mg was permitted on day 25 if required for tolerability; no dose increase was permitted. |
| **Optimization phase**[a] | **All patients** |
| Week 5 to 8 | Patients continued on the same dose of intranasal esketamine they received at the end of the induction period. The frequency of intranasal esketamine was reduced from twice weekly to once weekly. Administration of intranasal study drug was open label for direct-entry patients, and double blind for those transferred from study TRD3001 or TRD3002. |
| Week 8 | Patients with a MADRS score > 12 points continued with weekly esketamine until the end of the optimization phase.<br>In patients with a MADRS score ≤ 12 points, the frequency of esketamine was reduced to every 2 weeks. |
| Week 12 | In patients with a MADRS score > 12 points, the frequency of esketamine was increased to weekly.<br>Patients with a MADRS score ≤ 12 points continued on esketamine every 2 weeks. |
| **Maintenance phase**[a,b] | **All patients** |
| Week 17 | Patients previously receiving weekly intranasal study drug continued with this dosing frequency. Those patients on a biweekly dosing schedule continued on this frequency if their MADRS score was ≤ 12 points or had their frequency increased to weekly if the MADRS score was > 12 points. |
| Week 20 and every 4 weeks thereafter | Dosing frequency was evaluated every 4 weeks according to the following.<br>MADRS score ≤ 12 points:<br>• If the frequency was weekly, the frequency changed to biweekly |

| | Titration guidance |
|---|---|
| | • If the frequency was biweekly, there was no change<br><br>MADRS score > 12 points:<br>• If the frequency was weekly, there was no change<br>• If the frequency was biweekly, the frequency changed to weekly<br><br>A maximum of 3 changes were permitted to the frequency of the intranasal study drug. After 3 changes, if the patient could not sustain remission on the biweekly dosing schedule, then the intranasal study drug was administered weekly for the remainder of the maintenance phase. |

MADRS = Montgomery-Åsberg Depression Rating Scale.

[a] In Study TRD3003, the induction phase ran from week 1 to week 4, the optimization phase ran from week 5 to week 16, and the maintenance phase ran from week 17 until relapse or the study was stopped.

[b] Patients were randomized to intranasal esketamine (continued at same dose the patient was receiving previously) or placebo. Patients and investigators were blinded to the intranasal study drug during the maintenance phase. To maintain blinding, patients were administered 2 sprays from 3 devices at every study visit (placebo: 3 placebo devices; esketamine 56 mg: 2 esketamine and 1 placebo device; esketamine 84 mg: 3 esketamine devices).

Source: Clinical Study Report for Study TRD3003.[9]

## Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 12. These end points are further summarized as follows. A detailed discussion and critical appraisal of the outcome measures are provided in Appendix 4.

The primary outcome in the induction trials was the change from baseline to week 4 in the MADRS total score. In all trials, MADRS scores were assessed by a blinded, independent, remote (by phone) rater.

Key secondary outcomes in Study TRD3001 and Study TRD3002 included onset of clinical response by day 2, change from baseline in SDS and change from baseline in PHQ-9 total scores. The onset of clinical response by day 2 was defined as a 50% or greater reduction in MADRS total score, maintained from day 2 to 28. Patients were allowed 1 nonresponse value on day 8, 15, or 22 as long as at least a 25% improvement in MADRS score was reported. Patients who discontinued the study prior to week 4 were considered nonresponders. Other outcomes reported in the induction studies included onset of clinical response by day 8, the proportion of patients in remission (defined as MADRS score ≤ 12 points) or with response (≥ 50% reduction in MADRS score), and change from baseline in the EQ-5D-5L index score or EQ VAS (Table 12).

The primary outcome in Study TRD3003 was the time to relapse among patients in stable remission with intranasal esketamine plus oral antidepressant therapy. Relapse was defined as either:

- MADRS total score of 22 points or greater for 2 consecutive assessments that were 5 to 15 days apart
- Hospitalization for worsening depression or any other clinically relevant event that was suggestive of a relapse of depressive illness as per clinical judgment (e.g., suicide attempt, completed suicide, or hospitalization for prevention of suicide). Events that did not require hospitalization were adjudicated by an independent committee.

Secondary outcomes included the time to relapse among patients with stable response to esketamine plus oral antidepressant; and, for the stable remission population, the change from baseline in MADRS score, SDS, PHQ-9, and EQ-5D-5L index score and EQ VAS.

In all trials, suicidality was evaluated as a safety outcome with data captured using the C-SSRS instrument.

## Table 12: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

| Outcome measure | Study | | |
|---|---|---|---|
| **Induction studies** | **TRD3001** | **TRD3002** | **TRD3005** |
| Change from baseline to day 28 in the MADRS total score[a] | Primary | Primary | Primary |
| Onset of clinical response by day 2: proportion of patients who showed response by day 2 that was maintained through the end of the 4-week induction period[b] | Key secondary | Key secondary | NR |
| Change from baseline to day 28 in the SDS total score | Key secondary | Key secondary | Other[c] |
| Change from baseline to day 28 in the total score | Key secondary | Key secondary | Other[c] |
| Proportion of responders (≥ 50% reduction in MADRS score) at the end of the 4-week induction period | Other secondary | Other secondary | Secondary |
| Proportion of patients in remission (MADRS ≤ 12 points) at the end of the 4-week induction period | Other secondary | Other secondary | Secondary |
| Onset of clinical response by day 8: proportion of patients who showed response by day 8 that was maintained through the end of the 4-week induction period[d] | Other secondary | Other secondary | NR |
| Change from baseline to day 28 in the EQ-5D-5L index score and EQ VAS | Other secondary | Other secondary | Other secondary |
| C-SSRS | Other | Other | Other |
| **Relapse prevention study – maintenance phase** | **TRD3003** | | |
| Time from randomization to relapse for patients with stable remission at the end of the optimization phase[e] | Primary | | |
| Time from randomization to relapse for patients with stable response at the end of the optimization phase[e] | Secondary | | |
| Change from baseline in the following (stable remission population): | | | |
| • MADRS total score | Secondary | | |
| • PHQ-9 | Secondary | | |
| • EQ-5D-5L index score and EQ VAS | Secondary | | |
| • SDS | Secondary | | |
| C-SSRS | Other | | |

C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported; PHQ-9 = Patient Health Questionnaire-9; SDS = Sheehan Disability Scale.

[a] MADRS rating used 7-day recall.

[b] Response was defined as a ≥ 50% reduction in MADRS total score, maintained from day 2 to 28. Patients were allowed 1 nonresponse value on day 8, 15, or 22 as long as at least a 25% improvement in MADRS score was reported. Patients who discontinued the study prior to week 4 were considered nonresponders. MADRS rating was based on 24-hour recall on day 2; otherwise, a 7-day recall was used.

[c] SDS and PHQ-9 were removed as outcome measures in the third protocol amendment of Study TRD3003. Data for these outcomes were collected for most patients (50% to 88%) and results were reported by the sponsor; however, these data have not been summarized in this report.

[d] Response was defined as a 50% or greater reduction in MADRS total score, maintained from day 8 to 28. Patients were allowed 1 nonresponse value on day 15 or 22 as long as at least a 25% improvement in MADRS score was reported. Patients who discontinued the study prior to week 4 were considered nonresponders.

[e] Patients who completed Study TRD3003 and those who withdrew early but did not meet relapse criteria were censored.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] Study TRD3005,[7] and Study TRD3003.[9]

### *EuroQol 5-Dimensions 5-Levels*

HRQoL was measured using the EQ-5D-5L. The EQ-5D-5L descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each are rated on 5 levels of perceived problems (level 1 = no problem; 2 = slight

problems; 3 = moderate problems; 4 = severe problems; 5 = extreme problems) measured on that day. The value set for the EQ-5D-5L from Canada[30] was used to convert the descriptive system to the health status index score, which was anchored at zero (health state value = dead) and 1 (full health). A Canadian-specific MCID of 0.037 has been reported.[31,32] An MCID of the EQ-5D-5L was not identified in patients with MDD.

The instrument also includes a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS which best represents their health on that day. No MCID for the visual analogue scale in patients with depression was identified.

*Sheehan Disability Scale*

The SDS measures the extent to which the patient's global functioning is impaired by depressive symptoms. With this self-reported, 3-item scale, patients rate the extent to which their work, social life or leisure activities, and home life or family responsibilities are impaired by symptoms (0 = no disability; 10 = extreme disability). Total scores range from 0 to 30, with higher scores indicating more severe disability. The recall period was 7 days. The MCID is not known.

*Patient Health Questionnaire-9*

The PHQ-9 is a 9-item, patient-reported measure of depressive symptoms. It includes the 9 symptom domains of the *DSM-5* MDD criteria, which are each rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day). Responses to each item are summed to provide a total score (range = 0 to 27) with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks. There is evidence to support the validity of this instrument,[33] but data were lacking on reliability, responsiveness, or MCID.

*Montgomery-Åsberg Depression Rating Scale*

The MADRS is a physician-rated measure of the severity of depression symptoms. The MADRS includes 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), with a maximum total score of 60. Higher scores indicate more severe symptoms. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. A 7-day recall period was used for the primary efficacy evaluation in the included studies. There is evidence to support the validity of the MADRS, with a MCID of 2 in patients with MDD.

*Columbia-Suicide Severity Rating Scale*

The C-SSRS is a clinician-rated instrument consisting of 9 questions that evaluate the presence of suicidal ideation, behaviour, and severity. The C-SSRS events are categorized into scores ranging from 0 (no event that can be assessed on the basis of C-SSRS) to 10 (completed suicide). In the included studies, the maximum score assigned for each patient was summarized into 1 of 3 categories: no suicidal ideation or behaviour (0); suicidal ideation (1 to 5); and suicidal behaviour (6 to 10).There is evidence to support its validity in adolescents with MDD.

### *Harms*

All trials identified AEs of special interest and identified pre-specified groups of Medical Dictionary for Regulatory Activities (MedDRA) terms related to drug abuse, dependence, or withdrawal; increased blood pressure; dizziness or vertigo; impaired cognition; cystitis; increased blood pressure; and suicidality. The group labelled “drug abuse, dependence, and withdrawal” was based on the FDA Assessment of Abuse Potential of Drugs Guidance for Industry and included terms for dissociation, dizziness, somnolence, euphoria, hallucination, feeling drunk, feeling relaxation and mental impairment, as well as terms related to substance use disorder.

## Statistical Analysis

### *Induction Studies*

The sample sizes of Study TRD3001, Study TRD3002, and Study TRD3005 were calculated assuming a treatment difference of 6.5 points for the change from baseline in the MADRS score (SD = 12), with a 1-sided significance level of 0.025 and 25% withdrawal rate. The sponsor stated that the assumed treatment difference was based on data from phase II Study TRD2003 and clinical judgment. Study TRD3002 had 90% power to detect a difference between esketamine and placebo with 98 patients enrolled per group. For Study TRD3001, the trial had 90% power to detect a difference between any dose of esketamine and placebo with 116 patients per group, based on a 1-sided significance level of 0.0125 and no interim analysis. Study TRD3005 had 80% power to detect a difference between esketamine and placebo for the change from baseline in MADRS score with 74 patients enrolled per group (assuming no interim analysis).

Study TRD3001 planned 1 interim analysis to re-estimate the sample size or to stop the study due to futility. According to the statistical analysis plan, this unblinded analysis was conducted 4 weeks after randomizing 120 patients, and based on this analysis, the sample size was re-calculated to be 234 patients. Once this number was reached, the sites were informed to stop enrolling patients; however, any patient that was already in the screening process was allowed to continue. As a result, a total of 346 patients were randomized in the study. Study TRD3005 also included a planned unblinded interim analysis after 50 patients had been randomized per group. Based on the interim analysis, the maximum sample size was adjusted to 100 patients, but any patients already enrolled were allowed to continue, thus 138 patients were randomized. The sponsor stated that none of the esketamine team or site staff were made aware of the results of the interim analyses.

In the induction trials, the change from baseline in MADRS total score was analyzed based on the full analysis set (FAS) population using 2 different models: MMRM using OC data; and analysis of covariance (ANCOVA) using last observation carried forward (LOCF) for missing data. The ANCOVA model was specified as the primary analysis for the EU and the MMRM analysis was primary for other regions. The covariates included in the models are listed in Table 13. The primary outcomes in Study TRD3001 and Study TRD3005 were analyzed separately for stage 1 (for patients included in the interim analysis) and stage 2 (patients enrolled after the interim analysis), and the results were reported as the median unbiased point estimate and 95% CIs of the weighted combination of the 2 stages. Planned sensitivity analyses for the induction studies included ANCOVA models based on OC data, unweighted ANCOVA or MMRM models, and tipping point analyses to assess the potential impact of missing data in the MMRM model. In this analysis, a worsening adjustment (i.e., delta) was applied to patients who discontinued from the esketamine group. The delta

adjustment was increased until the results were no longer statistically significant (i.e., tipping point) (Table 13).

The change from baseline in SDS and PHQ-9 scores were analyzed using the same MMRM and ANCOVA models as described for the primary outcome (Table 13). The onset of clinical response outcomes were analyzed using a Cochran-Mantel-Haenszel chi-square test, with stratification by country (or region) and class of antidepressant (SSRI or SNRI). The proportion of patients who achieved response or remission, and the change from baseline in EQ-5D were reported descriptively: no between-group comparisons were conducted.

To control the type I error in Study TRD3001 and Study TRD3002, a serial gatekeeping approach was used for testing significance of the primary outcome (change from baseline to week 4 in MADRS total score) and 3 key secondary outcomes (onset of clinical response day 2, change in SDS score, and change in PHQ-9 score) (Table 14). In Study TRD3001 the gatekeeping procedures also included the dose groups, with the esketamine 84 mg dose tested first (1-sided test; alpha 0.025), and if significant then the 56 mg dose was tested (1-sided test; alpha 0.02125). Sequential testing was conducted, and subsequent outcomes could be deemed significant only if the previous outcome was statistically significant according to the statistical analysis plan. In Study TRD3005 there were no procedures implemented to control the type I error across the secondary outcomes analyzed.

*Relapse Prevention Study*

With a maximum of 84 relapse events, Study TRD3003 had 90% power to detect a HR of 0.493 (1-sided significance level of 0.025) for the time to relapse for esketamine versus placebo in patients with MDD in remission. A sample size of 211 patients in stable remission was planned, based on the sponsor's assumptions for accrual rate, maximum study duration, and withdrawal rate (35% over 6 months). An interim analysis was planned after 33 relapses had been reported to re-evaluate the sample size, or to stop the study for efficacy. Based on this, the number of relapses required to end the study was reduced to 59, which provided 90% power to detect a HR of 0.415 at a 1-sided significance level of 0.025. Based on the interim analysis, 154 patients were required to be randomized.

Among patients who achieved stable remission, the time from randomization to relapse was tested using a weighted combination log-rank test, calculated on the interim FAS and the FAS-remitters populations (Table 13). To account for the interim analysis, the significance level of the primary outcome was 0.046 (2-sided). The HR and 95% CI for the time to relapse were calculated using Cox proportional hazards model with weighted estimates based on Wassmer.[8]

The primary analysis of time to relapse assumed censoring was ignorable, thus sensitivity analyses were conducted to test this assumption. A tipping point analysis was completed that assigned a higher relapse hazard (via a delta parameter) to patients in the esketamine group who were censored for nonadministrative reasons (i.e., other than study termination). Delta values were increased until the result was no longer statistically significant. In addition, an unweighted log-rank test was conducted for the primary outcome.

Time to relapse among patients who had achieved stable response was analyzed using the Kaplan-Meier method and 2-sided log-rank test. The change from baseline in MADRS, PHQ-9, and SDS scores were reported descriptively for the induction and optimization phases. In the maintenance phase, the data for these outcomes were analyzed using

ANCOVA models with adjustment for country and baseline score, based on OC and LOCF for the FAS-remitters and FAS-responders populations. Descriptive data were provided for the change from baseline in EQ VAS scores. There was no control of type I error across the secondary or other outcomes in Study TRD3003.

## Table 13: Statistical Analysis of Efficacy End Points

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| **TRD3001** | | | |
| Change from baseline in MADRS score, SDS, and PHQ-9 | ANCOVA (FAS; LOCF[a]) (primary analysis for EU)<br><br>MMRM (FAS, OC) (primary analysis for non-EU) | ANCOVA: region, class of oral antidepressant (SSRI or SNRI), baseline outcome score<br><br>MMRM: region, class of oral antidepressant (SSRI or SNRI), baseline outcome score, day-by-treatment interaction as fixed effects, and random patient effect<br><br>The analyses were performed separately for stage 1 (patients included in interim analysis), stage 2 (patients enrolled after interim analysis), and a weighted combination of the 2 stages; the median unbiased point estimate and 95% CI were reported for the treatment difference; each esketamine dose was tested versus placebo | Primary outcome:<br>• Unweighted ANCOVA and MMRM model<br>• ANCOVA (OC)<br>• MMRM with delta adjustment multiple imputation for missing data (planned but not conducted due to failure to meet primary outcome) |
| Onset of clinical response by day 2: proportion of patients with clinical response by day 2 that was maintained to day 28 | Cochran-Mantel-Haenszel chi-square test | Region, class of oral antidepressant, using a weighted combination test for the 2 stages | Unweighted analysis |
| Onset of clinical response by day 8: Proportion of patients with clinical response by day 8 that was maintained to day 28 | Cochran-Mantel-Haenszel chi-square test | Country, class of oral antidepressant | NR |
| Change from baseline in EQ-5D-5L index score and EQ VAS | Descriptive data | NR | NR |
| Proportion of patients with response or remission | Descriptive data (OC and LOCF[a]) | NR | NR |
| **TRD3002** | | | |
| Change from baseline in MADRS score, SDS, PHQ-9 | ANCOVA (FAS; LOCF[a]) (primary analysis for EU)<br><br>MMRM (FAS, OC) (primary analysis for non-EU) | ANCOVA: country, class of oral antidepressant (SSRI or SNRI), baseline outcome score<br><br>MMRM: country, class of oral antidepressant (SSRI or SNRI), baseline outcome score, day-by-treatment interaction as fixed effects, and random patient effect | Primary outcome:<br>• ANCOVA (OC)<br>• MMRM with delta adjustment multiple imputation for missing data |

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| Onset of clinical response: proportion of patients with clinical response by day 2 or day 8 that was maintained to day 28 | Cochran-Mantel-Haenszel chi-square test | Country, class of oral antidepressant | NR |
| Change from baseline in EQ-5D-5L index score and EQ VAS | Descriptive data | NR | NR |
| Proportion of patients with response or remission | Descriptive data (OC and LOCF[a]) | NR | NR |
| **TRD3005** | | | |
| Change from baseline in MADRS score | ANCOVA (FAS; LOCF[a]) (primary analysis for EU)<br><br>MMRM (FAS, OC) (primary analysis for non-EU) | ANCOVA: region, class of oral antidepressant (SSRI or SNRI), baseline outcome score<br><br>MMRM: region, class of oral antidepressant (SSRI or SNRI), baseline outcome score, day-by-treatment interaction as fixed effects, and random patient effect.<br><br>The analyses were performed separately for stage 1 (patients included in interim analysis), stage 2 (patients enrolled after interim analysis), and a weighted combination of the 2 stages; the median unbiased point estimate and 95% CI were reported for the treatment difference | Primary outcome:<br>• ANCOVA (OC)<br>• MMRM with delta adjustment multiple imputation for missing data (planned but not conducted due to failure to meet primary outcome) |
| Proportion of patients with response or remission | Descriptive data (OC and LOCF[a]) | NR | NR |
| Change from baseline in EQ-5D-5L index score and VAS | Descriptive data | NR | NR |
| **TRD3003** | | | |
| Time to relapse in stable remitters | Weighted combination log-rank test Kaplan-Meier estimate<br><br>Cox proportional hazards model | Weighted 2-stage analysis was conducted to account for the interim analysis and re-adjustment of sample size | • Unweighted log-rank test and Cox proportional hazards model<br>• Tipping point analysis with higher relapse hazard for censored patients in ESK group<br>• Post hoc: evaluated effect of early relapse by censoring patients with relapse within week 1, 2, 3, and 4<br>• Post hoc: censoring placebo patients with change in dissociation symptoms |
| Time to relapse in stable responders | Log-rank test Kaplan-Meier estimate | NR | NR |

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| | Cox proportional hazards model | | |
| Change from baseline in MADRS score, SDS, and PHQ-9 | ANCOVA (FAS; LOCF[a] and OC) | Country and baseline outcome score | NR |
| Change from baseline in EQ-5D-5L index score and EQ VAS | Descriptive data | NR | NR |

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; ESK = esketamine; EU = European Union; FAS = full analysis set; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; NR = not reported; OC = observed case; PHQ-9 = Patient Health Questionnaire-9; SDS = Sheehan Disability Scale; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] Last post-baseline outcome value was carried forward.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] Study TRD3005,[7] and Study TRD3003.[9]

## Table 14: Statistical Testing Procedure to Control Type I Error for Efficacy End Points

| Study | Statistical procedure | Outcomes included |
|---|---|---|
| **Induction studies** | | |
| TRD3001 | Fixed sequence parallel gatekeeping method.<br><br>For each outcome, esketamine 84 mg dose was tested first (1-sided test, alpha = 0.025), and if significant then the 56 mg dose was tested (1-sided test, alpha = 0.02125). Both doses had to be significant for the prior outcome for testing of both doses to proceed for the next outcome. If only the 84 mg dose was significant (1-sided 0.025 significance level) then subsequent outcomes were tested for the 84 mg dose only, at a 1-sided alpha of 0.00375. | • Change in MADRS score<br>• Onset of clinical response by day 2<br>• Change in SDS<br>• Change in PHQ-9 |
| TRD3002 | Fixed sequence serial gatekeeping method.<br><br>End points were analyzed sequentially and were considered statistically significant at the 1-sided, 0.025 alpha level only if the end point was individually significant at the 1-sided, 0.025 alpha level and previous end points in the hierarchy were significant at the 1-sided 0.025, alpha level, including the primary end point. | • Change in MADRS score<br>• Onset of clinical response by day 2<br>• Change in SDS<br>• Change in PHQ-9 |

MADRS = Montgomery-Åsberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire-9; SDS = Sheehan Disability Scale.

Source: Clinical Study Reports for Study TRD3001[5] and Study TRD3002.[6]

### *Analysis Populations*

**Induction Studies**

In the 3 induction studies, the FAS included all randomized patients who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant in the double-blind induction phase.

The safety set included all randomized patients who received at least 1 dose of intranasal study drug or 1 dose of oral antidepressant in the double-blind induction phase. Patients who received the incorrect treatment were analyzed under the planned treatment.

The follow-up analysis set included all patients who entered the follow-up phase.

**Relapse Prevention Studies**

The all-enrolled set included any patients who entered the trial directly and those transferred from Study TRD3001 or Study TRD3002.

There were 4 FAS populations defined in Study TRD3003.

- Induction: all patients who received at least 1 dose of intranasal study drug and oral antidepressant in the induction phase.
- Optimization: all patients who received at least 1 dose of intranasal study drug and oral antidepressant in the optimization phase.
- Maintenance – Remitters (FAS-remitters): randomized patients who met the criteria for stable remission at the end of the maintenance phase and had received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant in the maintenance phase.
- Maintenance – Responders (FAS-responders): randomized patients who met the criteria for stable response at the end of the maintenance phase and had received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant in the maintenance phase.

Transferred patients who had been receiving intranasal placebo (and met stable response or remission criteria) were excluded from the FAS-remitters and FAS-responders populations

The safety set was also defined separately for each phase of the trial and included patients who received at least 1 dose of intranasal study drug or 1 dose of oral antidepressant in each phase of Study TRD3003. Transfer-entry patients who had received intranasal placebo were included in safety analyses.

## Results

### Patient Disposition

Of the patients enrolled in the 3 induction studies, 46% to 52% of patients completed the screening phase, met the criteria for treatment-resistant depression, and were randomized in the 4-week double-blind induction phase (Table 15). In Study TRD3002 and Study TRD3005, the proportion of patients who discontinued early was higher in the esketamine groups (14% to 16%) than placebo groups (9% to 11%). In Study TRD3001, withdrawals were more frequent in the esketamine 84 mg group (16%) than placebo (5%) or the esketamine 56 mg group (5%). In this trial, 11 of 19 patients who withdrew from the esketamine 84 mg group dropped out after receiving 1 dose of intranasal esketamine, and 5 of 7 patients in esketamine 56 mg group dropped out after a single dose. Overall, AEs were the most frequently reported reason for discontinuation among those who received esketamine (1% to 8%) in the induction studies.

## Table 15: Patient Disposition for Induction Studies

| Disposition | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg | ESK 84 mg | Placebo | ESK 56 or 84 mg | Placebo | ESK 28 to 84 mg | Placebo |
| **Screened, N** | 710 | | | 435 | | 302 | |
| **Randomized, N (%)** | 346 (49)[a] | | | 227 (52)[b] | | 138 (46)[c] | |
| | 117 | 116 | 113 | 116 | 111 | 72 | 66 |
| **Discontinued from study, n (%)** | 6 (5) | 19 (16) | 6 (5) | 18 (16) | 12 (11) | 10 (14) | 6 (9) |
| **Reason for discontinuation, n (%)** | | | | | | | |
| Adverse events | 1 (1) | 7 (6) | 2 (2) | 9 (8) | 1 (1) | 4 (6) | 2 (3) |
| Lack of efficacy | 1 (1) | 1 (1) | 0 | 2 (2) | 0 | 3 (4) | 1 (2) |
| Lost to follow-up | 0 | 1 (1) | 0 | 1 (1) | 1 (1) | 1 (1) | 0 |
| Protocol violation | 2 (2) | 1 (1) | 1 (1) | 2 (2) | 2 (2) | 0 | 1 (2) |
| Withdrawal by patient | 1 (1) | 5 (4) | 1 (1) | 4 (3) | 7 (6) | 1 (1) | 2 (3) |
| Other | 1 (1) | 4 (3) | 2 (2) | 0 | 1 (1) | 1 (1) | 0 |
| **FAS, N** | 115 | 114 | 113 | 114 | 109 | 72 | 65 |
| **Safety, N** | 115 | 116 | 113 | 115 | 109 | 72 | 65 |

ESK = esketamine; FAS = full analysis set.

[a] In Study TRD3001, 364 patients failed to meet the inclusion criteria and were excluded from the trial.

[b] A total of 199 patients in TRD3002 failed screening and 9 patients from 1 study site were excluded from the study due to Good Clinical Practice issues found on audit.

[c] In Study TRD3005, 163 patients failed screening, and 1 patient from 1 site was excluded due to Good Clinical Practice issues.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

For the relapse prevention study (TRD3003), 821 patients were screened and 437 patients (53%) met the criteria for treatment-resistant depression and entered the induction phase (Table 16). Of these direct-entry patients, 273 (62%) completed the induction phase, met the response criteria, and entered the optimization phase. Another 182 patients who were responders to esketamine in Study TRD3001 and Study TRD3002 entered the optimization phase of TRD3003; thus, in total, 455 patients receiving esketamine entered the optimization phase. Among these patients, 107 (24%) did not meet the criteria for the next phase and 51 (11%) withdrew for other reasons. Therefore, 297 patients of the 705 enrolled (42%) or 65% of the 455 responders who entered the optimization phase were eligible for randomization in the maintenance phase of the trial.

In total, 176 patients met the criteria for stable remission during the optimization phase and were randomized in the maintenance phase (Table 17). Nine percent of patients in the esketamine group and 11% in the placebo group withdrew early. Of the 121 patients who met the stable response criteria, 5% from the placebo and 8% from the esketamine groups withdrew from the trial. The reasons for withdrawal were similar between groups.

Study TRD3003 also included 86 patients transferred from Study TRD3001 and Study TRD3002 who were receiving intranasal esketamine. Of these patients, 55 (64%) entered the maintenance phase and were included in the safety analysis.

## Table 16: Patient Disposition for the Induction and Optimization Phases of the Relapse Prevention Study

| Disposition | TRD3003 | | |
|---|---|---|---|
| | Direct entry (ESK) | Transferred (ESK) | Transferred (placebo) |
| **Screened, N** | 821[a] | 276[a] | |
| **Enrolled, N (%)** | 437 (53) | 268 (97) | |
| **Induction phase** | | | |
| **Enrolled in induction phase, N** | 437 | NA | NA |
| **Discontinued from study, n (%)** | 164 (38) | NA | NA |
| **Reason for discontinuation, n (%)** | | | |
| Did not meet criteria for next phase | NA | NA | NA |
| Adverse event | [redacted] | NA | NA |
| Lack of efficacy | [redacted] | NA | NA |
| Lost to follow-up | [redacted] | NA | NA |
| Protocol violation | [redacted] | NA | NA |
| Withdrawn by patient | [redacted] | NA | NA |
| Other | [redacted] | NA | NA |
| **FAS, N** | 430 | NA | NA |
| **Safety, N** | 437 | NA | NA |
| **Enrolled in optimization phase, N (%)** | 273 (62) | 182 (100) | 86 (100) |
| **Optimization phase** | **Direct entry or transferred (ESK)** | | **Transferred (placebo)** |
| **Enrolled, N** | 455 | | 86 |
| **Discontinued from study, n (%)** | 158 (35) | | NA |
| **Reason for discontinuation, n (%)** | | | |
| Did not meet criteria for next phase[b] | [redacted] | | NA |
| Adverse event | [redacted] | | NA |
| Lack of efficacy | [redacted] | | NA |
| Lost to follow-up | [redacted] | | NA |
| MADRS score ≥ 22 for 2 consecutive visits[c] | [redacted] | | NA |
| Protocol violation | [redacted] | | NA |
| Withdrawn by patient | [redacted] | | NA |
| Other | [redacted] | | NA |
| **FAS, N** | 452 | | NA |
| **Safety, N** | 455 | | 86 |
| **Enrolled in maintenance phase, N (%)** | 297 (65) | | 55 (64) |

ESK = esketamine; FAS = full analysis set; MADRS = Montgomery-Åsberg Depression Rating Scale; NA = not applicable.

[a] In total there were 378 patients who failed to meet screening criteria (details not reported) plus 14 patients excluded from 1 site due to Good Clinical Practice violations.

[b] This criterion applied to patients enrolled prior to the third protocol amendment.

[c] Of these patients, 106 of 107 did not meet criteria for stable remission or stable response at the end of the optimization period, and 1 patient had 3 or more missing MADRS assessments.

Source: Clinical Study Report for Study TRD3003.[9]

## Table 17: Patient Disposition for the Maintenance Phase of the Relapse Prevention Study

| Disposition | TRD3003 | | | | |
|---|---|---|---|---|---|
| | Stable remitters | | Stable responders | | Transferred[a] |
| | ESK | Placebo | ESK | Placebo | Placebo |
| **Maintenance phase** | | | | | |
| **Enrolled/randomized, N** | 90 | 86 | 62 | 59 | 55 |
| **Discontinued from study, n (%)** | 8 (9) | 9 (11) | 5 (8) | 3 (5) | 1 (2) |
| **Reason for discontinuation, n (%)** | | | | | |
| Adverse events | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Pregnancy | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Withdrawal by patient | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Lost to follow-up | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Non-compliance with study drug | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Protocol violation | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| Other | [redacted] | [redacted] | [redacted] | [redacted] | NA |
| **FAS, N** | 90 | 86 | 62 | 59 | NA |
| **Safety, N** | 90 | 86 | 62 | 59 | 54 |

ESK = esketamine; FAS = full analysis set.

[a] Of the total number of patients transferred from the induction studies, 86 patients who had received intranasal placebo plus oral antidepressant were not included in the efficacy analysis but were included in safety data. Of these patients, 55 entered the maintenance phase.

Source: Clinical Study Report for Study TRD3003.[9]

### Exposure to Study Treatments

The median duration of exposure to intranasal study drug was [redacted] in the induction studies, with the mean duration per group [redacted] (Table 18). In Study TRD3001, [redacted] in the esketamine 84 group [redacted] of intranasal study drug [redacted] compared with placebo [redacted] or esketamine 56 mg [redacted]. In the other 2 induction studies, the proportion of patients [redacted] of intranasal study drug [redacted]. In the 2 studies with flexible dosing schedules, the mean daily dose of esketamine was [redacted] (see Table 18 for the proportion of patients receiving each dose).

The median duration of oral antidepressant therapy was [redacted] in the induction studies (range [redacted]). Table 18 shows the mean daily dose of escitalopram, sertraline, duloxetine, and venlafaxine.

In the relapse prevention study, the median duration of intranasal study drug was 25 days in the induction phase and 68 days in the optimization phase (Table 19). During the maintenance phase the duration of exposure to intranasal study drug and oral antidepressant was longer in the esketamine groups than placebo. The median duration of esketamine was 17.7 weeks and 19.4 weeks, and for placebo was 10.2 weeks and 10.1 weeks, in the FAS-remitters and FAS-responders populations, respectively. Fewer patients in the esketamine group stopped treatment within the first 4 weeks than in the placebo

group among stable remitters (8% versus 27%) and stable responders (5% versus 31%, respectively).

## Table 18: Exposure Duration in Induction Studies

| | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| **Exposure** | **ESK 56 mg N = 115** | **ESK 84 mg N = 114** | **Placebo N = 113** | **ESK 56 or 84 mg N = 114** | **Placebo N = 109** | **ESK 28 to 84 mg N = 72** | **Placebo N = 65** |
| **Intranasal study drug** | | | | | | | |
| **Duration, days** | | | | | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (range) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean daily dosage, mg (SD)** | | | | | | | |
| ESK | NA | NA | NA | [redacted] | NA | [redacted] | NA |
| **Frequency distribution of ESK dose on day 25, n (%)** | NA | NA | NA | NA | NA | [redacted] | NA |
| 28 mg | NA | NA | NA | NA | NA | [redacted] | NA |
| 56 mg | NA | NA | NA | [redacted] | NA | [redacted] | NA |
| 84 mg | NA | NA | NA | [redacted] | NA | [redacted] | NA |
| **Oral antidepressant** | | | | | | | |
| **Duration SSRI, days** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (range) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Duration SNRI, days (SD)** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | **n = [redacted]** | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (range) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean daily dose, mg (SD)** | | | | | | | |
| Escitalopram | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Sertraline | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Duloxetine | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Venlafaxine XR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ESK = esketamine; FAS = full analysis set; NA = not applicable; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

[a] FAS population.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 19: Exposure Duration in the Relapse Prevention Study

| TRD3003[a] | Induction phase | Optimization phase | Maintenance phase | | | |
|---|---|---|---|---|---|---|
| | | | Remitters | | Responders | |
| | ESK N = 430 | ESK N = 452 | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Intranasal study drug** | | | | | | |
| **Duration** | | | | | | |
| Mean (SD) | 23.4 days (5.7) | 63.1 days (14.7) | 21.1 weeks (16.3) | 16.0 weeks (16.1) | 23.4 weeks (20.3) | 13.3 weeks (13.5) |
| Median (range) | 25 days (1 to 36) | 68 days (1 to 77) | 17.7 weeks (0 to 83) | 10.2 weeks (0 to 72) | 19.4 weeks (3 to 91) | 10.1 weeks (0 to 70) |
| **Mean daily dosage, ESK mg (SD)** | 70.2 (10.5) | NR | NR | NA | NR | NA |
| **Frequency distribution of ESK dose, n (%)** | | | | | | |
| 56 mg | 150 (35) | 167 (37) | 40 (44) | NA | 20 (32) | NA |
| 84 mg | 276 (65) | 284 (63) | 50 (56) | NA | 41 (66) | NA |
| **Dosing frequency,[b] n (%)** | | | | | | |
| Weekly | NA | 252 (62) | 21 (23) | 27 (31) | 34 (55) | 36 (61) |
| Every 2 weeks | NA | 155 (38) | 62 (69) | 48 (56) | 21 (34) | 19 (32) |
| Both weekly and every 2 weeks | NA | NA | 7 (8) | 11 (13) | 7 (11) | 4 (7) |
| **Oral antidepressant** | | | | | | |
| **Duration SSRI, days** | NR | NR | n = 28 | n = 28 | n = 27 | n = 23 |
| Mean (SD) | NA | NA | 23.4 (19.0) | 15.3 (17.4) | 21.8 (18.1) | 13.8 (16.2) |
| Median (range) | NA | NA | 20 (3 to 83) | 7.1 (2 to 76) | 12.1 (4 to 66) | 7.0 (1 to 70) |
| **Duration SNRI, days (SD)** | NR | NR | n = 62 | n = 58 | n = 35 | n = 36 |
| Mean (SD) | NA | NA | 21.2 (15.2) | 17.6 (15.2) | 26.0 (21.6) | 14.8 (11.4) |
| Median (range) | NA | NA | 17.9 (1 to 64) | 13.9 (2 to 74) | 22.1 (5 to 92) | 12.4 (2 to 55) |
| **Mean daily dose, mg (SD)** | NA | NR | NR | NR | NR | NR |
| Escitalopram | 15.4 (3.3) | NA | NA | NA | NA | NA |
| Sertraline | 110.8 (27.2) | NA | NA | NA | NA | NA |
| Duloxetine | 56.5 (7.2) | NA | NA | NA | NA | NA |
| Venlafaxine XR | 147.0 (35.8) | NA | NA | NA | NA | NA |

ESK = esketamine; FAS = full analysis set; NA = not applicable; NR = not reported; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

[a] FAS population for induction, optimization, and maintenance phases.

[b] Data for the optimization phase was reported as proportional with weekly or every 2 weeks dosing frequency at week 8. Data for the maintenance phase was reported as the majority dose frequency, which was defined as the regimen the patient received at least 50% of the time in the maintenance period.

Source: Clinical Study Report for Study TRD3003.[9]

## Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported in the following. See Appendix 3 for detailed efficacy data.

### *Health-Related Quality of Life*

EQ-5D index score and EQ VAS data were reported descriptively in all trials, with no pre-planned statistical comparisons between treatment groups. Please refer to Appendix 3 (Table 51 and Table 52) for a summary of the EQ-5D-5L and EQ VAS data for the included studies.

For the induction trials, EQ-5D-5L index scores and EQ VAS scores were higher at day 28 than baseline for the esketamine and placebo groups. The change from baseline in EQ-5D-5L index scores was 0.22 (SD = 0.25) and 0.24 (SD = 0.24) for the esketamine 56 mg and 84 mg groups of Study TRD3001 compared with 0.18 (SD = 0.25) in the placebo group. In Study TRD3002, the mean change in index scores for the esketamine and placebo groups was 0.29 (SD = 0.23) and 0.23 (SD = 0.25), respectively. In the study that enrolled patients 65 years of age and older (TRD3005), the mean change from baseline was 0.08 (SD = 0.26) for esketamine and 0.03 (SD = 0.22) for placebo. Of note, some differences in the baseline index scores were seen between groups within trials (see Appendix 3, Table 51).

The sponsor supplied post hoc analyses of the change from baseline to day 15 or day 28 in the EQ-5D-5L index score and EQ VAS for Study TRD3002.[34] These analyses included patients in the FAS who had both baseline and end point outcome data. Data were missing for 4% and 9% of patients at day 15 and 28, respectively. The unadjusted mean difference between esketamine and placebo for the EQ-5D index score was 0.036 (SD = 0.031) at day 15 (analysis of variance [ANOVA] F-test P = 0.24) and was 0.075 (SD = 0.033) at day 28 (ANOVA F-test P = 0.024).[34] For the change from baseline in EQ VAS, the unadjusted mean difference versus placebo was 4.2 (SD = 3.17; ANOVA F-test P = 0.19) at day 15 and 9.1 (SD = 3.65; ANOVA F-test P = 0.014) at day 28.[34] No between-group comparisons were provided for the other included studies.

In the maintenance phase of Study TRD3003, the mean EQ-5D-5L index scores and EQ VAS scores decreased from baseline to end point for patients who received esketamine as well as placebo (Appendix 3, Table 52). The mean change in the index score was –0.07 (SD = 0.12) for esketamine and –0.10 (0.15) for placebo in the FAS-remitters population and –0.02 (SD = 0.08) and –0.07 (SD = 0.14), respectively, in the FAS-responders population.

### *Disability or Functional Status*

The change from baseline to day 28 in the SDS score was a key secondary outcome in 2 induction studies. For Study TRD3001, the LS mean difference between esketamine and placebo was 2.2 points (95% CI, –4.9 to 0.5) for the 84 mg dose group, and –2.5 points (95% CI, –5.3 to 0.2) for the 56 mg dose group, which were not statistically significant. In Study TRD3002, the LS mean difference between groups was –4.0 points (95% CI, –6.3 to –1.6). Due to failure of a prior outcome in the statistical hierarchy, statistical testing of this outcome was to stop. Of note, data were missing for 20% to 25% of patients per treatment group in the MMRM OC model. The results of the ANCOVA model were similar in magnitude and direction of effect.

## Table 20: Change From Baseline in SDS Total Score for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | |
|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 |
| **Change from baseline to day 28 in SDS total score[a]** | | | | | |
| Number of patients contributing to the analysis (%) | 88 (77) | 87 (76) | 90 (80) | 86 (75) | 85 (78) |
| Baseline, mean (SD) | 24.0 (4.1) | 24.7 (4.6) | 24.4 (3.9) | 24.0 (4.1) | 24.2 (4.4) |
| Day 28, mean (SD) | 13.4 (9.8) | 13.5 (10.1) | 16.0 (9.8) | 10.1 (7.7) | 14.8 (9.1) |
| Change from baseline, mean (SD) | –1.0 (9.3) | –11.1 (10.0) | –8.4 (9.7) | –13.6 (8.3) | –9.4 (8.4) |
| Difference of LS means versus placebo (95% CI) | –2.5 (–5.3 to 0.2)[b] | –2.2 (–4.9 to 0.5)[b] | Ref | –4.0 (–6.3 to –1.6) | Ref |
| P value (1-sided) | NS[b,c] | NS[b,c] | NA | NS[c] | NA |

CI = confidence interval; ESK = esketamine; FAS = full analysis set; LS = least squares; MMRM = mixed-effects model for repeated measures; NS = not statistically significant; ref = reference; SD = standard deviation; SDS = Sheehan Disability Scale; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] MMRM model with treatment, day, country or region, class of oral antidepressant (SNRI or SSRI), treatment-by-day interaction, and baseline value as covariates for the FAS observed case population. Negative differences favour ESK.

[b] Difference from placebo was based on the median unbiased estimate for the weighted combination of the LS means for stage 1 (patients enrolled prior to the interim analysis) and stage 2 (patients enrolled after the interim analysis) versus placebo.

[c] NS. Statistical testing stopped due to failure of a prior outcome in the statistical testing hierarchy.

Source: Clinical Study Reports for Study TRD3001[5] and Study TRD3002.[6]

In the maintenance phase of Study TRD3003, the LS mean difference in the change from baseline in the SDS score was –2.9 points (95% CI, –5.5 to –0.4) in the FAS-remitters population and –4.7 points (95% CI, –7.3 to –2.1) in the FAS-responder population (Table 21). This outcome was not controlled for type I error. Data were missing for 6% to 10% of patients (ANCOVA LOCF).

## Table 21: Change From Baseline in SDS Total Score for Relapse Prevention Study

| TRD3003 | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Change from baseline to end point in SDS total score[a]** | | | | |
| Number of patients contributing to the analysis (% of total N) | 82 (91) | 77 (90) | 58 (94) | 53 (90) |
| Baseline, mean (SD) | 2.6 (4.6) | 3.6 (5.7) | 6.7 (5.8) | 7.0 (6.7) |
| End point, mean (SD) | 6.6 (7.5) | 10.3 (9.0) | 8.9 (7.0) | 12.8 (8.3) |
| Change from baseline, mean (SD) | 4.7 (7.3) | 7.2 (10.4) | 2.2 (6.6) | 6.8 (7.6) |
| Difference of LS means versus placebo (95% CI) | –2.9 (–5.5 to –0.4) | Ref | –4.7 (–7.3 to –2.1) | Ref |
| P value (2-sided) | 0.025[b] | NA | < 0.001[b] | NA |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; ref = reference; SD = standard deviation; SDS = Sheehan Disability Scale.

[a] ANCOVA model with treatment, country, and baseline value as covariates for the FAS-remitters or FAS-responders population; LOCF for missing data. Negative differences favour ESK.

[b] No adjustment to control the type I error.

Source: Clinical Study Report for Study TRD3003.[9]

*Suicidality*

In all of the included studies, suicidality was reported as a safety outcome. Data from the C-SSRS have been summarized in Table 22. In addition, there is data related to suicidality in the Harms section of this report.

During the trials, most patients (65% to 95%) reported no suicidal ideation or behaviour. Three patients who received esketamine reported suicidal behaviour. There were no patients in the placebo groups who reported suicidal behaviour. The percentage of patients who reported suicidal ideation during the trials ranged from 5% to 35% and was generally similar within trials in the esketamine and placebo groups.

## Table 22: Most Severe Post-Baseline Suicide-Related Category on C-SSRS

| Study, treatment group | N | No suicidal ideation or behaviour, n (%) | Suicidal ideation, n (%) | Suicidal behaviour, n (%) |
|---|---|---|---|---|
| **TRD3001[a]** | | | | |
| ESK 56 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| ESK 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] |
| **TRD3002[a]** | | | | |
| ESK 56 mg or 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] |
| **TRD3005[a]** | | | | |
| ESK 28 mg to 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] |
| **TRD3003[a]** | | | | |
| **Induction phase** | | | | |
| ESK 56 mg or 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| **Optimization phase** | | | | |
| ESK 56 mg or 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| **Maintenance phase** | | | | |
| ESK 56 mg or 84 mg | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] |
| **Follow-up phase** | | | | |
| ESK | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] |

C-SSRS = Columbia-Suicide Severity Rating Scale; ESK = esketamine.

[a] Safety set.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] Study TRD3005,[7] and Study TRD3003.[9]

*Response and Remission*

The percentage of patients who achieved remission (defined as MADRS score ≤ 12 points) and remission (defined as ≥ 50% reduction in MADRS score) at week 4 of the induction studies, is presented in Figure 4 and Appendix 3 (Table 53). Remission and response data

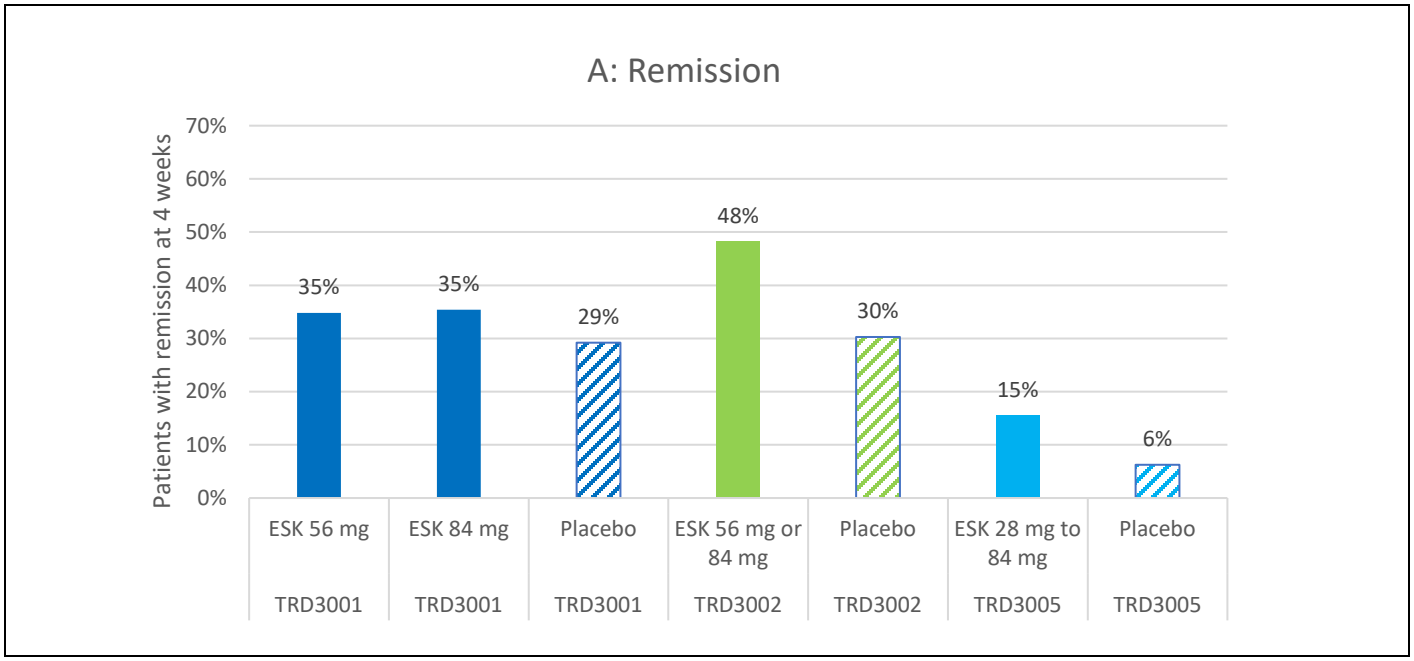
for Study TRD3003 are in Table 24. All data were reported descriptively, with no between-group statistical comparisons.

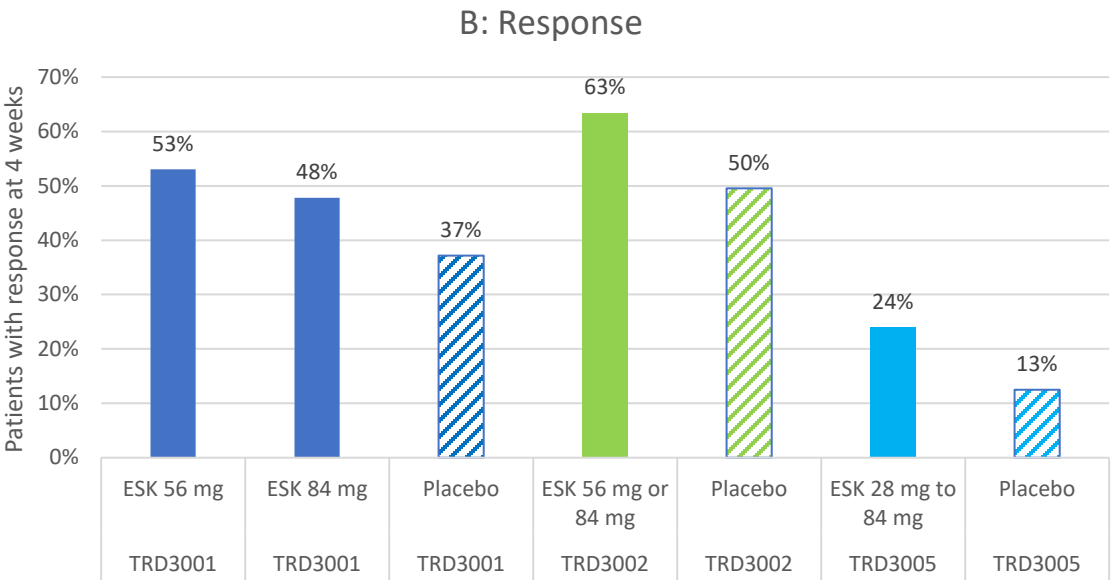
**Induction Studies**

In Study TRD3001, 35% of patients in each of the esketamine groups were in remission at 4 weeks compared with 29% in the placebo group. The percentage remission in Study TRD3002 was 48% for the esketamine group and 30% for the placebo group. Fewer patients achieved remission in the trial that enrolled older adults (≥ 65 years), which reported that 15% in the esketamine group and 6% in the placebo group were in remission.

In Study TRD3001, 53%, 48%, and 37% of patients in the esketamine 56 mg, esketamine 84 mg, and placebo groups, respectively, met the criteria for response at week 4. Response was reported for 63% of esketamine patients and 50% of placebo patients in Study TRD3002. In the trial of elderly patients (TRD3005), 24% in the esketamine group and 13% in the placebo group responded during the induction phase.

## Figure 4: Percentage of Patients With Response and Remission in Induction Studies






ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale.

Note: FAS population with LOCF for missing data. Remission defined as MADRS score of 12 points or less at day 28. Response defined as 50% or greater improvement in MADRS score from baseline at day 28.

Source: Generated by CADTH using data from Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

Two induction trials reported on the onset of clinical response by day 2 (or day 8) that was maintained to day 28 (Table 23). In Study TRD3001, 10.4% and 8.8% in the esketamine groups versus 1.8% in the placebo group, met the criteria for onset of clinical response by day 2. The odds ratios for esketamine versus placebo favoured active treatment; however, the 95% CIs were wide, and due to failure of a prior outcome in the statistical hierarchy, statistical testing of this outcome was to stop. For Study TRD3002, 7.9% and 4.6% in the esketamine and placebo groups, respectively, met the criteria for clinical response by day 2. The odds ratio of clinical response by day 2 was 1.79 (95% CI, 0.57 to 5.67; P = 0.16) for esketamine versus placebo, which was not statistically significant.

The onset of clinical response by day 8 is summarized in Table 9 and these results were generally similar to the data described for onset by day 2. Note that onset by day 8 was not part of the serial gatekeeping procedures and thus the type I error has not been controlled.

## Table 23: Onset of Clinical Response for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | |
|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 |
| **Onset of clinical response at day 2 maintained to day 28** | | | | | |
| n (%) | 12 (10.4) | 10 (8.8) | 2 (1.8) | 9 (7.9) | 5 (4.6) |
| OR (95% CI) | 6.47 (1.38 to 60.45) | 5.34 (1.09 to 50.91) | Ref | 1.79 (0.57 to 5.67) | Ref |
| P value (1-sided) | NS[a,b] | NS[a,b] | NA | 0.161[c] | NA |
| **Onset of clinical response at day 8 maintained to day 28** | | | | | |
| n (%) | 15 (13.0) | 13 (11.4) | 4 (3.5) | 12 (10.5) | 7 (6.4) |
| OR (95% CI) | 3.98 (1.28 to 12.31) | 3.83 (1.18 to 12.44) | Ref | 1.74 (0.65 to 4.70) | Ref |
| P value (1-sided) | 0.005[c,d] | 0.009[c,d] | NA | 0.137[c,d] | NA |

CI = confidence interval; ESK = esketamine; FAS = full analysis set; NS = not statistically significant; OR = odds ratio; ref = reference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] Fisher exact test for weighted mean score difference between treatments for FAS. Weighted difference estimated using asymptotic standard error and difference in response rate at each stage (i.e., stage 1 before interim analysis and stage 2 after interim analysis).

[b] NS due to failure of a prior outcome in the statistical testing hierarchy.

[c] Cochran-Mantel-Haenszel test for mean score difference between treatments adjusting for country and class of oral antidepressant (SNRI or SSRI) for FAS population.

[d] No adjustment to control the type I error and thus P value is not inferential.

Source: Clinical Study Reports for Study TRD3001[5] and Study TRD3002.[6]

### Relapse Prevention Study

In Study TRD3003, all but 1 patient in the FAS-remitters population were in remission at the start of the maintenance phase and 65% remained in remission in the esketamine group compared with 42% in the placebo group at the last time point measured (Table 24). The percentage of patients who achieved response was higher in the esketamine group than the placebo group (75% versus 56%).

Among the FAS-responders population, 66% and 34% still met the criteria for response at the last time point measured (Table 24). In this patient population, 60% and 64% met remission criteria at the start of the maintenance period, and 47% and 25% were in remission at the end of the study in the esketamine and placebo groups, respectively.

## Table 24: Response and Remission Outcomes for Relapse Prevention Study

| TRD3003 | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Response (≥ 50% improvement in MADRS score)[a]** | | | | |
| Baseline, n/N (%) | 90/90 (100) | 86/86 (100) | 62/62 (100) | 59/59 (100) |
| End point, n/N (%) | 67/89 (75) | 48/86 (56) | 41/62 (66) | 20/59 (34) |
| **Remission (MADRS score ≤ 12 points)[a]** | | | | |
| Baseline, n/N (%) | 90/90 (100) | 85/86 (99) | 37/62 (60) | 38/59 (64) |
| End point, n/N (%) | 58/89 (65) | 36/86 (42) | 29/62 (47) | 15/59 (25) |

ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale.

[a] Based on the FAS-remitters or FAS-responders population in the maintenance phase; LOCF for missing data.

Source: Clinical Study Report for Study TRD3003.[9]

*Hospitalization or Emergency Room Visits*

Hospitalizations or emergency room visits were not systematically captured and analyzed as a measure of efficacy in any of the included studies. Narrative data on health care resource utilization was collected in the studies but these data have not been summarized in this report.

*Symptom Severity Score Rated by Patient*

The change from baseline to day 28 in the PHQ-9 score was a key secondary outcome in 2 of the induction studies (Table 25). In Study TRD3001, the difference in the LS means for esketamine 56 mg versus placebo was –2.3 points (95% CI, –4.3 to –0.3) and for esketamine 86 mg was –2.2 points (95% CI, –4.3 to –0.2). In Study TRD3002, the LS mean difference between esketamine and placebo was –2.4 points (95% CI, –4.2 to –0.7). This outcome was part of the serial gatekeeping procedures to control the type I error; however, statistical testing stopped due to failure of a prior outcome.

Data were missing for 4% to 13% of patients per group in the trials (MMRM analysis). The results of the ANCOVA model were similar in magnitude and direction of effect.

## Table 25: Change From Baseline in PHQ-9 Score for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | |
|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 |
| **Change from baseline to day 28 in PHQ-9 total score[a]** | | | | | |
| Number of patients contributing to the analysis (% of total N) | 110 (96) | 99 (87) | 108 (96) | 104 (91) | 100 (92) |
| Baseline, mean (SD) | 20.3 (4.1) | 20.7 (3.6) | 20.8 (3.7) | 20.2 (3.6) | 20.4 (3.7) |
| Day 28, mean (SD) | 9.3 (7.6) | 9.2 (7.8) | 11.7 (8.4) | 7.3 (5.7) | 10.2 (7.7) |
| Change from baseline, mean (SD) | –11.0 (8.1) | –11.7 (7.7) | –9.1 (8.4) | –13.0 (6.4) | –10.2 (7.8) |
| Difference of LS means versus placebo (95% CI) | –2.3 (–4.3 to –0.3)[b] | –2.2 (–4.3 to –0.2)[b] | Ref | –2.4 (–4.2 to –0.7) | Ref |
| P value (1-sided) | NS[b,c] | NS[b,c] | NA | NS[c] | NA |

CI = confidence interval; ESK = esketamine; FAS = full analysis set; LS = least squares; MMRM = mixed-effects model for repeated measures; NS = not statistically significant; PHQ-9 = Patient Health Questionnaire-9; ref = reference; SD = standard deviation SNRI= serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] MMRM model with treatment, day, country or region, class of oral antidepressant (SNRI or SSRI), treatment-by-day interaction, and baseline value as covariates for the FAS observed case population. Negative differences favour ESK. Data were missing for 4% to 13% of patients per group in the trials.

[b] Difference from placebo was based on the median unbiased estimate for the weighted combination of the LS means for stage 1 (patients enrolled prior to the interim analysis) and stage 2 (patients enrolled after the interim analysis).

[c] NS due to failure of a prior outcome in the statistical testing hierarchy.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

In the relapse prevention study, the mean PHQ-9 scores increased from baseline to the last time point measured in both the esketamine and placebo groups (Table 26). The difference between groups favoured esketamine over placebo with a LS mean difference of –2.4 points (95% CI, –4.2 to –0.7) for the FAS-remitters population, and –3.0 points (95% CI, –4.9 to –1.2) for the FAS-responders population. However, the interpretation of these data should take into consideration that there was no control for type I error for secondary outcomes in Study TRD3003.

## Table 26: Change From Baseline in PHQ-9 Total Score for Relapse Prevention Study[a]

| TRD3003 | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Change from baseline to end point in PHQ-9 total score[a]** | | | | |
| Number of patients contributing to the analysis (% of total N) | 89 (99) | 86 (100) | 61 (98) | 58 (98) |
| Baseline, mean (SD) | 1.7 (2.0) | 1.8 (1.9) | 5.0 (3.0) | 4.3 (3.1) |
| End point, mean (SD) | 5.0 (5.4) | 7.7 (6.9) | 6.7 (5.6) | 8.9 (5.8) |
| Change from baseline, mean (SD) | 3.3 (5.6) | 5.9 (7.1) | 1.7 (5.0) | 4.7 (5.5) |
| Difference of LS means versus placebo (95% CI) | –2.4 (–4.2 to –0.7) | NA | –3.0 (–4.9 to –1.2) | NA |
| P value (2-sided) | 0.008[b] | NA | 0.002[b] | NA |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; PHQ-9 = Patient Health Questionnaire-9; ref = reference; SD = standard deviation.

[a] ANCOVA model with treatment, country, and baseline value as covariates for the FAS-remitters or FAS-responders population; LOCF for missing data. Negative differences favour ESK.

[b] No adjustment to control the type I error and thus P value is not inferential.

Source: Clinical Study Report for Study TRD3003.[9]

*Symptom Severity Score Rated by Physician*

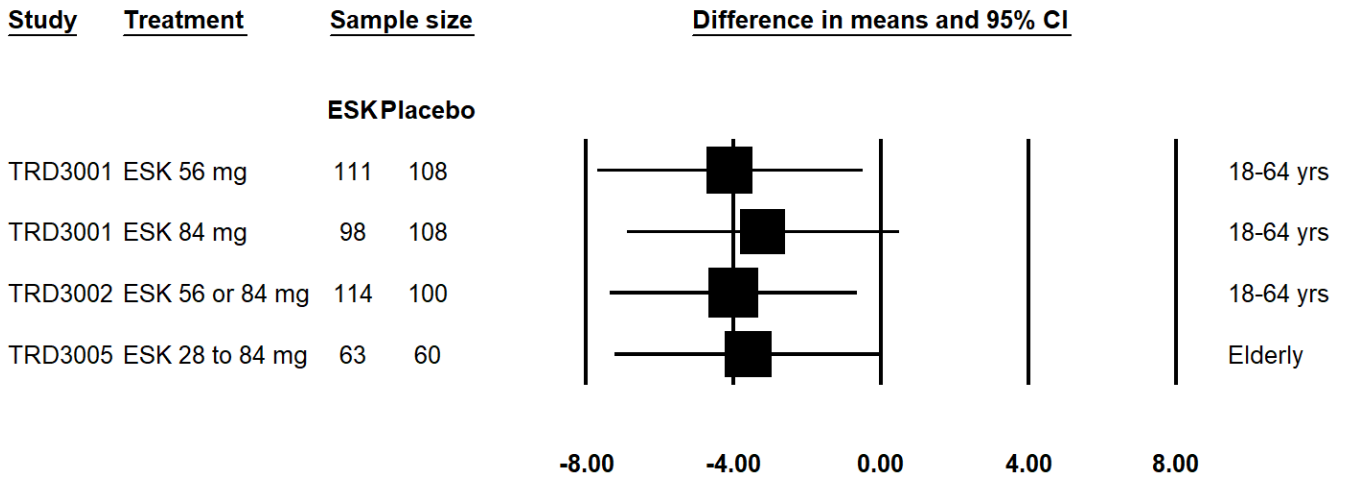
The change from baseline to day 28 in the MADRS total score was the primary outcome in all 3 induction studies. Both the esketamine and placebo groups showed a reduction in MADRS scores over time with mean change from baseline values ranging from –10.0 (SD = 12.7) to –1.4 (SD = 12.3) for the esketamine groups, and from –6.3 (SD = 8.9) to –17.0 (SD = 13.9) for the placebo groups (MMRM model; Table 27). In Study TRD3002, the LS mean difference between esketamine and placebo was –4.0 points (95% CI, –7.3 to –0.6), which was statistically significant (1-sided P = 0.010, MMRM). In Study TRD3001, the LS mean difference of –3.2 points (95% CI, –6.9 to 0.5, MMRM) between esketamine 84 mg and placebo did not reach statistical significance, and according to the statistical analysis plan, testing of the 56 mg dose was to stop. The LS mean difference for esketamine 56 mg versus placebo was –4.1 points (95% CI, –7.7 to –0.5, MMRM). In the MMRM analysis, data were missing for 3% to 14% of patients per group in Study TRD3001 and Study TRD3002.

In Study TRD3005, which enrolled patients 65 years or older, the LS mean difference between esketamine and placebo for the change from baseline in MADRS score was –3.6 points (95% CI, –7.2 to 0.07, MMRM), which was not statistically significant with a 1-sided P value of 0.029 (data missing for 8% and 12%).

The results based on ANCOVA models that used LOCF for missing data were generally consistent with the MMRM results. With the ANCOVA model, there was a shift toward the null for the esketamine 84 mg dose in Study TRD3001; this group had a higher frequency of early withdrawals (16%) compared with the placebo group (5%) or the esketamine 56 mg group (5%). Figure 5 and Figure 6 show the LS mean difference between groups for the MMRM (OC) and ANCOVA (LOCF) models. Study TRD3002 also reported a tipping point analysis designed to assess the missing at random assumption in the MMRM model. In the most conservative analysis, the results still favoured esketamine over placebo until the

missing change in MADRS scores for the esketamine patients were 9 points worse after discontinuation than expected if they were missing at random.

## Figure 5: Mean Difference Versus Placebo for the Change From Baseline in MADRS Score – Induction Studies (MMRM OC)

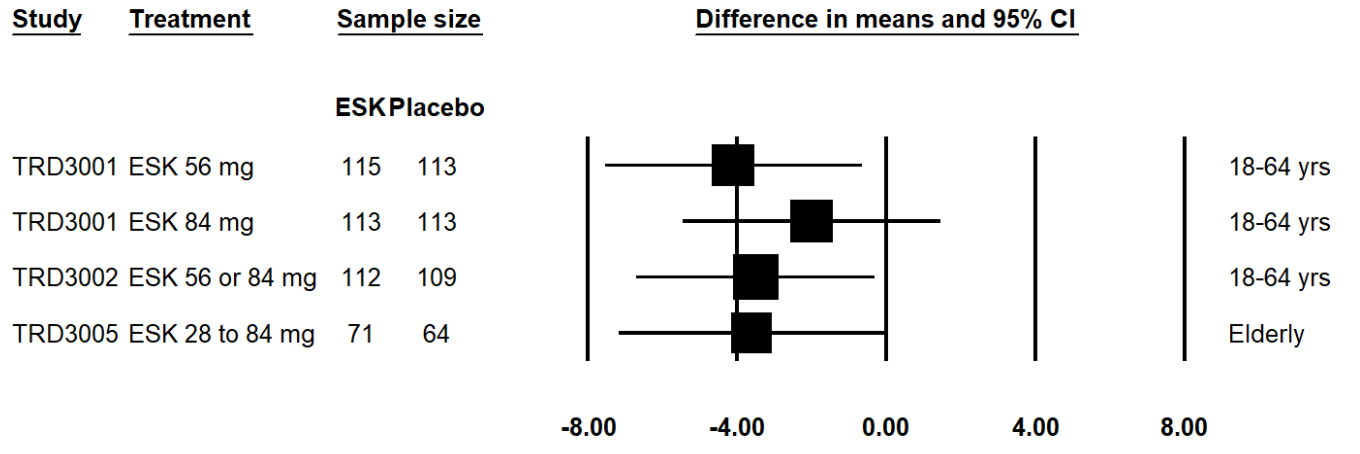



CI = confidence interval; ESK = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; OC = observed case; yrs = years.

Note: Negative values favour ESK.

Source: Generated by CADTH using data from Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Figure 6: Mean Difference Versus Placebo for the Change From Baseline in MADRS Score – Induction Studies (ANCOVA LOCF)




ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; yrs = years.

Note: Negative values favour ESK.

Source: Generated by CADTH using data from Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 27: Change From Baseline to Day 28 in MADRS Total Score for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Change from baseline to day 28 in MADRS total score** | | | | | | | |
| **MMRM (OC)[a]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 111 (97) | 98 (86) | 108 (96) | 101 (89) | 100 (92) | 63 (88) | 60 (92) |
| Baseline, mean (SD) | 37.4 (4.8) | 37.8 (5.6) | 37.5 (6.2) | 37.0 (5.7) | 37.3 (5.7) | 35.5 (5.9) | 34.8 (6.4) |
| Day 28, mean (SD) | 18.5 (13.3) | 19.4 (13.9) | 22.8 (13.7) | 15.5 (10.7) | 20.6 (12.7) | 25.4 (12.7) | 28.7 (10.1) |
| Change from baseline, mean (SD) | –19.0 (13.9) | –18.8 (14.1) | –14.8 (15.1) | –21.4 (12.3) | –17.0 (13.9) | –10.0 (12.7) | –6.3 (8.9) |
| Difference of LS means versus placebo (95% CI) | –4.1 (–7.7 to –0.5)[b] | –3.2 (–6.9 to 0.5)[b] | Ref | –4.0 (–7.3 to –0.6) | Ref | –3.6 (–7.2 to 0.07)[b] | Ref |
| P value (1-sided) | NS[b,c] | 0.044 NS[b] | NA | 0.010 | NA | 0.029 NS[b] | NA |
| **ANCOVA (LOCF)[d]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 115 (100) | 113 (99) | 113 (100) | 112 (98) | 109 (100) | 71 (99) | 64 (98) |
| Baseline, mean (SD) | 37.4 (4.8) | 37.8 (5.6) | 37.5 (6.2) | 37.0 (5.7) | 37.3 (5.7) | 35.5 (5.9) | 34.8 (6.4) |
| End point, mean (SD) | 19.1 (13.5) | 20.6 (14.0) | 23.1 (13.6) | 17.4 (12.2) | 21.0 (12.9) | 26.3 (12.3) | 29.2 (10.1) |
| Change from baseline, mean (SD) | –18.3 (14.2) | –17.4 (14.3) | –14.3 (15.0) | –19.6 (13.6) | –16.3 (14.2) | –9.3 (12.3) | –5.6 (9.1) |
| Difference of LS means versus placebo (95% CI) | –4.1 (–7.5 to –0.6)[b] | –2.0 (–5.5 to 1.4)[b] | Ref | –3.5 (–6.7 to –0.3) | NA | –3.6 (–7.2 to –0.03)[b] | NA |
| P value (1-sided) | NS[b,c] | 0.12[b] | NA | 0.017 | NA | 0.026 NS[b] | NA |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; NS = not statistically significant; OC = observed case; ref = reference; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] MMRM model with treatment, day, country or region, class of oral antidepressant (SNRI or SSRI), treatment-by-day interaction, and baseline value as covariates for the FAS OC population (no imputation for missing data). Negative differences favour ESK.

[b] Difference from placebo was based on the median unbiased estimate for the weighted combination of the LS means for stage 1 (patients enrolled prior to the interim analysis) and stage 2 (patients enrolled after the interim analysis).

[c] NS due to failure to reject the null for the ESK 84 mg dose versus placebo for the change from baseline in MADRS score.

[d] ANCOVA model with change from baseline as the response variable and treatment, country or region, class of oral antidepressant (SNRI or SSRI), and baseline value as covariates, for FAS population with LOCF for missing data. Negative differences favour ESK.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

At the start of the maintenance phase of Study TRD3003, the mean MADRS scores were low in the FAS-remitters population (esketamine, 3.7 [SD = 3.3]; placebo, 4.7 [SD = 3.7]) and increased over time in both groups. The between-group difference favoured esketamine with a LS mean difference of –5.2 points (95% CI, –8.8 to –1.6; P = 0.005) versus placebo. For the FAS-responders population, the LS mean difference was –7.4 points (95% CI, –11.3 to –3.6; P < 0.001) favouring esketamine over placebo. There was no adjustment to control the type I error.

## Table 28: Change From Baseline to End Point in MADRS Total Score for Relapse Prevention Study[a]

| TRD3003 | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Change from baseline to end point in MADRS total score[a]** | | | | |
| Number of patients contributing to the analysis (% of total N) | 89 (99) | 86 (100) | 62 (100) | 59 (100) |
| Baseline, mean (SD) | 3.7 (3.3) | 4.7 (3.7) | 10.7 (5.3) | 10.3 (4.9) |
| End point, mean (SD) | 11.3 (11.7) | 17.2 (13.2) | 15.1 (11.4) | 21.8 (11.3) |
| Change from baseline, mean (SD) | 7.5 (11.6) | 12.5 (13.6) | 4.4 (11.4) | 11.4 (12.0) |
| Difference of LS means versus placebo (95% CI) | –5.2 (–8.8 to –1.6) | NA | –7.4 (–11.3 to –3.6) | NA |
| P value (2-sided) | 0.005[b] | NA | < 0.001[b] | NA |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; ref = reference; SD = standard deviation.

[a] ANCOVA model with treatment, country, and baseline value as covariates for the FAS-remitters or FAS-responders population, LOCF for missing data. Negative differences favour ESK.

[b] No adjustment to control the type I error and thus P value is not inferential.

Source: Clinical Study Report for Study TRD3003.[9]

*Relapse*

Time to relapse for the FAS-remitters population was the primary outcome of Study TRD3003. Among patients who achieved stable remission at the end of the optimization period, 24 patients (27%) relapsed in the esketamine group and 39 patients (45%) relapsed in the placebo group (Table 29). Most of the patients who relapsed met the relapse criteria based on MADRS score. Relapse was delayed in the esketamine group relative to placebo with a HR of 0.49 (95% CI, 0.29 to 0.84; P = 0.003). Figure 7 shows the Kaplan-Meier curve for time to relapse in the FAS-remitters population.

The pre-specified sensitivity analyses supported the findings of the primary analysis (Appendix 3, Table 54). Additional post hoc sensitivity analyses were conducted to explore the impact of early relapses, which were reported more frequently in the placebo than esketamine groups. Unblinding was 1 potential explanation for the early placebo relapses, if patients switched to placebo were no longer experiencing the dissociation and other acute AEs associated with esketamine. A post hoc sensitivity analysis that censored 3 patients who reported a difference in dissociation symptoms (based on the Clinician Administered Dissociative States Scale) after switching to intranasal placebo reported a HR of 0.50 (95% CI, 0.30 to 0.84; P = 0.008). A second analysis that censored 7 patients with differences in dissociation-related adverse effect showed a HR of 0.56 (95% CI, 0.33 to 0.95; P = 0.03). Other post hoc analyses were conducted that censored patients with relapse within 1, 2, 3, or 4 weeks of randomization. Data for the week 1 and week 2 analysis were similar to the primary results; the week 1 HR was 0.47 (95% CI, 0.28 to 0.78) and week 2 HR was 0.54 (95% CI, 0.32 to 0.91). However, when relapses in the first 3 or 4 weeks were censored, the differences between esketamine and placebo were no longer statistically significant with a week 3 HR of 0.64 (95% CI, 0.37 to 1.12) and week 4 HR of 0.71 (95% CI, 0.38 to 1.31).

In the FAS-responders population, relapse was delayed in the esketamine versus placebo group with a HR of 0.30 (95% CI, 0.16 to 0.55; P < 0.001) (Table 29). The Kaplan-Meier curve of time to relapse is shown in Figure 8.

## Table 29: Time to Relapse in Study TRD3003

| TRD3003[a] | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Time to relapse** | | | | |
| Number of patients contributing to the analysis (% of total N) | 90 (100) | 86 (100) | 62 (100) | 59 (100) |
| Number of relapses, n (%) | 24 (26.7) | 39 (45.3) | 16 (26) | 34 (58) |
| 25th percentile time to relapse, days (95% CI) | 153 (105 to 225) | 33 (22 to 48) | 217 (56 to 635) | 24 (17 to 46) |
| Median time to relapse, days (95% CI) | NE | 273 (97 to NE) | 635 (264 to 635)[b] | 88 (46 to 196) |
| HR (95% CI) | 0.49 (0.29 to 0.84)[c] | Ref | 0.30 (0.16 to 0.55)[d] | Ref |
| P value (2-sided) | 0.003[e] | NA | < 0.001[f] | NA |
| **Reason for relapse, n (%)** | | | | |
| MADRS ≥ 22 points | 18 (20) | 38 (44) | 16 (26) | 33 (56) |
| Hospitalization | 3 (3) | 0 | 0 | 0 |
| Clinical relapse event | 3 (3) | 1 (1) | 0 | 1 (2) |
| **Relapse in week 1 to 4, n (%)** | | | | |
| Week 1 | 0 | 0 | NR | NR |
| Week 2 | 0 | 6 (7) | NA | NA |
| Week 3 | 1 (1) | 13 (15) | NA | NA |
| Week 4 | 4 (4) | 19 (22) | NA | NA |

CI = confidence interval; ESK = esketamine; FAS = full analysis set; HR = hazard ratio; MADRS = Montgomery-Åsberg Depression Rating Scale; NE = not estimable; NR = not reported; ref = reference.

[a] Based on the FAS-remitters and FAS-responders populations.

[b] Influenced by 1 patient who had a long time to relapse (635 days).

[c] HR and 95% CI calculated based on weighted estimates as per Wassmer (2006).[8]

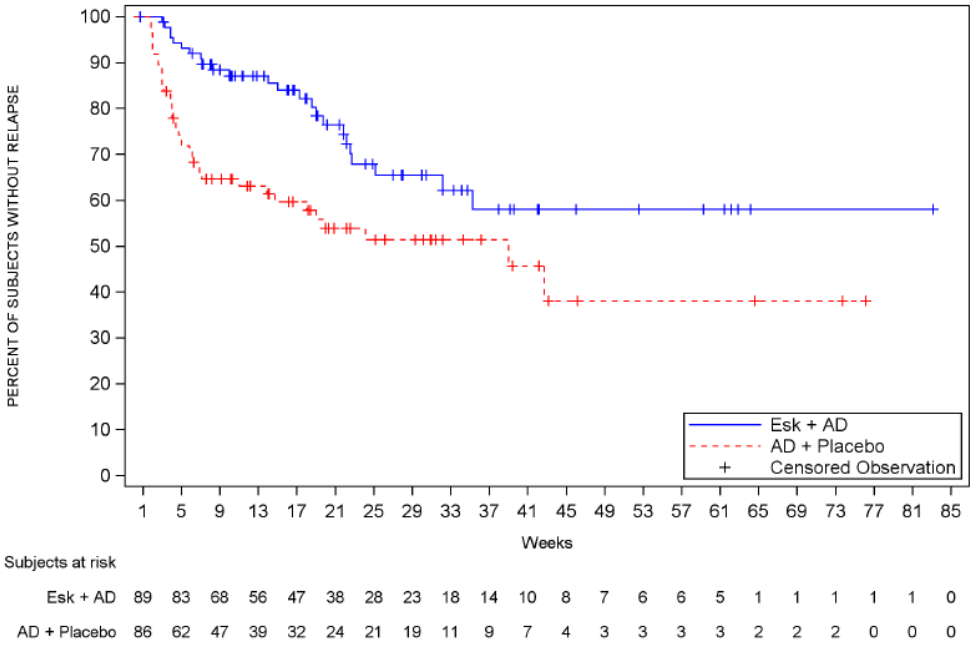
[d] Based on Cox proportional hazards model with treatment as a factor.

[e] Based on weighted combination of the log-rank test. Two-sided significance level of 0.046 to control type I error due to interim analysis.

[f] Based on log-rank test. No adjustment to control the type I error and thus P value is not inferential.

Source: Clinical Study Report for Study TRD3003.[9]

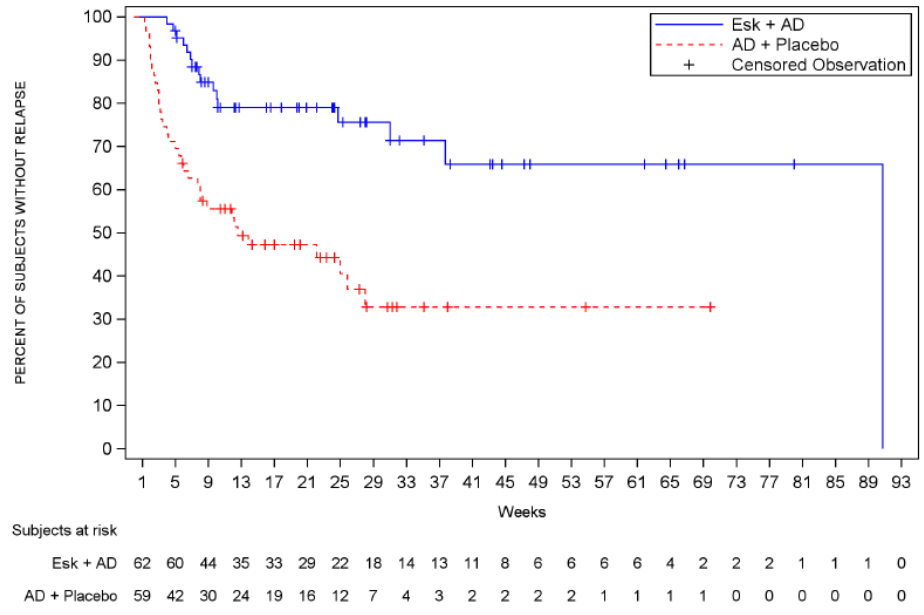
## Figure 7: Time to Relapse in Stable Remission FAS Population of Study TRD3003




AD = antidepressant; ESK = esketamine; FAS = full analysis set.

Source: Reproduced from Clinical Study Report for Study TRD3003.[9]

## Figure 8: Time to Relapse in Stable Response FAS Population of Study TRD3003




AD = antidepressant; ESK = esketamine; FAS = full analysis set.

Source: Reproduced from Clinical Study Report for Study TRD3003.[9]

### *Withdrawals or Discontinuation of Treatment*

Withdrawals or discontinuations of treatments were not analyzed in any of the studies as a measure of the overall efficacy and tolerability of esketamine. Descriptive data on study withdrawals are included in the Disposition section of this report and discontinuation due to AEs are listed in the Harms section.

## Harms

Only those harms identified in the review protocol are reported as follows. For detailed harms data see Table 30 to Table 34 in this section of the report and Table 55 to Table 57 in Appendix 3.

### *Adverse Events*

In the induction studies, the proportion of patients who reported AEs was higher among those who received esketamine (71% to 89%) than placebo (60% to 68%) (Table 30). In the esketamine groups the most commonly reported AEs were dissociation (13% to 28%), dizziness (21% to 28%), vertigo (11% to 26%), nausea (18% to 32%), dysgeusia (6% to 24%), and somnolence (1% to 21%). Headache (3% to 17%) and dysgeusia (5% to 15%) were the most commonly reported AEs in the placebo groups. Most AEs occurred on dosing days, including 87% to 92% of events in the esketamine groups and 64% to 71% of events in the placebo groups (Appendix 3, Table 55). Among those who received esketamine, 86% of 94% of events resolved on the same day, compared with 58% to 85% of events in the placebo groups.

During the induction and optimization phases of the relapse prevention trial (TRD3003), 77% and 74% of patients treated with esketamine reported 1 or more AEs, and during the maintenance phase, 82% in the esketamine group versus 46% in the placebo group experienced an AE (Table 31). The most commonly reported events in the esketamine groups were dissociation, dizziness, vertigo, nausea, dysgeusia, and somnolence, which were reported by 11% to 27% of patients. These events were reported less frequently among patients who received placebo (0% to 7%).

A summary of AEs is provided in Appendix 3 (Table 56) for patients in Study TRD3003 who transferred into the trial and continued to receive intranasal placebo plus oral antidepressant. Of these patients, 62% (53 of 86) and 69% (37 of 54) reported an AE during the optimization phase and maintenance phases, respectively. One patient experienced a SAE (clavicle fracture) and 2 patients stopped intranasal study drug due to AEs (blood pressure increased; rash and nail infection). There was 1 patient who reported a TEAE related to suicidality.

## Table 30: Summary of Most Common Adverse Events for Induction Studies

| Adverse events | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 116 | Placebo N = 113 | ESK 56 or 84 mg N = 115 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Patients with ≥ 1 adverse event** | | | | | | | |
| n (%) | 100 (87) | 103 (89) | 77 (68) | 98 (85) | 66 (61) | 51 (71) | 39 (60) |
| **Most common adverse events[b], n (%)** | | | | | | | |
| Dysgeusia | 17 (15) | 20 (17) | 17 (15) | 28 (24) | 13 (12) | 4 (6) | 3 (5) |
| Dizziness | 32 (28) | 26 (22) | 10 (9) | 24 (21) | 5 (5) | 15 (21) | 5 (8) |
| Headache | 23 (20) | 24 (21) | 19 (17) | 23 (20) | 19 (17) | 9 (13) | 2 (3) |
| Somnolence | 24 (21) | 21 (18) | 13 (12) | 15 (13) | 7 (6) | 1 (1) | 3 (5) |
| Paresthesia | 19 (17) | 11 (10) | 3 (3) | 13 (11) | 1 (1) | 4 (6) | 2 (3) |
| Dizziness postural | 7 (6) | 7 (6) | 0 | 8 (7) | 1 (1) | 2 (3) | 0 |
| Hypoesthesia | 14 (12) | 16 (14) | 2 (2) | 8 (7) | 1 (1) | 4 (6) | 1 (2) |
| Sedation | 6 (5) | 8 (7) | 1 (1) | 5 (4) | 1 (1) | NR | NR |
| Lethargy | 7 (6) | 5 (4) | 1 (1) | 1 (1) | 0 | NR | NR |
| Tremor | 4 (4) | 6 (5) | 2 (2) | 2 (2) | 0 | NR | NR |
| Mental impairment | 6 (5) | 3 (3) | 1 (1) | 2 (2) | 1 (1) | 0 | 1 (2) |
| Dissociation | 30 (26) | 32 (28) | 4 (4) | 30 (26) | 4 (4) | 9 (13) | 1 (2) |
| Dysphoria | NR | NR | NR | 0 | 2 (2) | 4 (6) | 0 |
| Anxiety | 10 (9) | 9 (8) | 7 (6) | 12 (10) | 5 (5) | 2 (3) | 5 (8) |
| Insomnia | 10 (9) | 8 (7) | 11 (10) | 11 (10) | 5 (5) | 4 (6) | 3 (5) |
| Euphoric mood | 8 (7) | 2 (2) | 2 (2) | 5 (4) | 0 | 1 (1) | 1 (2) |
| Nausea | 31 (27) | 37 (32) | 12 (11) | 30 (26) | 7 (6) | 13 (18) | 3 (5) |
| Vomiting | 7 (6) | 14 (12) | 2 (2) | 11 (10) | 2 (2) | 5 (7) | 1(2) |
| Diarrhea | 8 (7) | 5 (4) | 3 (3) | 10 (9) | 10 (9) | 3 (4) | 1 (2) |
| Dry mouth | 5 (4) | 5 (4) | 4 (4) | 9 (8) | 3 (3) | 1 (1) | 0 |
| Hypoesthesia oral | 16 (14) | 12 (10) | 2 (2) | 9 (8) | 1 (1) | 5 (7) | 0 |
| Paresthesia oral | 9 (8) | 1 (1) | 2 (2) | 9 (8) | 1 (1) | NR | NR |
| Vertigo | 24 (21) | 24 (21) | 2 (2) | 30 (26) | 3 (3) | 8 (11) | 2 (3) |
| Feeling drunk | 7 (6) | 3 (3) | 0 | 9 (8) | 1 (1) | NR | NR |
| Fatigue | 12 (10) | 8 (7) | 5 (4) | 5 (4) | 6 (6) | 9 (13) | 5 (8) |
| Throat irritation | 5 (4) | 9 (8) | 4 (4) | 9 (8) | 5 (5) | 0 | 2 (3) |
| Nasal discomfort | 4 (4) | 5 (4) | 7 (6) | 8 (7) | 2 (2) | 1 (1) | 0 |
| Vision blurred | 8 (7) | 9 (8) | 0 | 14 (12) | 3 (3) | 2 (3) | 0 |
| Blood pressure increased | 8 (7) | 11 (10) | 5 (4) | 11 (10) | 0 | 9 (13) | 3 (5) |
| Pollakiuria | 6 (5) | 2 (2) | 1 (1) | 3 (3) | 0 | 1 (1) | 0 |
| Urinary tract infection | 3 (3) | 1 (1) | 2 (2) | 2 (2) | 1 (1) | 6 (8) | 1 (2) |

ESK = esketamine; NR = not reported.

[a] Safety population.

[b] Frequency of 5% or greater in at least 1 treatment group among the induction studies.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 31: Summary of Most Common Adverse Events for Relapse Prevention Study

| TRD3003[a] | Induction phase | Optimization phase | Maintenance phase | |
|---|---|---|---|---|
| | ESK N = 437 | ESK N = 455 | ESK N = 152 | Placebo N = 145 |
| **Patients with ≥ 1 adverse event** | | | | |
| n (%) | 336 (77) | 335 (74) | 125 (82) | 66 (46) |
| Most common adverse events[b], n (%) | | | | |
| Dizziness | 97 (22) | 61 (13) | 31 (20) | 7 (5) |
| Dysgeusia | 90 (21) | 79 (17) | 41 (27) | 10 (7) |
| Somnolence | 65 (15) | 63 (14) | 32 (21) | 3 (2) |
| Headache | 60 (14) | 57 (13) | 27 (18) | 14 (10) |
| Paresthesia | 48 (11) | 24 (5) | 11 (7) | 0 |
| Sedation | 44 (10) | 19 (4) | 10 (7) | 1 (1) |
| Dizziness postural | 33 (8) | 26 (6) | 10 (7) | 3 (2) |
| Hypoesthesia | 30 (7) | 24 (5) | 9 (6) | 0 |
| Dissociation | 82 (19) | 73 (16) | 35 (23) | 0 |
| Anxiety | 31 (7) | 11 (2) | 12 (8) | 5 (3) |
| Confusional state | 13 (3) | 9 (2) | 9 (6) | 0 |
| Nausea | 94 (22) | 48 (11) | 25 (16) | 1 (1) |
| Hypoesthesia oral | 32 (7) | 34 (8) | 20 (13) | 0 |
| Vomiting | 29 (7) | 17 (4) | 10 (7) | 1 (1) |
| Paresthesia oral | 16 (4) | 13 (3) | 8 (5) | 1 (1) |
| Vertigo | 99 (23) | 91 (20) | 38 (25) | 8 (6) |
| Nasal discomfort | 29 (7) | 26 (6) | 11 (7) | 4 (3) |
| Throat irritation | 26 (6) | 16 (4) | 8 (5) | 1 (1) |
| Vision blurred | 45 (10) | 30 (7) | 24 (16) | 1 (1) |
| Diplopia | 16 (4) | 10 (2) | 9 (6) | 0 |
| Blood pressure increase | 34 (8) | 26 (6) | 10 (7) | 5 (3) |
| Viral upper respiratory tract infection | 5 (1) | 22 (5) | 11 (7) | 12 (8) |

ESK = esketamine.

[a] Safety population.

[b] Frequency of 5% or greater in at least 1 treatment group among the induction studies.

Source: Clinical Study Report for Study TRD3003.[9]

### *Serious Adverse Events*

The frequency of SAEs ranged from 0% to 4% in the esketamine groups and 0% to 3% in the placebo groups during the induction phase of Study TRD3001, Study TRD3002, and Study TRD3005 (Table 32). In Study TRD3003, 3% and 2% of patients experienced a SAE during the induction and optimization phase (all patients receiving esketamine plus oral antidepressant). During the maintenance phase, 3% in the esketamine group and 1% in the placebo group reported a SAE (Table 33). Worsening depression, anxiety, increased blood pressure, cerebral hemorrhage, and dizziness and vertigo were among the SAEs reported in the 4 trials.

Appendix 3 (Table 57) summarizes AEs reported for patients who entered the follow-up phase of Study TRD3001, Study TRD3002, Study TRD3005, or Study TRD3003. Eight of 626 patients who had received esketamine reported a SAE including depression, insomnia, anxiety, mania, cerebral hemorrhage, chest pain, and intervertebral disc protrusion. One patient who had received placebo reported a SAE of suicidal ideation (N = 124). The person-years of follow-up were not reported.

*Withdrawals Due to Adverse Events*

The percentage of patients who stopped intranasal study drug treatment due to AEs ranged from 1% to 7% of patients who received esketamine in the induction studies (Table 32) and was 5% during the induction period of Study TRD3003 (Table 33). Among those who received intranasal placebo, 1% to 3% stopped treatment due to AEs. During the maintenance phase of Study TRD3003, 3% and 2% of patients discontinued intranasal study drug in the esketamine and placebo groups, respectively (Table 33). The more common reasons for discontinuation of esketamine were nausea, vomiting, depression, dizziness, dissociation, anxiety, and increased blood pressure.

The percentage of patients who stopped oral antidepressant drugs due to AEs during the induction, optimization, or maintenance phases of the trials was generally low, ranging from 0% to 4% in the esketamine groups and 0% to 2% in the placebo groups (Table 32 and Table 33).

*Mortality*

During the 4 included studies there was 1 death in Study TRD3002 in a patient who received esketamine. This patient died of injuries sustained in a road traffic accident, which was not considered study drug-related by the sponsor.

There were 3 completed suicides among 1,861 patients who received esketamine in the phase II and III studies (1,045 patient-years) and no completed suicides among 486 patients who received intranasal placebo (100 patient-years).[25]

## Table 32: Summary of Serious Adverse Events, Discontinuations, and Notable Harms for Induction Studies

| Serious adverse events | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 116 | Placebo N = 113 | ESK 56 or 84 mg N = 115 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Deaths** | | | | | | | |
| n (%) | 0 | 0 | 0 | 1 (1) | 0 | 0 | 0 |
| Description | NA | NA | NA | [redacted] | NA | NA | NA |
| **Patients with ≥ 1 SAE** | | | | | | | |
| n (%) | 2 (2) | 0 | 0 | 1 (1) | 1 (1) | 3 (4) | 2 (3) |
| Description of events | [redacted] | NA | NA | [redacted] | [redacted] | [redacted] | [redacted] |
| **Patients who stopped intranasal treatment due to adverse events** | | | | | | | |
| n (%) | 1 (1) | 7 (6) | 2 (2) | 8 (7) | 1 (1) | 4 (6) | 2 (3) |

| Serious adverse events | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 116 | Placebo N = 113 | ESK 56 or 84 mg N = 115 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| Description of events | [redacted] | | | | | | |
| **Patients who stopped oral antidepressant due to adverse events** | | | | | | | |
| n (%) | 0 | 1 (1) | 2 (2) | 4 (4) | 0 | 1 (1) | 1 (2) |
| Description of events | NA | [redacted] | | | NA | | |
| **Notable harms** | | | | | | | |
| n (%) | | | | | | | |
| TEAE suggestive of abuse | 65 (57) | 60 (52) | 20 (18) | 58 (50) | 14 (13) | 21 (29) | 9 (14) |
| Dizziness or vertigo | 52 (45) | 50 (43) | 13 (12) | 59 (51) | 9 (8) | 20 (28) | 7 (11) |
| Impaired cognition | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cystitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Suicidality | 1 (1) | 2 (2) | 1 (1) | 0 | 1 (1) | 1 (1) | 0 |
| Increased blood pressure | 9 (8) | 14 (12) | 5 (4) | 12 (10) | 1 (1) | 10 (14) | 4 (6) |

ESK = esketamine; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Safety population.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 33: Summary of Serious Adverse Events, Discontinuations, and Notable Harms for Relapse Prevention Study

| TRD3003[a] | Induction phase | Optimization phase | Maintenance phase | |
|---|---|---|---|---|
| | ESK N = 437 | ESK N = 455 | ESK N = 152 | Placebo N = 145 |
| **Deaths** | | | | |
| n (%) | 0 | 0 | 0 | 0 |
| **Patients with ≥ 1 SAE** | | | | |
| n (%) | 13 (3) | 11 (2) | 4 (3) | 1 (1) |
| Events reported by > 1 patient (number of patients) | [redacted] | | | |
| **Patients who stopped intranasal treatment due to adverse events** | | | | |
| n (%) | 22 (5) | 5 (1) | 4 (3) | 3 (2) |

| TRD3003[a] | Induction phase | Optimization phase | Maintenance phase | |
|---|---|---|---|---|
| | ESK N = 437 | ESK N = 455 | ESK N = 152 | Placebo N = 145 |
| Events reported by > 1 patient (number of patients) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Patients who stopped oral antidepressant due to adverse events** | | | | |
| n (%) | 8 (2) | 2 (< 1) | 3 (2) | 0 |
| Events reported by > 1 patient (number of patients) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Notable harms** | | | | |
| n (%) | | | | |
| TEAE suggestive of abuse | 205 (47) (2 SAE: disorientation, sedation) | 170 (37) | 75 (49) | 9 (6) |
| Dizziness or vertigo | 214 (49) | 161 (35) | 66 (43) | 17 (12) |
| Impaired cognition | 0 | 0 | 0 | 0 |
| Suicidality | 5 (1.1) (1 SAE: suicidal ideation)] | 1 (0.2) | 3 (2.0) | 1 (0.7) |
| Cystitis | 2 (0.5) | 1 (0.2) | 2 (1.3) | 1 (0.7) |
| Increased blood pressure | 40 (9) (1 SAE: autonomic nervous system imbalance) | 30 (7) (1 SAE: hypertensive crisis) | 13 (9) | 5 (3) |

ESK = esketamine; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Safety population.

Source: Clinical Study Report for Study TRD3003.[9]

*Notable Harms*

Events that were potentially suggestive of abuse were defined as AEs of special interest in all trials. These events included nervous system disorders, such as dizziness, somnolence, and mental impairment; psychiatric disorders, such as dissociation, euphoric mood, disorientation, and hallucination; and general disorders, such as feeling drunk or abnormal. TEAEs suggestive of abuse were reported more frequently among patients who received esketamine than placebo in the induction studies. The frequency ranged from 29% to 57% in the esketamine groups and from 13% to 18% in the placebo groups (Table 32). During the induction and optimization phases of Study TRD3003, 47% and 37% of patients reported TEAE suggestive of abuse, and during the maintenance phase the frequency of these events was higher for esketamine than placebo (49% versus 6%) (Table 33).

Dizziness and vertigo were also reported more frequently among patients receiving esketamine (28% to 51%) versus placebo (8% to 12%) (Table 32 and Table 33). No patients reported AEs related to impaired cognition and few patients reported cystitis (0% to 1.3%).

Increased blood pressure was reported by 7% to 14% of patients receiving esketamine and 1% to 6% of those receiving placebo (Table 32 and Table 33). Two patients in Study

TRD3003 had SAEs related to increased blood pressure including 1 patient treated with esketamine who experienced hypertensive crisis (Table 33).

Suicidality was reported by 0% to 2% of patients treated with esketamine and 0% to 1% of placebo-treated patients during the treatment phases of the trials (Table 32 and Table 33). The sponsor provided a summary of suicide-related AEs during the treatment and follow-up phases of all phase III studies in Table 34. The frequency of AEs ranged from 0% to 4.0% among patients who had received esketamine and from 0% to 2.5% among those who had received placebo.

## Table 34: Incidence of Suicidality in Phase III Trials

| Study/Phase | ESK | | Placebo | |
|---|---|---|---|---|
| | Total N | TEAE suicidality, n (%) | Total N | TEAE suicidality, n (%) |
| **Pooled TRD3001/3002** | **Total ESK[a]** | | | |
| Induction phase | 346 | 4 (1.2) | 222 | 2 (0.9) |
| Follow-up phase | 133 | 1 (0.8) | 121 | 3 (2.5) |
| **TRD3005** | **ESK 28 to 84 mg** | | | |
| Induction phase | 72 | 1 (1.4) | 65 | 0 (0) |
| Follow-up phase | 12 | 0 (0) | 3 | 0 (0) |
| **TRD3003** | **ESK 56 or 84 mg** | | | |
| Induction phase | 437 | 6 (1.4) | NA | NA |
| Optimization phase | 455 | 3 (0.7) | NA | NA |
| Maintenance phase | 152 | 3 (2.0) | 145 | 1 (0.7) |
| Follow-up phase | 481 | 3 (0.6) | 64[b] | 0 (0) |
| **TRD3004** | **ESK 28 to 84 mg** | | | |
| Induction phase | 779 | 20 (2.6) | NA | NA |
| Optimization/maintenance phase | 603 | 24 (4.0) | NA | NA |
| Follow-up phase | 357 | 3 (0.8) | NA | NA |

ESK = esketamine; NA = not applicable; TEAE = treatment-emergent adverse event.

Note: TEAEs in the category of suicidality included completed suicide, depression suicidal, intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self-injurious behaviour, self-injurious ideation, suicidal behaviour, suicidal ideation, and suicide attempt. Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

[a] Total ESK row includes both the fixed-dose and flexible dose ESK groups.

[b] Placebo group in follow-up phase for Study TRD3003 includes subjects who received placebo for all previous phases in the study.

Source: Adapted from Janssen Health Authority Response to Notice of Deficiency.[25]

### Critical Appraisal

#### *Internal Validity*

All studies used accepted methods to randomize and allocate patients to treatments, and the baseline characteristics of patients appear to be balanced between groups within studies. The trials included an enriched population who were adherent to treatment through the screening phases, and for Study TRD3003 patients had to show treatment response and acceptable tolerability to the study drugs before randomization. Although all trials took steps to blind patients and study site personnel to treatment allocation, there was potential for unblinding due to the frequency of acute adverse effects (e.g., sedation, dissociation, nausea, and cardiovascular changes) that are known to be associated with ketamine and esketamine. To mitigate unblinding, the trials used identical intranasal devices for placebo

and active drug, with a bittering agent added to placebo to mimic the taste of esketamine, and the assessment of the depression symptoms (i.e., MADRS score) was conducted by offsite blinded raters based on patients' responses via the phone. However, if there was unblinding due to adverse effects, it is possible that patients' responses to assessors, and other patient-reported outcomes (EQ-5D, SDS, PHQ-9) or reporting of harms, may have been influenced by expectations of treatment. Given the characteristics of the drug, maintenance of blinding was a challenge for the sponsor and unblinding was raised as a potential source of bias by regulatory and other health technology assessment organizations.[22,24,26,35,36] Although sensitivity analyses were conducted to explore the impacts of unblinding, the possibility of bias cannot be ruled out. Since the sponsor did not conduct any evaluations on the extent of unblinding, there remains some uncertainty regarding the possible impact unblinding may have had on the results.

The trials compared esketamine to placebo plus a newly initiated oral antidepressant, and thus cannot be used to assess how esketamine compares to other options available to patients with treatment-resistant depression such as adjunctive therapy. Health Canada commented that the initiation of study drug and new antidepressant (rather than add-on to existing antidepressant therapy) was an unusual trial design but it was consistent with the FDA and European Medicines Agency regulatory guidance for development of drug treatments for treatment-resistant depression.[24] The treatment duration of the induction studies was limited to 4 weeks, which means the maximal effectiveness of concurrent antidepressant therapy would not have been reached, as most oral antidepressant trials require at least 6 to 8 weeks of therapy to demonstrate treatment effects. The doses of esketamine used in the trials were consistent with the doses in the product monograph, and the clinicians consulted stated that the mean daily doses of escitalopram, sertraline, and venlafaxine XR exceeded minimum therapeutic doses used in clinical practice. The mean dose of duloxetine ranged from 49.8 mg (SD = 7.4) to 58.1 mg (SD = 3.8), which was lower than the minimum therapeutic dose of 60 mg daily; thus, some duloxetine treated patients may have received a subtherapeutic dose.

The primary outcome of the trials was based on MADRS, a clinician-rated measure of depression symptom severity. This outcome measure has evidence of reliability and validity in patients with MDD, with a MCID of 2 points reported in the literature. The MADRS is sensitive to treatment-related change; however, it does not capture all the core symptoms of depression in the *DSM-5* criteria. The esketamine trials defined remission as MADRS score of 12 points or less, which is within the range of cut points reported in the literature.[37,38] However, it is less stringent than other values reported, with some studies recommending values less than 10 (see Appendix 4).[38-40] The clinical experts stated that the majority of patients with a MADRS score of 12 points or less would still be experiencing symptoms of depression, and may have functional or cognitive impacts that are not captured by the MADRS and that may be slow to respond to treatment. Three trials evaluated patient-reported symptom severity based on the PHQ-9, and functional impact based on SDS, and while these instruments have some evidence of validity and reliability, there is no known MCID. HRQoL was assessed using the EQ-5D, however these data were reported descriptively, with no pre-planned between-group comparisons, thus the utility of these data are limited. After review of the draft Clinical Report, the sponsor provided between-group comparison EQ-5D data for Study TRD3002; however, these analyses were conducted post hoc and were not part of the planned statistical analysis or statistical testing hierarchy to control the family-wise type I error. In addition, the analyses did not control for baseline EQ-5D values, which showed some difference between groups at baseline. The proportion of patients who achieved response and remission, which were outcomes of

interest to this review, were also reported descriptively. The trials were not designed to assess the impact of esketamine on hospitalizations, emergency department visits, or to reduce the risk of suicide.

Efficacy analyses were conducted based on the FAS population, not a true intention-to-treat population, but the number of patients excluded was low in all trials. The change from baseline outcomes were analyzed using 2 different models: an MMRM model, which assumes patients are missing at random; and an ANCOVA model that use LOCF for missing data. The missing at random assumption may not be met, as patients who withdraw from trials tend to be those with poor outcomes or tolerability. The LOCF method also has limitations; it assumes that there is no change in outcomes at subsequent time points, which may not be a valid assumption. In the induction studies, more patients withdrew from the esketamine groups than the placebo groups. It should be noted that any patients who withdrew early did not have ongoing assessment as part of the FAS population, but instead, these patients entered a separate follow-up phase of the trials. Given the excess withdrawals in most esketamine groups, the OC data used in the MMRM analysis may inflate the treatment effects of esketamine relative to placebo, as those who remained in the trial until day 28 reflect those who were more likely to show a positive outcome. The tipping point analysis conducted in Study TRD3002 reported that the patients with missing data in the esketamine group would need to have MADRS scores that were 9 points worse after discontinuation in order to change the overall result to be not statistically significant. With baseline MADRS scores of 37 points and change from baseline values of –21 points (SD = 12) for esketamine, a 9-point difference for missing patients was plausible. Thus, there is some uncertainty regarding the robustness in the results of the primary outcome of Study TRD3002. Across the induction trials the MMRM and ANCOVA models generally showed similar findings, except for the esketamine 84 mg group in Study TRD3001. For this comparison, the ANCOVA model (which may be considered more conservative) shifted the point estimate and 95% CI for the change from baseline in MADRS scores toward the null. Other outcome measures had issues with missing data, particularly the change from baseline in SDS. In Study TRD3001 and Study TRD3002, 20% to 25% of patients were missing day 28 SDS data (MMRM analysis), and 6% to 10% were missing SDS outcome data in Study TRD3003. PHQ-9 data were missing for 4% to 13% of patients per group in the induction trials (MMRM). The extent of missing data for most other analyses was generally low.

Of the 3 induction studies, only 1 showed statistically significant results for the primary outcome. It is not uncommon for antidepressant trials to fail to demonstrate statistical differences versus placebo, which has been associated with a number of factors including the lack of statistical power, issues related to the complex and variable presentation of MDD, frequent interactions and monitoring by clinical experts, and limitations of the composite scales used to measure treatment effects.[41,42] The placebo response in Study TRD3001 and Study TRD3002 was higher than expected by the clinical experts and regulatory agencies, given that the trials enrolled patients with treatment-resistant depression.[22,24,26] As for Study TRD3005, this trial may have been underpowered to detect a difference between treatments. The sponsor based the power calculations on 1-week data from a phase II trial (in a younger population) that showed a mean difference of 6.5 points (SD = 12) in the change from baseline in MADRS scores. None of the trials achieved a mean difference of 6.5 points, and in Study TRD3005 specifically, the within-group change from baseline was lower than the induction trials in the younger populations.

The longer-term Study TRD3003 used a withdrawal design in an enriched population that included patients who demonstrated response to esketamine during an induction phase (4 weeks) and an optimization phase (12 weeks). Thus, those who were randomized represent a select population of adherent patients with favourable responsiveness and tolerance to esketamine. Patients were randomized to switch to intranasal placebo or continue esketamine and followed until relapse. The clinical experts consulted by CADTH stated that the composite definition of relapse that was used in Study TRD3003 was acceptable (MADRS score22 points or greater and hospitalization for worsening depression or other clinical events suggestive of relapse). As described for the induction studies, this trial also had the potential for unblinding in patients switched to placebo who would be familiar with the acute adverse effects of esketamine. This could have impacted outcome reporting, and unblinding may have contributed to the higher number of early relapses reported in the placebo group. Health Canada commented that the sensitivity analyses that censored patients with changes in dissociative symptoms may not be sufficient to address concerns regarding unblinding.[24]

Study TRD3001 and Study TRD3002 used a serial gatekeeping approach to control the type I error for the primary and key secondary outcomes. According to the statistical analysis plan, testing was to continue only if prior outcomes in the hierarchy were statistically significant. Study TRD3001 failed on the primary outcome, and Study TRD3002 failed on the first secondary outcome; thus, no conclusions can be drawn from all subsequent outcomes (see Table 14 for hierarchy details). Study TRD3005 and Study TRD3003 did not control the type I error for secondary outcomes. Thus, for Study TRD3003, statistically significant results for the change from baseline in SDS, PHQ-9, and MADRS scores should be interpreted with an understanding that the end points are prone to increased risk of a type I error. In Study TRD3001 and Study TRD3005, P values for the primary outcome analyses were adjusted for the interim analyses, and the methods used to combine the overall results were appropriate.

### *External Validity*

The trials enrolled those with treatment-resistant depression, defined as patients with MDD who had shown nonresponse to at least 2 antidepressants for the current MDE. The FDA accepted the definition proposed by the sponsor; however, currently there is no consensus on what constitutes treatment-resistant depression.[12] At the start of the screening phase, less than 20% of patients were treated with antidepressant combination therapy or with augmentation therapy, and few patients had received psychotherapy, electroconvulsive, or repetitive transcranial stimulation. Most patients had not received 3 or more prior antidepressant trials before enrolment. There were few Canadians included in the studies, and data in older adults was limited. Although the clinical experts consulted stated that the baseline demographics of the patients were generally reflective of a subset of patients seeking treatment in Canada, all trials excluded those with comorbid psychiatric conditions, substance use disorder, recent suicidality, or cardiovascular risk factors. Approximately half of those screened were eligible for and enrolled in the trials, suggesting there may be differences between the screened and enrolled populations. Few details were available on the patients screened; thus, there is no information which can be used to assess the similarity between patients enrolled and those seeking care at the study sites. It should be noted that those enrolled reflect an enriched population, as only patients who were adherent to treatments during the screening phase entered the induction phase of all trials. Although clinical trials in MDD often restrict enrolment to patients who are adherent to treatments, in Canada, adherence to treatments is a major issue among patients with MDD.

As a result, the effects observed in the trials would likely overestimate the true benefits of esketamine in the real world. In the relapse prevention study (TRD3003), patients underwent 2 rounds of enrichment during the induction and optimization phases and only those patients who were responsive to esketamine and had shown acceptable tolerability were randomized. Approximately one-third of patients were withdrawn in each phase of enrichment; thus, those who remained represent a select population that were responsive and tolerant to esketamine. Although the inclusion of responders is standard for randomized withdrawal design studies, these trials likely overestimate the true benefits that may be observed in clinical practice. Furthermore, these trials do not provide a way for prescribers to prospectively identify patients with a greater likelihood of response or to predict the magnitude of response in an unselected patient. Thus, the findings of this longer-term esketamine trial may have limited generalizability to the broader population of patients with treatment-resistant depression.

There is no evidence available comparing esketamine to other therapeutic options for treatment-resistant MDD, as all the trials were placebo controlled. The clinical experts consulted agreed that the choice of antidepressants administered as co-interventions were reasonable, although in usual practice it would be uncommon to start 2 new therapies at the same time. The doses of esketamine and oral antidepressants were consistent with the product monographs or clinical guidelines, except for duloxetine, which reported mean daily doses below the minimum therapeutic threshold. Three of the trials were 4 weeks in duration which is not consistent with the standard of care in Canada and does not provide information on long-term tolerability or persistence with treatment. In all trials, esketamine was administered under supervision of a health care provider, and required monitoring of acute adverse effects until patients were stable. In addition, patients were prohibited from driving for 24 hours after each dose. These requirements limit the settings in which esketamine can be safety administered and will be factors in the real-world application of this drug.

## Indirect Evidence

Given the lack of head-to-head studies comparing esketamine to other drugs for treatment-resistant depression, CADTH conducted a supplemental literature search for indirect evidence. No relevant indirect comparisons were found in the literature, so the sponsor was contacted regarding the availability of indirect evidence. A network meta-analysis had been commissioned by the sponsor's UK branch. This report evaluated the efficacy and safety of esketamine versus pharmaceutical and non-pharmaceutical treatments in adults with depression that had failed to respond to 2 or more antidepressants.

Upon review by CADTH, the network meta-analysis had a number of important limitations that may threaten the validity of the results. For example, there were issues with the study selection process and relevant studies may have been excluded; there was heterogeneity in the study designs, populations, interventions, outcome timing, and definitions, and consequently the transitivity assumption may not be met; and the network was sparse, with multiple links between esketamine and other comparators, which increased uncertainty. For some comparisons, the 95% credible intervals were implausibly large. Although the results were favourable toward esketamine, the sponsor stated that the network meta-analysis was not robust and it included comparators that were not relevant to the Canadian context; thus, for these reasons, the sponsor had not included this report in the CADTH submission. CADTH agreed that the findings were not robust, and may potentially be misleading, therefore the indirect comparison was not summarized in this formulary review.

## Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

### Long-term Uncontrolled Studies

Two long-term uncontrolled trials (TRD3004 and TRD3008) have been summarized to provide additional evidence on the safety of intranasal esketamine.

#### *Methods*

Study TRD3004 was a 1-year, open-label, uncontrolled phase III clinical trial in 802 patients with MDD who had shown inadequate response to 2 antidepressant drugs. Patients could enter the study via 2 mechanisms, either direct entry or transfer from Study TRD3005. Patients who entered the trial directly underwent an induction phase, as described for Study TRD3002. Patients received 4 weeks of intranasal esketamine plus a newly initiated oral antidepressant, and those who met the response criteria (defined as ≥ 50% reduction in the MADRS total score) were eligible to continue in the 48-week maintenance phase. For placebo and patients treated with esketamine who were transferred from Study TRD3005, those who had shown nonresponse to study drug entered the induction phase of Study TRD3004, and those who had responded entered the maintenance phase. The trial was to stop when 300 patients had received treatment for 6 months and 100 had received treatment for 12 months.

Study TRD3008 is an ongoing open-label extension study for patients who participated in Study TRD3001, Study TRD3002, Study TRD3005, Study TRD3003, Study TRD3004, and Study TRD3006 (an ongoing RCT). Patients who were nonresponders to esketamine in the previous trial or who had relapsed in Study TRD3003 entered the induction phase of Study TRD3008, and those who were responders to esketamine entered the maintenance phase. The interim analysis reported data from 1,140 patients who had received intranasal esketamine during the extension study.

The objective of these trials was to assess the long-term safety and tolerability of intranasal esketamine in patients with treatment-resistant depression.

#### *Populations*

In Study TRD3004, the following inclusion criteria for direct-entry patients were consistent with those reported for the induction studies:

- aged 18 years or older who met *DSM-5* diagnostic criteria for recurrent MDD or single-episode MDD (with duration ≥ 2 years) without psychotic features
- nonresponse to 2 or more oral antidepressant drugs in the current episode
- MADRS total score of 22 or greater.

Patient who completed the induction phase of Study TRD3005 were also eligible for Study TRD3004.

The patients enrolled in Study TRD3004 had a mean age of 52.2 years (SD = 13.7), 63% were female, and 86% were White. The mean MADRS score at baseline was 31.4 points (SD = 5.4). A total of 178 patients were 65 years of age or older, and 19 patients were 75

years of age or older. Most patients had previously been treated with 2 antidepressants (58%), or 3 or more drugs (40%), and had recurrent MDD (86%) (Table 35).

Study TRD3008 enrolled patients who had participated in Study TRD3001, Study TRD3002, Study TRD3005, Study TRD3003, Study TRD3004, or Study TRD3006 and who had met the inclusion criteria of these studies. At baseline, the mean age of patients enrolled was 49.7 years (SD = 12.3), and most patients were female (67%) and White (87%). The majority of patients (60%) were employed (Table 35).

## Table 35: Summary of Baseline Characteristics of Uncontrolled Studies

| Characteristics | TRD3004[a] N = 802 | TRD3008[a] N = 1,140 |
|---|---|---|
| Age, years, mean (SD) | 52.2 (13.7) | 49.7 (12.3) |
| Female, n (%) | 502 (63) | 760 (67) |
| Race, n (%) | | |
| White | 686 (86) | 991 (87) |
| Black | 15 (2) | 43 (4) |
| Asian | 81 (10) | 45 (4) |
| Other or unknown | 20 (2) | 61 (5) |
| BMI kg/m$^2$, mean (SD) | 27.9 (5.7) | 28.8 (6.2) |
| Employment status, n (%) | | |
| Any type of employment | 450 (56) | 687 (60) |
| Any type of unemployment | 175 (22) | 280 (25) |
| Other | 177 (22) | 173 (15) |
| MADRS score, mean (SD) | 31.4 (5.4) | NR |
| Suicidal ideation in past 6 months, n (%)[b] | 215 (27) | NR |
| Suicidal behaviour in past 12 months, n (%)[b] | 2 (0.3) | NR |
| Duration of current MDE, weeks, median (range) | 66.5 (6 to 2,184) | NR |
| Number of prior antidepressants, n (%) | | |
| 1 | [redacted] | NR |
| 2 | [redacted] | NR |
| 3 | [redacted] | NR |
| ≥ 4 | [redacted] | NR |
| Number of MDE,[c] n (%) | | |
| 1 | 111 (14) | NR |
| 2 to 5 | 534 (67) | NR |
| ≥ 6 | 156 (19) | NR |

BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; NR = not reported; SD = standard deviation.

[a] All enrolled patients. All patients received intranasal esketamine plus oral antidepressant.

[b] Based on screening C-SSRS.

[c] Including current episode.

Source: Clinical Study Reports for Study TRD3004[43] and Study TRD3008.[44]

*Interventions*

During the induction phase of Study TRD3004, patients self-administered open-label intranasal esketamine twice a week for 4 weeks with a flexible dose regimen depending on age (56 mg or 84 mg for patients younger than 65 years, and 28 mg, 56 mg, or 84 mg for patients 65 years or older). Esketamine was administered at the study site under supervision of a health care provider. Patients also received 1 of the following newly initiated oral antidepressant drugs: duloxetine, escitalopram, sertraline, or venlafaxine XR. Patients who entered the maintenance phase continued the same dose of esketamine (28 mg to 84 mg) administered weekly for the first 4 weeks, then dosing frequency was changed to weekly or every 2 weeks depending on treatment response. Oral antidepressants were continued throughout the maintenance phase.

In Study TRD3008, the same age-based, flexible dosing regimen as described for Study TRD3004, was used for patients who entered the induction phase. In the maintenance phase, patients self-administered esketamine (28 mg, 56 mg, or 84 mg), as a flexible dose regimen with adjustments based on efficacy and tolerability. After 4 weeks the dosing frequency was adjusted based on the Clinical Global Impression–Severity (CGI-S) score to a weekly, biweekly, or every 4 weeks dosing regimen. All patients were taking an oral antidepressant during the extension study (no details provided).

*Outcomes*

Although the primary objective of the trials was to assess safety, Study TRD3004 also reported descriptive data for the change from baseline in MADRS, PHQ-9, SDS, EQ-5D-5L, and EQ VAS. No efficacy outcomes were reported in the interim clinical study report for Study TRD3008.

Both trials reported the proportion of patients with AEs, SAEs, WDAEs, and notable harms of interest to this formulary review.

*Statistical Analysis*

In Study TRD3004, efficacy results were reported descriptively for the induction and maintenance phases based on LOCF and OC data. Efficacy analyses were based on the FAS populations, which were defined as the patients who entered the induction or maintenance phases and received at least 1 dose of esketamine or oral antidepressant during that phase.

Safety data were reported for all enrolled, which included all patients who were eligible to enter the study and who received at least 1 dose of intranasal study medication for Study TRD3008, or 1 dose of intranasal study drug or 1 dose of oral antidepressant in Study TRD3004.

*Patient Disposition*

A total of 802 patients were enrolled in Study TRD3004, including 779 patients who entered the induction phase and 603 patients who entered the maintenance phase (Table 36). Of the 25% of patients who discontinued from the induction phase, the most common reasons for discontinuation were that patients did not meet the criteria for the maintenance phase (11%) or AEs (7%). During the maintenance phase, 75% of patients discontinued. The most common reasons for discontinuation were as follows: study was terminated by the sponsor (55%); withdrawal by patient (5%); AEs (4%); and lack of efficacy (4%).

In Study TRD3008, 1140 patients were enrolled. Of the 453 patients who entered the induction phase, 92% went onto the maintenance phase and 8% withdrew. During the maintenance phase, 202 of 1,101 patients discontinued (18%), with reported reasons of AEs (4%), withdrawal by patient (4%), lack of efficacy (4%), or other reasons (7%) (Table 36).

## Table 36: Disposition for Uncontrolled Studies

| Disposition | TRD3004 | TRD3008 |
|---|---|---|
| **Screened, N** | NR | NA |
| **Enrolled, N** | 802 | 1,140 |
| **Induction phase** | | |
| **Entered, N** | **779** | **453** |
| **Discontinued from induction phase, n (%)** | 198 (25) | 35 (8) |
| Did not meet criteria for next phase/nonresponder | [redacted] | [redacted] |
| Adverse events | [redacted] | [redacted] |
| Withdrawal by patient | [redacted] | [redacted] |
| Lack of efficacy | [redacted] | [redacted] |
| Lost to follow-up | [redacted] | [redacted] |
| Death | [redacted] | [redacted] |
| Other | [redacted] | [redacted] |
| **Maintenance phase** | | |
| **Entered, N** | 603[a] | 1,101 |
| **Discontinued from maintenance phase, n (%)** | 453 (75) | 202 (18) |
| Study terminated by sponsor | [redacted] | [redacted] |
| Adverse events | [redacted] | [redacted] |
| Withdrawal by patient | [redacted] | [redacted] |
| Lack of efficacy | [redacted] | [redacted] |
| Lost to follow-up | [redacted] | [redacted] |
| Death | [redacted] | [redacted] |
| Other | [redacted] | [redacted] |

NA = not applicable; NR = not reported.

[a] Includes 23 patients who transferred from Study TRD3005 and were responders to esketamine induction therapy.

Source: Clinical Study Reports for Study TRD3004[43] and Study TRD3008.[44]

### *Exposure to Study Treatments*

Of the 802 patients enrolled in Study TRD3004, 364 patients (45%) were treated with esketamine for 6 months and 136 patients (17%) for 12 months. The median treatment duration was 22.9 weeks (range 0 to 56 weeks) and mean was 24.9 weeks (SD = 18.5).

In Study TRD3008, 979 patients (86%) received 6 months of esketamine, 702 (62%) received 12 months, and 157 (14%) had received 18 months of esketamine at the time of the interim analysis (N = 1,140). The mean duration of exposure during the extension study was 13.7 months (SD = 5.9) and the median duration was 15.4 months (range = 0 to 31 months). The mean total exposure duration for patients during the phase III trials plus Study TRD3008 was 19.1 months (SD = 8.1). The final dose of esketamine in the maintenance phase was 28 mg, 54 mg, and 84 mg for 2%, 29%, and 69% of patients, respectively. At 24

weeks, 47% of patients were dosed weekly, 42% were dosed every 2 weeks, and 11% were dosed every 4 weeks (N = 945).

There was no data on the extent of exposure to oral antidepressants in either trial. In Study TRD3004 the proportion of patients who received duloxetine, escitalopram, sertraline, and venlafaxine XR was 31%, 30%, 20%, and 20%, respectively. No details were reported on the oral antidepressants that patients received during Study TRD3008.

*Efficacy*

Descriptive data for the change from baseline in MADRS, PHQ-9, SDS, and EQ-5D are summarized in Table 37. Outcome scores appeared to remain constant during the maintenance phase among patients who remained in the study. Figure 9 shows the MADRS scores over time based on the OC data.

## Table 37: Summary of Efficacy Results in Study TRD3004

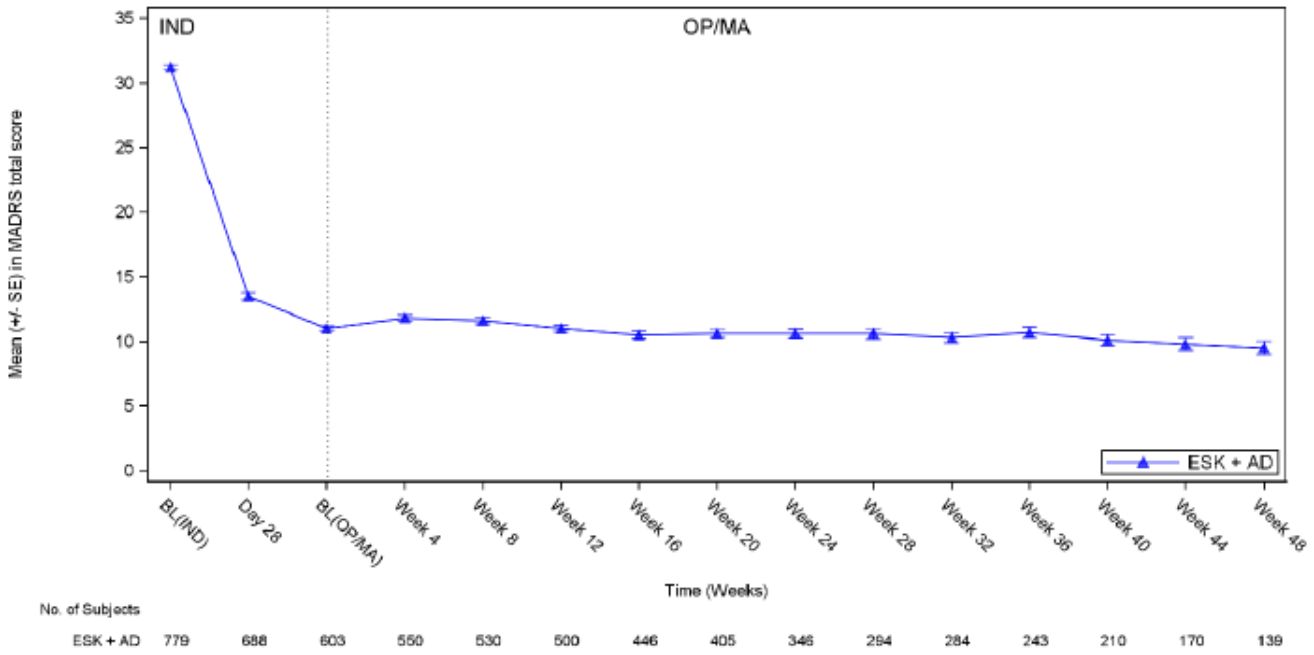
| Treatment phase | MADRS total score | PHQ-9 total score | SDS total score | EQ-5D-5L index score | EQ VAS |
|---|---|---|---|---|---|
| **Induction phase[a]** | | | | | |
| Number of patients contributing to the analysis | 756 | 746 | 626 | 745 | 746 |
| Baseline, mean (SD) | 31.2 (5.3) | 17.3 (5.0) | 22.2 (5.5) | 0.601 (0.206) | 44.7 (20.5) |
| End point, mean (SD) | 14.8 (8.8) | 8.4 (5.8) | 12.8 (7.9) | 0.792 (0.173) | 62.2 (20.6) |
| Change from baseline, mean (SD) | –16.4 (8.8) | –8.9 (6.7) | –9.3 (7.9) | 0.190 (0.214) | 17.0 (21.7) |
| **Maintenance phase[a]** | | | | | |
| Number of patients contributing to the analysis | 603 | 603 | 541 | 603 | 603 |
| Baseline, mean (SD) | 11.0 (4.5) | 6.5 (4.2) | 11.3 (7.3) | 0.838 (0.119) | 67.6 (17.0) |
| End point, mean (SD) | 11.3 (7.9) | 6.3 (5.3) | 9.5 (7.9) | 0.829 (0.152) | 69.2 (19.8) |
| Change from baseline, mean (SD) | 0.3 (8.1) | –0.2 (5.7) | –1.6 (8.3) | –0.009 (0.141) | 1.6 (18.5) |

EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FAS = full analysis set; MADRS = Montgomery-Åsberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire-9; SD = standard deviation; SDS = Sheehan Disability Scale.

[a] FAS for induction or maintenance phase.

Source: Clinical Study Report for Study TRD3004.[43]

## Figure 9: MADRS Score Over Time in Study TRD3004 (Observed Case)




AD = antidepressant; BL = baseline; ESK = esketamine; IND = induction phase; MADRS = Montgomery-Åsberg Depression Rating Scale; No. = number; OP/MA = optimization/maintenance phase; SE = standard error.

Source: Reproduced from Clinical Study Report for Study TRD3004.[43]

### *Harms*

Most patients in Study TRD3004 and Study TRD3008 experienced 1 or more adverse effects (90% and 89%), with dizziness, dissociation, headache, and nausea reported by more than 20% of patients in each trial (Table 38).

SAEs were reported in 7% of patients in Study TRD3004 and 8% in Study TRD3008 (Table 39). There were 2 deaths in Study TRD3004 and three deaths in Study TRD3008. These events included 2 completed suicides, and deaths due to myocardial infarction, acute cardiac and respiratory failure, and injuries from a road traffic accident. Suicidality was reported by 42 patients (5%) in Study TRD3004, and in 37 patients (3%) in Study TRD3008.

TEAEs suggestive of abuse were reported by 54% and 45% of patients, and dizziness or vertigo were reported by 47% and 42% of patients in Study TRD3004 and Study TRD3008, respectively. In both trials, 13% of patients reported increased blood pressure, and cystitis was reported by less than 1% and 4% of patients in Study TRD3004 and Study TRD3008, respectively (Table 39).

## Table 38: Summary of Most Common Adverse Events in Uncontrolled Studies

| Adverse events | TRD3004[a] N = 802 | TRD3008[a] N = 1,140 |
|---|---|---|
| **Patients with ≥ 1 adverse event** | | |
| n (%) | 723 (90) | 1,012 (89) |
| Most common adverse events,[b] n (%) | | |
| Dizziness | 264 (33) | 290 (25) |
| Headache | 200 (25) | 262 (23) |
| Somnolence | 134 (17) | 213 (19) |
| Dysgeusia | 95 (12) | 189 (17) |
| Hypoesthesia | 95 (12) | 99 (9) |
| Dissociation | 221 (28) | 238 (21) |
| Anxiety | 72 (9) | 121 (11) |
| Vertigo | 88 (11) | 169 (15) |
| Blood pressure increased | 75 (9) | 121 (11) |
| Nausea | 201 (25) | 276 (24) |
| Vomiting | 87 (11) | 123 (11) |
| Viral upper respiratory tract infection | 82 (10) | NR |
| Nasopharyngitis | NR | 163 (14) |

NR = not reported.

[a] Induction and maintenance phase.

[b] Frequency of 10% or greater.

Source: Clinical Study Reports for Study TRD3004 [43] and Study TRD3008.[44]

## Table 39: Summary of SAEs, Withdrawals, and Notable Harms in Uncontrolled Studies

| Serious adverse events | TRD3004[a] N = 802 | TRD3008[a] N = 1,140 |
|---|---|---|
| **Deaths** | | |
| n (%) | 2 (0.2) | 3 (0.3) |
| Description of events | Suicide, acute cardiac and respiratory failure | Suicide, myocardial infarction, injuries from road traffic accident |
| **Patients with ≥ 1 SAE** | | |
| n (%) | 55 (7) | 91 (8) |
| Events reported in ≥ 2 patients (number of patients) | Depression (8), suicidal ideation (6), suicide (6), anxiety (2), gastroenteritis (2) | Back pain, anxiety, depression, suicidal ideation, suicide attempt, cholelithiasis, pneumonia, overdose, carotid artery aneurysm, headache, atrial fibrillation, infection, lower limb fracture, myocardial infarction, pancreatitis, asthma, stress urinary incontinence, vertigo, hypertensive emergency |
| **Patients who stopped intranasal treatment due to adverse events** | | |
| n (%) | 76 (10) | 47 (4) |
| Events reported in ≥ 2 patients (number of patients) | Anxiety (9), suicidal ideation (7), depression (6), dissociation (5), suicide attempt (2), dizziness (6), headache (2), sedation (2), somnolence (2), blood | Blood pressure increased including hypertensive emergency, ischemic stroke, depression, suicidal ideation, dissociation, anxiety |

| Serious adverse events | TRD3004[a] | TRD3008[a] |
|---|---|---|
| | N = 802 | N = 1,140 |
| | pressure increased (6), muscular weakness (4), vomiting (3), nausea (2), hypertension (3), vertigo (2) | |
| **Patients who stopped oral antidepressant due to adverse events** | | |
| n (%) | 33 (4) | NR |
| **Notable harms** | | |
| n (%) | | |
| TEAE suggestive of abuse | 429 (54) | 518 (45) |
| Dizziness or vertigo | 373 (47) | 473 (42) |
| Impaired cognition | 0 | 1 (0.1) |
| Cystitis | 5 (0.6) | 44 (4) |
| Suicidality | 42 (5) | 37 (3) |
| Increased blood pressure | 103 (13) | 148 (13) |

NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Induction and maintenance phase.

Source: Clinical Study Reports for Study TRD3004[43] and Study TRD3008.[44]

*Critical Appraisal*

**Internal Validity**

Although the longer-term treatment duration of Study TRD3004 and Study TRD3008 is generally more reflective of the management of MDD in clinical practice, these trials are limited by their open-label study design and lack of randomization or control groups. The demographics of patients enrolled were generally similar to those in the RCTs; however, patients who participate in extension studies represent a selective population of patients who have responded and/or tolerated treatment during the initial RCTs. Both trials included enrichment strategies and allowed only those who had demonstrated response to esketamine to continue treatment in the longer-term maintenance period. Moreover, efficacy data based on OC data may inflate the treatment response as patients with poor outcomes tend to drop out. In Study TRD3004, the magnitude of early withdrawals was substantial with 25% of patients dropping out before the study was terminated. No efficacy results were reported for Study TRD3008, but data from Study TRD3004 should be interpreted with caution. The absence of a comparator group makes it challenging to interpret changes from baseline in efficacy outcomes, and expectations of treatment may bias reporting of subjective outcomes (e.g., MADRS, SDS, and PHQ-9) in open-label studies. Considering the potential selection and attrition biases, these data likely overestimate effects that may be observed in clinical practice. While these trials provide longer-term safety outcomes, which is of interest to decision-makers, these data cannot be used to draw conclusions on the comparative safety of esketamine.

**External Validity**

According to the clinical experts consulted for this review, the baseline characteristics of the patients enrolled are consistent with patients in Canada with more difficult to treat MDD, although they stated that in practice, patients are considered treatment refractory if they have shown nonresponse to several antidepressants, not just 2. These trials also excluded important subpopulations of patients with MDD who may be seeking care, such as those

with comorbid psychiatric conditions, substance use disorder, or recent suicidal ideation or behaviour. For these trials, the issues with selection and attrition bias, which affect the internal validity, also limit the generalizability of the results.

## Studies in Patients at Risk of Suicide

The sponsor submitted 2 phase III RCTs (ASPIRE1[45]: N = 226; ASPIRE 2[46]: N = 230) to provide additional evidence on the efficacy and safety for intranasal esketamine in adult patients with MDD and imminent risk for suicide.

While these trials likely include some patients who had shown an inadequate response to 2 prior antidepressants and thus would match the population criteria specified in the formulary review protocol, this population was not a predefined subgroup and the sponsor was not able to identify the patients enrolled that would meet this criteria.[47] For this reason, these trials were excluded from the systematic review but have been summarized as supplementary data.

### *Methods*

Both trials were multi-centre, double-blind, placebo-controlled RCTs (Table 40). The ASPIRE 2 study enrolled Canadian patients. The primary objective of the 2 trials was to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in reducing the symptoms of MDD, including suicidal ideation, in patients who were assessed to be at imminent risk for suicide. After screening, eligible patients were randomly assigned to receive esketamine or placebo in a 1:1 ratio based on a computer-generated randomization schedule. The randomization was stratified by study centre and by the physician's assessment of the patient's need for standard of care antidepressant treatment (e.g., antidepressant monotherapy or an antidepressant plus augmentation therapy). The investigator and patients were blinded to the treatment allocation. In addition, different raters performed efficacy and safety assessments. Clinicians who performed the MADRS and suicidality assessments did not provide clinical care for the patients, while clinical care of patients was performed by clinicians at the study site who were not MADRS or suicidality raters. Patients received intranasal esketamine or placebo for 25 days, followed by a 65-day follow-up period. The primary and key secondary efficacy end points in the 2 trials were the change from baseline to 24 hours after the first dose (day 2) in the MADRS total score and in the CGI-SS-R for the double-blind treatment phase.

## Table 40: Details of Included Studies in Patients at Risk of Suicide

| | Study information | ASPIRE 1 (SUI3001) | ASPIRE 2 (SUI3002) |
|---|---|---|---|
| Designs and Populations | **Study design** | Double-blind RCT | Double-blind RCT |
| | **Locations** | Europe, US, Asia, South Africa | Canada, US, Europe, Argentina, Brazil |
| | **Randomized/enrolled (N)** | 226 | 230 |
| | **Inclusion criteria** | • Aged 18 to 64 years who met *DSM-5* diagnostic criteria for MDD, without psychotic features<br>• Current suicidal ideation with intent as confirmed within 24 hours prior to randomization based on MINI responses<br>• Acute psychiatric hospitalization was warranted due to risk of suicide<br>• MADRS total score > 28<br>• Patient voluntarily agreed to standard of care therapy (hospitalization for at least 5 days and administration of non-investigational antidepressant therapy for double-blind period) | |
| | **Exclusion criteria** | • Current diagnosis of bipolar or related disorders, antisocial personality disorder, or obsessive-compulsive disorder<br>• Current diagnosis of borderline personality disorder<br>• Current clinical diagnosis of autism, dementia, or intellectual disability<br>• Current or prior diagnosis of psychotic disorder or MDD with psychotic features<br>• Moderate or severe substance or alcohol use disorder < 6 months before screening; a history (lifetime) of ketamine, PCP, LSD, or MDMA hallucinogen-related use disorder was exclusionary<br>• History or current liver or renal insufficiency<br>• Clinically significant cardiac or vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disease<br>• Uncontrolled hypertension for at least 2 weeks at screening or any past history of hypertensive crisis | |
| Drugs | **Intervention** | Esketamine 84 mg nasal spray twice weekly plus standard of care therapy | Esketamine 84 mg nasal spray twice weekly plus standard of care therapy |
| | **Comparator(s)** | Placebo nasal spray plus standard of care therapy | Placebo nasal spray plus standard of care therapy |
| Duration | **Phase** | | |
| | Double-blind | 25 days | 25 days |
| | Follow-up | 65 days | 65 days |
| Outcomes | **Primary end point** | Change from baseline of MADRS score at 24 hours post-first dose | |
| | **Secondary and exploratory end points** | Change from baseline in CGI-SS-R at 24 hours post-first dose<br>Day 25:<br>• Percentage in remission<br>• Change in MADRS score<br>• CGI-SS-R<br>• CGI-SR-I<br>• EQ-5D-5L and EQ VAS<br>• Harms | |
| Notes | **Publications** | Fu et al. (2020)[48] | Ionescu et al. (2020)[49] |

CGI-SR-I = Clinician Global Impression–Imminent Suicide Risk; CGI-SS-R = Clinician Global Impression–Severity of Suicide (Revised); *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; LSD = lysergic acid diethylamide; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDMA = 3,4-methylenedioxy-methamphetamine; MINI = Mini International Neuropsychiatric Interview; PCP = phencyclidine; RCT = randomized controlled trial.

Sources: Clinical Study Reports for the ASPIRE 1 study [45] and the ASPIRE 2 study[46].

*Populations*

In the ASPIRE 1 and ASPIRE 2 studies, adult patients (18 to 64 years of age, inclusive) who met the *DSM-5* criteria for MDD and had current suicidal ideation with intent as evaluated by affirmative responses to the Mini International Neuropsychiatric Interview as assessed within 24 hours prior to randomization were eligible to be enrolled. In addition, acute psychiatric hospitalization was clinically warranted due to the patient's imminent risk of suicide. Patients were also required to have a MADRS total score of greater than 28 at baseline. Details of inclusion and exclusion criteria in the ASPIRE 1 and 2 studies are presented in Table 40.

In general, the patient baseline characteristics were balanced between the 2 treatment groups (Table 41). The patients enrolled in the ASPIRE studies had a mean age of 38 to 41 years. The majority of patients were female (58% to 65%) and White (66% to 81%). The mean MADRS score at baseline was 40 to 41 points. Most patients were classified as "moderately suicidal" to "severely suicidal" (86% to 91%) or had moderate to severely imminent suicide risk (82% to 86%). In the ASPIRE 1 study, more patients received antidepressant monotherapy than antidepressant plus augmentation therapy, while in the ASPIRE 2 study, more patients received antidepressant augmentation therapy than antidepressant alone. Details regarding augmentation therapy were not specified in the ASPIRE studies.

## Table 41: Summary of Baseline Characteristics of ASPIRE 1 and ASPIRE 2 Studies (Full Analysis Set)

| Characteristics | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Age, years, mean (SD)** | 40.8 (13.17) | 37.9 (12.54) | 40.2 (12.73) | 41.4 (13.43) |
| **Female, n (%)** | 65 (58.0) | 73 (65.2) | 69 (60.5) | 67 (59.3) |
| **Race, n (%)** | | | | |
| White | 77 (68.8) | 74 (66.1) | 92 (80.7) | 87 (77.0) |
| Black | 4 (3.6) | 7 (6.3) | 7 (6.1) | 8 (7.1) |
| Asian | 28 (25.0) | 28 (25.0) | 1 (0.9) | 2 (1.8) |
| Other | 3 (2.7) | 3 (2.7) | 14 (12.4) | 16 (13.4) |
| **BMI, kg/m$^2$, mean (SD)** | 26.7 (6.28) | 26.4 (7.13) | 27.6 (6.4) | 28.3 (7.56) |
| **MADRS score, mean (SD)** | 41.3 (5.87) | 41.0 (6.29) | 39.5 (5.19) | 39.9 (5.76) |
| **CGI-SS-R, n (%)** | | | | |
| Normal, not at all suicidal | 0 | 0 | 0 | 0 |
| Questionably suicidal | 5 (4.5) | 3 (2.7) | 1 (0.9) | 3 (2.7) |
| Mildly suicidal | 6 (5.4) | 11 (9.8) | 10 (8.8) | 6 (5.3) |
| Moderately suicidal | 29 (26.1) | 28 (25.0) | 35 (30.7) | 33 (29.2) |
| Markedly suicidal | 38 (34.2) | 42 (37.5) | 48 (42.1) | 42 (37.2) |
| Severely suicidal | 29 (26.1) | 27 (24.1) | 17 (14.9) | 28 (24.8) |
| Among the most extremely suicidal patients | 4 (3.6) | 1 (0.9) | 3 (2.6) | 1 (0.9) |
| **CGI-SR-I, n (%)** | | | | |
| No imminent suicide risk | 3 (2.7) | 2 (1.8) | 3 (2.6) | 0 |
| Minimal imminent suicide risk | 5 (4.5) | 7 (6.3) | 4 (3.5) | 4 (3.5) |

| Characteristics | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| Mild imminent suicide risk | 9 (8.1) | 8 (7.1) | 8 (7.0) | 10 (8.8) |
| Moderate imminent suicide risk | 26 (23.4) | 31 (27.7) | 30 (26.3) | 33 (29.2) |
| Marked imminent suicide risk | 38 (34.2) | 37 (33.0) | 37 (32.5) | 43 (38.1) |
| Severely imminent suicide risk | 27 (24.3) | 26 (23.2) | 28 (24.6) | 21 (18.6) |
| Extreme imminent suicide risk | 3 (2.7) | 1 (0.9) | 4 (3.5) | 2 (1.8) |
| **Duration of current MDE, months, median (range)[a]** | 15.9 (1 to 249) | 13.3 (2 to 339) | 16.5 (2 to 341) | 21.2 (2 to 445) |
| **Standard of care AD as randomized, n (%)** | | | | |
| AD monotherapy | 59 (52.7) | 65 (58.0) | 45 (39.5) | 43 (38.1) |
| AD plus augmentation therapy | 53 (47.3) | 47 (42.0) | 69 (60.5) | 70 (61.9) |

AD = antidepressant; BMI = body mass index; CGI-SR-I = Clinician Global Impression–Imminent Suicide Risk; CGI-SS-R = Clinician Global Impression–Severity of Suicide (Revised); ESK = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; SD = standard deviation.

[a] Including current episode.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Interventions*

In both trials, eligible patients were randomized to self-administered intranasal esketamine 84 mg or placebo twice a week for 4 weeks, in addition to the standard of care antidepressant treatment. To maintain the blinding of intranasal study drug, a bittering agent (denatonium benzoate) was added to the placebo solution for the purpose of simulating the taste of esketamine. The first dose of study drug was administered in the emergency room or other permitted setting. Patients were expected to remain in the inpatient psychiatry unit for a recommended duration of 5 days. Following discharge from the inpatient unit, subsequent visits for the double-blind treatment phase were to be conducted twice weekly at an outpatient psychiatric facility through day 25. After day 1, a single dose reduction from esketamine 84 mg to esketamine 56 mg or placebo was permitted (blinded) if a patient was unable to tolerate the esketamine 84 mg or placebo dose. In this case, patients continued to receive the reduced dose for the duration of the double-blind treatment phase.

The standard of care antidepressant treatment (monotherapy or augmentation therapy) was initiated or optimized for all patients at the time of randomization on day 1. Patients who were on antidepressant monotherapy or augmentation therapy from day 1 were to remain on the original regimen through the end of the double-blind phase (day 25). Dose titration or adjustments of newly initiated or optimized standard of care antidepressant treatment were to occur during the first 2 weeks of double-blind treatment, with doses remaining stable thereafter through the end of the double-blind phase.

During the follow-up phase, no intranasal study drug was administered while antidepressant treatment was managed based on the clinician's judgment.

*Outcomes*

In the ASPIRE 1 and ASPIRE 2 studies, efficacy of esketamine was measured by change from baseline in patient-reported HRQoL (EQ-5D-5L health status index score and EQ VAS), clinician-rated depression symptom severity (MADRS total score), and clinician-rated

severity of suicidality (CGI-SS-R) or clinician-rated imminent suicide risk (Clinician Global Impression–Imminent Suicide Risk [CGI-SR-I]).

Both trials reported the proportion of patients with AEs, SAEs, WDAEs, and notable harms of interest to this formulary review.

### *Statistical Analysis*

Efficacy analyses were based on the FAS populations, which were defined as all randomized patients who received at least 1 dose of double-blind study drug and had both a baseline and a post-baseline evaluation for the MADRS total score or CGI-SS-R. Multiplicity was controlled by a fixed sequence testing procedure, where the key secondary hypothesis was tested only after the null hypothesis for the primary end point was rejected. The primary efficacy end point (change from baseline to 24 hours after the first dose in MADRS total score) was analyzed using an ANCOVA model, with factors for treatment, analysis centre, and standard of care antidepressant treatment as randomized, and baseline MADRS total score as a continuous covariate. LOCF data were used if a patient had a MADRS total score at a time earlier than 24 hours after the first dose but did not have the 24-hour value. The key secondary efficacy end point (change from baseline for CGI-SS-R at 24 hours after the first dose) was analyzed based on LOCF data using an ANCOVA model on the ranks of change with factors for treatment, analysis centre, and standard of care antidepressant treatment as randomized and baseline CGI-SS-R as a covariate. The treatment difference was estimated using the Hodges-Lehmann estimate. For another secondary end point, CGI-SR-I that measures the imminent risk of suicide, frequency distributions of the CGI-SR-I score, and change from baseline were reported for both the OC and LOCF data. Two-sided P values were only presented for the primary and key secondary end point in the ASPIRE studies. Point estimates of the treatment differences and 95% CIs were presented for other end points.

Safety analyses for the double-blind treatment phase was performed on the safety analysis set, which included all randomized patients who received at least 1 dose of study drug in the double-blind treatment phase. The number of patients with AEs, SAEs, WDAEs, and notable harm of particular interest were summarized.

### *Patient Disposition*

A total of 226 and 230 patients were enrolled in the ASPIRE 1 and ASPIRE 2 studies, respectively. In the ASPIRE 1 study, of the 13.7% of patients who discontinued from the double-blind treatment phase, the most common reasons for discontinuation were AEs (4.4%) in the esketamine group, and AEs (4.5%), lack of efficacy (5.4%), and withdrawal by patient (5.4%) in the placebo group. In the ASPIRE 2 study, of the 20% of patients who discontinued from the double-blind treatment phase, the most common reasons for discontinuation were AEs (7.8%) and withdrawal by patient (8.7%) in the esketamine group, and lack of efficacy (5.4%) and withdrawal by patient (4.3%) in the placebo group (Table 42).

## Table 42: Patient Disposition for ASPIRE 1 and 2 During the Double-Blind Phase

| Disposition | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg | Placebo | ESK 56 or 84 mg | Placebo |
| **Screened, N** | 270 | | 273 | |
| **Randomized, n (%)** | 226 | | 230 | |
| | 114 | 112 | 115 | 115 |
| **Completed study, n (%)** | 102 (89.5) | 93 (83.0) | 90 (78.3) | 94 (81.7) |
| **Discontinued from study, n (%)** | 12 (10.5) | 19 (17.0) | 25 (21.7) | 21 (18.3) |
| **Reason for discontinuation, n (%)** | | | | |
| Adverse events | [redacted] | [redacted] | [redacted] | [redacted] |
| Lack of efficacy | [redacted] | [redacted] | [redacted] | [redacted] |
| Lost to follow-up | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from voluntary to involuntary hospitalization | [redacted] | [redacted] | [redacted] | [redacted] |
| Withdrawal by patient | [redacted] | [redacted] | [redacted] | [redacted] |
| Protocol violation | [redacted] | [redacted] | [redacted] | [redacted] |
| Other | [redacted] | [redacted] | [redacted] | [redacted] |
| **FAS, n (%)** | 112 (98.2) | 112 (100) | 114 (99.1) | 113 (98.3) |
| **SAS, n (%)** | 113 (99.1) | 112 (100) | 114 (99.1) | 113 (98.3) |
| **Follow-up set, n (%)** | 101 (88.6) | 91 (81.3) | 89 (77.4) | 94 (81.7) |

ESK = esketamine; FAS = full analysis set; SAS = safety analysis set.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Exposure to Study Treatments*

In the 2 trials, the median treatment duration was 25 days (range = 1 to 34 days), and the median total number of days with a treatment was 8 days (range = 1 to 8 days) for both the esketamine group and placebo group (Table 43). During the double-blind treatment phase, 24 of 113 (21.2%) and 21 of 114 (18.4%) of patients treated with esketamine received less than 84 mg of esketamine on at least 1 dosing day in the ASPIRE 1 and ASPIRE 2 studies, respectively.

There were no data reported on the oral antidepressants patients received in either trial.

## Table 43: Exposure Duration in ASPIRE 1 and 2 (Safety Analysis Set)

| Exposure | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 113 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Total duration of exposure, days** | | | | |
| Median (range) | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total number of days dosed** | | | | |
| Median (range) | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |

ESK = esketamine; SD = standard deviation.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Efficacy*

**Health-Related Quality of Life**

EQ-5D-5L was not included in the fixed sequence testing procedure. Descriptive data for the change from baseline in EQ-5D-5L are summarized in Table 44. In the 2 trials, the mean health status index scores and the EQ VAS scores at day 25 increased from baseline in both the esketamine group and placebo group.

## Table 44: Change From Baseline in EQ-5D-5L in ASPIRE 1 and 2 (Full Analysis Set)

| Outcome measures | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Change from baseline to day 25 in EQ-5D-5L health status index score** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 104 (93) | 97 (87) | 92 (81) | 96 (85) |
| Baseline, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| End point, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Change from baseline to day 25 in EQ VAS** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 104 (93) | 97 (87) | 92 (81) | 96 (85) |
| Baseline, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| End point, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |

EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; ESK = esketamine; SD = standard deviation.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Suicidality*

The change in CGI-SS-R from baseline to 24 hours after the first dose (day 2) in the double-blind treatment phase was a key secondary efficacy end point in the ASPIRE studies and was included in the fixed sequence testing procedure to control for inflated type I error due to multiplicity. This is a clinician-rated measure of severity of suicidality. Negative change in score indicates improvement and a higher score indicates a more severe condition. The analysis was performed on the FAS with LOCF data using an ANCOVA model. Results showed that in both trials at day 2, there were no statistically significant differences in the CGI-SS-R score between the esketamine group and the placebo group (P = 0.107 in ASPIRE 1 and P = 0.379 in ASPIRE 2). The changes from baseline for this outcome at day 25 and day 90 were also similar between the 2 treatment groups.

CGI-SR-I was a secondary efficacy end point in the ASPIRE studies. This scale summarizes the clinician's best assessment of the likelihood that the patient will attempt suicide in the next 7 days. In both trials, the changes from baseline in CGI-SR-I score were similar for the 2 treatment groups at day 2 and day 25 during the double-blind treatment phase, and day 90 during follow-up.

Details of suicidality assessment are presented in Table 45.

## Table 45: Change From Baseline in CGI-SS-R and CGI-SR-I in ASPIRE 1 and 2 (Full Analysis Set)

| Outcome measures | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Change from baseline to day 2 in CGI-SS-R** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 112 (100) | 112 (100) | 113 (99) | 113 (100) |
| Baseline, median (range) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 2.0 (0 to 6) | 2.5 (0 to 5) | 2.0 (0 to 5) | 3 (0 to 6) |
| Change from baseline, median (range) | –1.0 (–6 to 2) | –1.0 (–5 to 1) | –1.0 (–6 to 2) | –1.0 (–5 to 2) |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (–1 to 0) | | 0 (0 to 0) | |
| P value | 0.107 | | 0.379 | |
| **Change from baseline to day 25 in CGI-SS-R** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 96 (86) | 93 (83) | 85 (75) | 88 (78) |
| Baseline, median (range) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 1 (0 to 5) | 1 (0 to 5) | 0 (0 to 4) | 1 (0 to 5) |
| Change from baseline, median (range) | –3 (–6 to 1) | –3 (–5 to 1) | –3 (–6 to 1) | –3 (–5 to 2) |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (–1 to 0) | | 0 (–1 to 0) | |
| **Change from baseline to day 90 in CGI-SS-R[a]** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 101 (90) | 91 (81) | 89 (78) | 94 (83) |
| Baseline, median (range) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 1 (0 to 5) | 0 (0 to 5) | 0 (0 to 6) | 0 (0 to 5) |
| Change from baseline, median (range) | –3 (–6 to 3) | –3 (–5 to 1) | –3 (–6 to 1) | –3 (–6 to 2) |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (0 to 1) | | 0 (0 to 0) | |
| **Change from baseline to day 2 in CGI-SR-I** | | | | |
| Number of patients contributing to the analysis (% of total N) | 112 (100) | 112 (100) | 108 (95) | 111 (98) |
| Baseline, median (range) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 2 (0 to 6) | 2.5 (0 to 5) | 2 (0 to 6) | 3 (0 to 6) |
| Change from baseline, median (range) | –1 (–5 to 2) | –1 (–5 to 2) | –1 (–6 to 2) | –1 (–4 to 2) |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (0 to 0) | | 0 (–1 to 0) | |
| **Change from baseline to day 25 in CGI-SR-I** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 96 (86) | 93 (83) | 85 (75) | 88 (78) |
| Baseline, median (range) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 0.5 (0 to 5) | 1 (0 to 5) | 0 (0 to 4) | 1 (0 to 5) |
| Change from baseline, median (range) | –3 (–6 to 1) | –3 (–5 to 2) | –3 (–6 to 1) | –3 (–5 to 2) |

| Outcome measures | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (–1 to 0) | | 0 (–1 to 0) | |
| **Change from baseline to day 90 in CGI-SR-I[a]** | | | | |
| Number of patients contributing to the analysis, n (% of total N) | 100 (89) | 91 (81) | 88 (77) | 94 (83) |
| Baseline, median (range) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (0 to 6) | 4.0 (1 to 6) |
| End point, median (range) | 0 (0 to 5) | 0 (0 to 4) | 0 (0 to 6) | 0 (0 to 5) |
| Change from baseline, median (range) | –3 (–6 to 3) | –3 (–5 to 1) | –3 (–6 to 1) | –3 (–6 to 2) |
| Hodges-Lehmann estimate of treatment difference vs. placebo (95% CI) | 0 (0 to 1) | | 0 (0 to 0) | |

ANCOVA = analysis of covariance; CGI-SR-I = Clinician Global Impression–Imminent Suicide Risk; CGI-SS-R = Clinician Global Impression–Severity of Suicide (Revised); CI = confidence interval; ESK = esketamine; vs. = versus.

Note: Negative change in CGI-SS-R or CGI-SR-I score indicates improvement. Analysis of CGI-SS-R was based on ANCOVA model on ranks with treatment, analysis centre, and standard of care AD treatment as randomized as factors, and baseline value (unranked) as a covariate.

[a] Follow-up analysis set.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

### Symptom Severity Score Rated by Physician

Change from baseline of the MADRS total score at day 2 was the primary efficacy end point in the ASPIRE studies and was included in the fixed sequence testing procedure. A decrease in this score indicates improvement in the depressive symptoms. In both trials, patients in the esketamine group had statistically significantly lower MADRS total score compared to the placebo group 24 hours after the first dose. In the ASPIRE 1 study, the MADRS total score was decreased by 3.8 points (95% CI, –6.6 to –1.1; P = 0.006) and in the ASPIRE 2 study it was decreased by 3.9 points (95% CI, –6.6 to –1.1; P = 0.006). The between-group differences were considered clinically relevant, according to the clinical experts consulted for this review. At day 25, the reductions from baseline in the MADRS total score were maintained in both the esketamine group and placebo group. Patients in the esketamine group had greater reduction compared to those in the placebo group.

Details of the changes in MADRS total score in the 2 trials are presented in Table 46.

## Table 46: Change From Baseline in MADRS Total Score for ASPIRE 1 and 2 (Full Analysis Set)

| Outcome measures | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 112 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Change from baseline to day 2 in MADRS total score, ANCOVA (LOCF)** | | | | |
| Number of patients contributing to the analysis (% of total N) | 112 (100) | 112 (100) | 113 (99) | 113 (100) |
| Baseline, mean (SD) | 41.3 (5.87) | 41.0 (6.29) | 39.5 (5.19) | 39.9 (5.76) |
| End point, mean (SD) | 24.7 (12.12) | 28.2 (11.97) | 23.7 (11.75) | 27.5 (11.13) |
| Change from baseline, mean (SD) | –16.4 (11.95) | –12.8 (10.73) | –15.7 (11.56) | –12.4 (10.43) |
| Difference of LS means versus placebo (95% CI) | –3.8 (–6.56 to –1.09) | | –3.9 (–6.60 to –1.11) | |
| P value | 0.006 | | 0.006 | |
| **Change from baseline to day 25 in MADRS total score, MMRM (observed case)** | | | | |
| Number of patients contributing to the analysis (% of total N) | 96 (86) | 92 (82) | 85 (75) | 88 (78) |
| Change from baseline, LS mean | –24.3 | –21.7 | –25.3 | –21.5 |
| Difference of LS means versus placebo (95% CI) | –2.6 (–5.86 to 0.68) | | –3.7 (–7.09 to –0.38) | |
| P value (1-sided) | NR | | NR | |

ANCOVA = analysis of covariance; CI = confidence interval; ESK = esketamine; LOCF = last observation carried forward; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; NR = not reported; SD = standard deviation.

Note: Analysis for day 2 data was based on ANCOVA model with treatment, analysis centre, and standard of care antidepressant treatment as randomized as factors and baseline value as a covariate. Negative change in score indicates improvement.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Harms*

Most patients in the ASPIRE studies experienced 1 or more AEs. In the ASPIRE 1 study, 88.5% experienced AEs with esketamine versus 74.1% with placebo and in the ASPIRE 2 study, 91.2% experienced AEs with esketamine versus 77.0% with placebo. Dizziness, dissociation, and nausea were reported by more than 20% of patients treated with esketamine in each trial.

SAEs were reported in 4.4% of patients in the ASPIRE 1 study and 4.8% in the ASPIRE 2 study. WDAEs were reported in 4.4% of patients in the ASPIRE 1 study and 5.3% in the ASPIRE 2 study. There were no deaths during the double-blind treatment phase in either study, while in the ASPIRE 1 study, 1 completed suicide occurred in the esketamine group during the follow-up phase. This death was not considered related to the study drug as assessed by the investigator. Compared to placebo, more patients treated with esketamine experienced TEAEs suggestive of abuse.

Details of harm outcomes are presented in Table 47.

## Table 47: Summary of Harm Outcomes for ASPIRE 1 and 2 (Safety Analysis Set, Double-Blind Phase)

| Adverse events | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 113 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Patients with ≥ 1 AEs, n (%)** | 100 (88.5) | 83 (74.1) | 104 (91.2) | 87 (77.0) |
| Most common adverse events[a] | | | | |
| Dysgeusia | 16 (14.2) | 11 (9.8) | 29 (25.4) | 18 (15.9) |
| Dizziness | 40 (35.4) | 10 (8.9) | 47 (41.2) | 21 (18.6) |
| Headache | 21 (18.6) | 20 (17.9) | 25 (21.9) | 26 (23.0) |
| Somnolence | 21 (18.6) | 11 (9.8) | 26 (22.8) | 12 (10.6) |
| Paresthesia | 3 (2.7) | 0 | 23 (20.2) | 7 (6.2) |
| Hypoesthesia | 8 (7.1) | 2 (1.8) | 12 (10.5) | 1 (0.9) |
| Sedation | 7 (6.2) | 2 (1.8) | 16 (14.0) | 3 (2.7) |
| Dissociation | 33 (29.2) | 4 (3.6) | 44 (38.6) | 9 (8.0) |
| Anxiety | 6 (5.3) | 10 (8.9) | 17 (14.9) | 7 (6.2) |
| Euphoric mood | 4 (3.5) | 0 | 13 (11.4) | 1 (0.9) |
| Nausea | 23 (20.4) | 15 (13.4) | 38 (33.3) | 16 (14.2) |
| Vomiting | 8 (7.1) | 7 (6.3) | 18 (15.8) | 5 (4.4) |
| Constipation | 15 (13.3) | 5 (4.5) | 7 (6.1) | 9 (8.0) |
| Paresthesia oral | 2 (1.8) | 0 | 14 (12.3) | 3 (2.7) |
| Vision blurred | 10 (8.8) | 5 (4.5) | 17 (14.9) | 6 (5.3) |
| Blood pressure increased | 19 (16.8) | 6 (5.4) | 7 (6.1) | 3 (2.7) |
| **Patients with ≥ 1 SAEs, n (%)** | 4 (3.5) | 6 (5.4) | 5 (4.4) | 6 (5.3) |
| Events (n) | Suicidal depression (2), depression (1), suicide attempt (1), diabetic ketoacidosis (1) | Suicidal depression(1), depression (1), suicide attempt (1), aggression (1), suicidal ideation (2), hypertransaminasemia (1) | Suicide attempt (3), depersonalization/ derealization disorder (1), suicidal ideation (1) | Suicide attempt (3), suicidal ideation (2), depression (1), arrhythmia (1), pericardial effusion (1), pneumothorax (1) |
| **Patients with ≥ 1 WDAEs, n (%)** | 5 (4.4) | 5 (4.5) | 9 (7.9) | 3 (2.7) |
| Events | Dizziness, headache, hypoesthesia, sedation, somnolence, confusional state, dissociation, hallucination, blood pressure increased, pharyngeal hypoesthesia | Aggression, suicidal ideation, blood pressure diastolic increased, atrioventricular block first degree, hypertransaminasemia | Dissociation, dizziness postural, blood pressure increased, paresthesia oral, depersonalization/ derealization disorder, nausea and vomiting, throat irritation, nasal discomfort, and dyspepsia | Pericardial effusion, depression and suicidal, arrhythmia, pneumothorax |

| Adverse events | ASPIRE 1 | | ASPIRE 2 | |
|---|---|---|---|---|
| | ESK 84 mg N = 113 | Placebo N = 112 | ESK 84 mg N = 114 | Placebo N = 113 |
| **Mortality, n** | DB phase: 0<br><br>Follow-up: 1 (suicide) | 0 | 0 | 0 |
| **Notable harms, n (%)** | | | | |
| TEAE suggestive of abuse potential | 70 (61.9) | 25 (22.3) | 76 (66.7) | 33 (29.2) |
| Dizziness or vertigo | 52 (46.0) | 13 (11.6) | 62 (54.4) | 22 (19.5) |
| Impaired cognition | 0 | 0 | 0 | 0 |
| Cystitis | 2 (1.8) | 1 (0.9) | 5 (4.4) | 1 (0.9) |
| Suicidality | 7 (6.2) | 7 (6.3) | 10 (8.8) | 10 (8.8) |
| Increased blood pressure | 25 (22.1) | 10 (8.9) | 9 (7.9) | 4 (3.5) |

AE = adverse event; DB = double blind; ESK = esketamine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency of greater than 10%.

Sources: Clinical Study Reports for the ASPIRE 1[45] study and the ASPIRE 2[46] study.

*Critical Appraisal*

**Internal Validity**

The 2 ASPIRE studies used appropriate methods to randomize patients to treatments. The baseline patient characteristics were generally balanced between groups within studies. Although efforts had been made (e.g., different raters performed efficacy and safety assessments) to blind patients and the study site personnel to treatment allocation, there was potential for unblinding due to the frequency of acute adverse effects that are known to be associated with esketamine. Potential unblinding may make it challenging to interpret changes from baseline in some of the outcomes measures, particularly for the subjective outcomes such as MADRS score or suicidality-related outcomes. There were no data on previous antidepressant treatments and whether a washout period was needed; therefore, it is unknown whether the patient's prior treatment history was balanced between the treatment groups.

In terms of the statistical methods, all efficacy analyses were conducted based on the FAS population. The number of patients excluded from the overall population was low at day 2, while over the longer term, more patients were excluded (e.g., 14% to 25% of patients were excluded from the analysis for suicidality-related outcomes). Multiplicity was controlled for the primary and key secondary efficacy outcomes by a fixed sequence testing procedure, where the key secondary hypothesis was tested only after the null hypothesis for the primary end point was rejected. Sensitivity analysis for missing data was not performed because only 0.5% of the primary end point data at day 2 were missing. It is unlikely that the missing data would have a significant impact on the short-term results; however, it may have an impact on the long-term outcomes.

**External Validity**

The ASPIRE studies provided evidence of efficacy and safety of intranasal esketamine in adult patients with MDD and at imminent risk for suicide. However, this is not consistent with the target population of the current CADTH review, in that adult patients with treatment-resistant depression (defined as patients who had not responded adequately to

at least 2 different antidepressants of adequate dose and duration in the current depressive episode) were enrolled. According to the sponsor's response to CADTH's query, study participants' past treatment history was not captured in the ASPIRE 1 and 2 studies; therefore, it is unclear what proportion of patients in the ASPIRE studies would meet the criteria for treatment-resistant depression. Generalizability of the results of these 2 trials to patients with treatment-resistant depression is limited. In addition, due to the short duration of the ASPIRE studies (up to 90 days), the long-term efficacy and safety of esketamine in the study population is uncertain.

# Discussion

## Summary of Available Evidence

Three 4-week double-blind RCTs (TRD3001, TRD3002, and TRD3005), and 1 double-blind, randomized withdrawal study (TRD3003) met the inclusion criteria for the systematic review. These trials enrolled adult patients with MDD who had shown nonresponse to at least 2 antidepressant drugs, 1 of which was documented during the screening phase of the trials. In the induction studies, patients received intranasal esketamine (with fixed or flexible dosing) or placebo, plus a newly initiated oral antidepressant (duloxetine, sertraline, escitalopram, or venlafaxine XR) and were assessed for the change from baseline in MADRS total score at 4 weeks. Study TRD3003 randomized patients who had achieved response or remission to esketamine plus an oral antidepressant to either continuing esketamine therapy or switching to intranasal placebo. The primary outcome was time to relapse.

The patients enrolled were predominantly female (62% to 71%) and White (77% to 95%), with moderate-to-severe MDD. The mean age was mid 40's in Study TRD3001, Study TRD3002, and Study TRD3003, whereas study TRD3005 enrolled older adults with a mean age of 70 years. The number of patients enrolled in the trials ranged from 138 patients in Study TRD3005 to 705 patients in Study TRD3003, with 59 to 115 patients per randomized treatment group.

This report also includes a summary of 4 trials that provide supplementary data on esketamine, including 2 open-label uncontrolled trials (TRD3004, N = 802; TRD3008, N = 1,140) and 2 trials in patients at imminent risk of suicide (ASPIRE 1, N = 226; ASPIRE 2 N = 230). No indirect treatment comparisons of adequate methodological quality were identified.

## Interpretation of Results

### Efficacy

Although HRQoL and suicidality were identified as key efficacy outcomes of interest to patients, none of the included studies were designed or powered to evaluate these outcomes. Other outcomes of interest (i.e., hospitalizations, emergency room visits, or withdrawal frequency) were not analyzed as a measure of efficacy in any of the included studies. All trials reported data for the EQ-5D and EQ VAS, with placebo and active treatment groups showing improvement in HRQoL scores. These data, however, were reported descriptively, with no pre-planned between-group comparisons; thus, no inferences can be drawn from the results. Suicidality was also reported descriptively using the C-SSRS and through reporting of AEs. During the trials, suicidal behaviour was infrequent but data on suicidality should be interpreted cautiously given that all treatment-resistant depression trials excluded those with suicidal ideation or intent to act prior to enrolment. Further discussion of suicide-related events is included in the Harms section.

Patients indicated that depression affects many aspects of life including the ability to work and to do the activities they used to enjoy, as well as the tasks of daily life such as getting out of bed and getting ready, preparing meals, or tidying the house. In the trials, functional impacts were assessed using the SDS, a 30-point scale where patients rate the extent to which their work, social life or leisure activities, and home life or family responsibilities are

impaired by symptoms. In the induction studies, the between-group differences were not statistically significant for Study TRD3001, and the SDS results in Study TRD3002 were inconclusive due to the failure of a prior outcome in the statistical testing procedure. These data were also limited by the extent of missing data, with 20% to 25% of patients not reporting day 28 results. The relapse prevention trial also reported data for SDS during the maintenance phase. The LS mean differences favoured esketamine versus placebo in the stable remitter and the stable responder populations, with 95% CI that excluded the null; however, there was no control for multiple testing and these data should be interpreted in light of the inflated risk of type I error. In addition, the clinical importance of these findings is unclear given the uncertain validity of the SDS and the lack of a MCID.

With regards to clinician-rated depression symptom severity, only 1 of the 3 induction studies demonstrated a statistically significant difference between esketamine and placebo for the primary outcome (change from baseline to day 28 in the MADRS total score). In Study TRD3002, the between-group difference in MADRS score was –4.0 points (95% CI, –7.3 to –0.6), which exceeded the published MCID of 2 points for this instrument. The other 2 trials reported LS mean differences that were similar in magnitude (LS mean difference –3.2 to –4.1 points) but with a 95% CI that included the null, or in the case of the esketamine 56 mg dose group in Study TRD3001, significance was not tested due to failure of the 84 mg dose group. It is not uncommon for antidepressant trials to fail to demonstrate statistical differences versus placebo. The proportion of antidepressant RCT "failure" has been reported to be as high as 50%, and has been associated with a number of factors including the lack of statistical power, issues related to the complex and variable presentation of MDD, and limitations of the composite scales used to measure treatment effects.[41,42] Moreover, expectancy may confound patient recall and has been shown to inflate both placebo and active treatment response.[42] In clinical trials, all patients receive frequent interactions and monitoring by clinical experts, which may have benefits in relieving depressive symptoms for both placebo and active treatment groups.[42] As shown in Study TRD3001 and Study TRD3002, about 30% of patients who received placebo achieved remission and 37% to 50% showed response at 4 weeks, which the clinical experts and regulatory agencies commented was higher than expected considering the population enrolled.[22,24,26] All patients enrolled in the trials were switched to a new oral antidepressant and some treatment effects would be apparent by week 4. As for the trial that enrolled older adults (TRD3005), this trial may have been underpowered to detect a difference between treatments. Interpretation of the change in MADRS data should take into consideration the potential for unblinding, and the differential frequency of withdrawals. Due to the characteristics of the drug, maintaining blinding was a challenge for the sponsor, and it is possible that patients' responses to MADRS assessors, and other patient-reported outcomes (EQ-5D, SDS, PHQ-9) or reporting of harms, may have been influenced by expectations of treatment. Although sensitivity analyses were conducted to explore the impacts of unblinding, the possibility of bias cannot be ruled out. Also, considering the excess withdrawals in the esketamine groups, the OC data used in the MMRM analysis may inflate the treatment effects of esketamine relative to placebo, as those who remained in the trial until day 28 likely reflect those with a positive outcome. The tipping point analysis conducted in Study TRD3002 reported that the patients with missing data in the esketamine group would need to have MADRS scores that were 9 points worse after discontinuation in order to change the overall result to non-statistically significant. Considering the baseline and change values observed for esketamine, a 9-point difference for missing patients was plausible. The ANCOVA LOCF and MMRM analyses in this trial however, showed similar results, albeit with upper values of the 95% CI showing differences versus placebo that

were not clinically important (MMRM = –0.6 points; ANCOVA = –0.3 points). Data for depression symptom severity reported by patients (PHQ-9) were inconclusive due to failure of a prior outcome in the serial gatekeeping procedures to control the type I error. Given these limitations described above, there is uncertainty in the short-term effects of esketamine on depression symptom severity. Based on Study TRD3005, Health Canada concluded that evidence of efficacy was not established for patients 65 years of age and older, and esketamine is not recommended in these patients.[4]

The proportion of patients in the esketamine groups who met the criteria for response or remission was nominally higher than in the placebo groups, but no between-group comparisons were conducted. To evaluate the potential for rapid treatment response, 2 induction trials reported on the onset of clinical response by day 2 (or day 8) that was maintained to day 28. For Study TRD3002, 8% and 5% in the esketamine and placebo groups, respectively, had onset of response by day 2, with no statistically significant differences between groups. In Study TRD3001, 10% and 9% in the esketamine groups versus 2% in the placebo group met the criteria for onset of clinical response by day 2. The analysis of between-group differences showed wide 95% CIs which were inconclusive due to failure of a prior outcome in the statistical hierarchy.

In the longer-term study (TRD3003), among patients who achieved stable remission at the end of the optimization period, relapse was delayed in the esketamine group relative to placebo. Similar results were observed among patients in the stable responder population. In the stable remitter population, approximately half of patients in the placebo group relapsed within the first 4 weeks after randomization, compared with 20% with early relapse for esketamine. The FDA and Health Canada raised the issue that unblinding may have contributed to the early relapses in the placebo group.[22,24] Patients who perceived a difference after receiving placebo could assume negative consequences from no longer receiving active drug, even with an ongoing background oral antidepressant. A number of pre-planned and post hoc sensitivity analyses were conducted, but the potential impact of unblinding on the results remains unclear. The increased illness risk and vulnerability of the population without treatment may also have contributed to the early relapses.[22] The enrolment of an enriched population should also be considered when interpreting the results of this trial. Only those patients who responded to and tolerated esketamine in the induction and optimization phases were randomized; thus, these patients may overestimate the treatment effects, relative to the overall population with treatment-resistant depression.

Data from 4 supplementary trials were provided in this report including 2 open-label uncontrolled trials, and trials in patients at imminent risk of suicide (ASPIRE 1 and 2). Although the ASPIRE studies were multi-centre, randomized, double-blind studies, the patient population enrolled was not consistent with the target population of the current CADTH review. As a result, the generalizability of the efficacy data of these 2 trials to patients with treatment-resistant depression is limited. Esketamine for the treatment of MDD in patients at risk of suicide is currently under review in the US.[16] One of the uncontrolled open-label trials reported efficacy data for the MADRS, PHQ-9, SDS, and EQ-5D. For these measures, the outcome scores showed improvement and appeared to remain constant during the maintenance phase among patients who remained in the study; however, these data should be interpreted with caution given the potential for selection, attrition, and reporting bias, and the lack of a control group.

All of the included studies were placebo controlled thus there is no head-to-head data comparing esketamine to other treatment options. At CADTH's request, the sponsor

provided a network meta-analysis of therapies for treatment-resistant depression, but this report had a number of important limitations, such as exclusion of relevant studies, heterogeneity across trials, and sparse networks. Both CADTH and the sponsor agreed that the results were likely not robust, and so these data have not been summarized in this report. The Institute for Clinical and Economic Review recently conducted a review of esketamine for treatment-resistant depression and concluded that heterogeneity across trials precluded conducting indirect treatment comparisons.[36] Consequently, data are lacking to inform decisions on the relative treatment effects of esketamine versus other treatments within the paradigm.

External validity of the studies' findings is limited by the enrolment of an enriched population with demonstrated adherence to treatments (all trials) and those who were responsive and tolerant to esketamine (TRD3005). As such, the results likely overestimate the real-world effectiveness of the esketamine. The trials excluded patients with comorbid psychiatric disorders, substance use disorder, or recent suicidality, thus the generalizability to these populations may be limited.

## Harms

AEs were reported more frequently among patients who received esketamine than placebo in all studies. The most common AEs reported more frequently in esketamine versus placebo groups were dissociation, dizziness, vertigo, nausea, and somnolence. More than 20% of patients in the extension studies reported dissociation, dizziness, and nausea, which suggests that these acute effects may not wane over time in those who receive longer-term therapy. Overall, there were more patients in the esketamine groups that withdrew due to AEs than the placebo groups during the induction studies; however, the overall frequency was low (≤ 7%). The frequency of SAEs was generally low in the RCTs for both active and placebo groups (0% to 4%), and in the 2 longer-term uncontrolled studies, 7% and 8% of patients experienced a SAE. There were 6 deaths among patients who received esketamine and none among placebo patients in the RCTs and extension studies.

The sponsor reported 3 completed suicides among esketamine treatment patients during the phase II and phase III trials in treatment-resistant depression (2.9 events per 1,000 patient-years). No suicides were reported among those who received placebo (100 patient-years). The frequency of treatment-emergent suicidality ranged from 0% to 4.0% in the treatment and follow-up phases of the RCTs and extension studies among patients who received esketamine. In comparison, the frequency of treatment-emergent suicidality in placebo-treated patients ranged from 0% to 2.5%, although it should be noted that the total follow-up time for placebo groups was limited. Based on the data available, it is not clear if esketamine has an impact on the occurrence of suicidal ideation or behaviour, especially considering that those with recent suicidality were excluded from the trials in patients with treatment-resistant depression.

Increased blood pressure was reported more frequently among patients who received esketamine than placebo in all the RCTs, and there were some patients who experienced SAEs that were cardiovascular, cerebrovascular, or hemodynamic related. Increases in blood pressure is a known adverse effect of ketamine, and thus the esketamine trials excluded any patients with cardiovascular or other conditions that may be adversely affected by changes in blood pressure. Due to the hemodynamic and cognitive adverse effects, and the abuse potential of esketamine, the drug is only available in the US through a restricted access program.[14] In Canada the details of the controlled distribution system

have yet to be defined. According to the product monograph, esketamine requires supervised administration with monitoring until the patient is stable.[4] Patients are also advised to avoid driving or engaging in potentially hazardous activities until the day after dosing.[4] These requirements may limit the settings in which esketamine can be provided and may be important factors for patients and clinicians when evaluating esketamine as a treatment option.

There is uncertainty regarding the longer-term tolerability and adverse effects of esketamine in patients with treatment-resistant depression, many of whom will require life-long pharmacological treatment. Ketamine has been used as an anesthetic in Canada for many years; however, clinical trial evidence for its use in depression is sparse and longer-term adverse effects are uncertain.[13,50] Comparative safety data for esketamine was limited to 3 short-term RCTs (4 weeks) and 1 longer-term RCT, in which patients had a median treatment duration of 10 months.[29] As with most RCTs, these studies were not designed or powered to detect rare adverse effects or those with a lag time. Given the number of withdrawals observed in the 4-week period, there is uncertainty regarding tolerability. No new safety signals were identified from 2 longer-term uncontrolled studies that had a median treatment duration of 6 months (TRD3004) and 15 months (TRD3008). Supplementary safety data were available from 2 RCTs in patients who were hospitalized due to the risk of imminent suicide (ASPIRE 1 and ASPIRE 2). The AEs described in these studies were comparable to those reported among patients with treatment-resistant depression, and overall, the frequency of suicide-related AEs was similar in the esketamine and placebo groups. However, due to the short duration of the trials, the long-term safety of esketamine in the study population is unclear.

Patients expressed a desire for novel treatments with minimal adverse effects, and wished to avoid the weight gain, memory loss, decreased sexual functioning, and worsening of comorbid conditions that are associated with some oral antidepressants. Based on existing evidence, esketamine will be administered in combination with an SNRI or SSRI, thus avoidance of these common adverse effects may not be possible.

## Conclusions

Among adult patients with MDD who had an inadequate response to at least 2 prior antidepressant therapies, esketamine nasal spray plus a newly initiated oral antidepressant was associated with short-term improvement in depression symptom severity scores relative to placebo plus new oral antidepressant therapy. Statistical differences between esketamine and placebo, however, were not consistently observed across trials, and while the point estimates for the change from baseline in MADRS scores suggest the differences may be clinically meaningful, the 95% CIs include values of minimal clinical importance.

In patients who had achieved remission with esketamine plus an oral antidepressant, relapse was delayed among those who remained on esketamine compared with patients switched to placebo. However, due to the selection of an enriched population that had maintained a favourable response and tolerability to esketamine over 4 months, the generalizability of these findings to patients with MDD in Canada may be limited.

In all trials the possibility of reporting bias cannot be ruled out due to the challenges in maintaining blinding with a drug that has frequent acute adverse effects. No inferences can be drawn from the SDS data due to the extent of missing data, or statistical issues related to lack of control of type I error, or failure of a prior outcome in the statistical testing procedure. Thus, the impact of esketamine on disability is unclear. No conclusions can be drawn regarding the effect of esketamine on HRQoL, suicidality, hospitalization, or emergency department visits, as the trials were not designed or powered to evaluate these outcomes.

Esketamine was associated with increased frequency of AEs compared with placebo including dissociation, dizziness, vertigo, nausea, somnolence, and increased blood pressure. Longer-term safety of esketamine is uncertain. Due to the hemodynamic and cognitive adverse effects, and the abuse potential of esketamine, the drug will be available through a controlled distribution program, but the details have not yet been determined.

# Appendix 1: Literature Search Strategy

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | MEDLINE All (1946-present)<br>Embase (1974-present)<br>APA PsycInfo (1806-present)<br>Cochrane Central Register of Controlled Trials (CCTR)<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | February 3, 2020 |
| Alerts: | Weekly search updates until project completion |
| Study Types: | No filters used |
| Limits: | Publication date limit: No date limits used<br>Humans<br>Language limit: English- and French-language<br>Conference abstracts: excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| .fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj# | Requires terms to be adjacent to each other within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .kw | Author keyword (Embase); keyword (CDSR and DARE) |
| .pt | Publication type |
| .mp | Mapped term |
| .rn | Registry number |
| .yr | Publication year |
| .jw | Journal word title |
| freq=# | Requires terms to occur # number of times in the specified fields |
| medall | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| oemezd | Ovid database code; Embase, 1974 to present, updated daily |
| cctr | Ovid database code; Cochrane Central Register of Controlled Trials |

| OVERVIEW | |
|---|---|
| 1. | (Spravato* or esketamine* or Vesierra* or Ketanest* or "s ketamine" or "s ketamin" or s-ketamin* or "(s)-ketamine" or "(s)-ketamin" or Kataved* or "L ketamine" or "l ketamin" or l-ketamin* or "(l)-ketamine" or "(l)-ketamin" or L8P1H35P2Z).ti,ab,ot,rn,nm,hw,kf. |
| 2. | 1 use medall |
| 3. | 1 use psyh |
| 4. | *esketamine/ |
| 5. | (Spravato* or esketamine* or Vesierra* or Ketanest* or "(s)-ketamine" or "(s)-ketamin" or "S ketamine" or s-ketamine* or Kataved* or "(l)-ketamine" or "(l)-ketamin" or "L ketamine" or l-ketamin*).ti,ab,kw,dq. |
| 6. | 4 or 5 |
| 7. | 6 use oemezd |
| 8. | 2 or 3 or 7 |
| 9. | conference abstract.pt. |
| 10. | 8 not 9 |
| 11. | (depress* or anti-depress* or antidepress*).ti,ab,hw,kf,kw. |
| 12. | 10 and 11 |
| 13. | remove duplicates |

| CLINICAL TRIAL REGISTRIES | |
|---|---|
| ClinicalTrials.gov | Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.<br>[esketamine and depression] |
| WHO ICTRP | International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.<br>[esketamine and depression] |

| OTHER DATABASES | | |
|---|---|---|
| PubMed | Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. | |
| Cochrane Central Register of Controlled Trials | Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform. | |
| CINAHL | Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings. | |

### Grey Literature

| | |
|---|---|
| Search dates: | February 5, 2020 |
| Keywords: | Esketamine and depression |
| Limits: | Publication years: no date limits used |
| Updated: | Search updated prior to the completion of stakeholder feedback period |

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- internet search.

# Appendix 2: Excluded Studies

## Table 48: Excluded Studies

| Reference | Reason for exclusion |
|---|---|
| 1. Clinical Study Report: ESKETINTRD3004. An open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression safety and sustenance of esketamine treatment response with repeated doses at intervals determined by symptom severity (SUSTAIN-2) (phase III) [CONFIDENTIAL internal sponsor's report]. Raritan (NJ): Janssen Research & Development 2018 Aug 14.<br>2. Clinical Study Report: 54135419TRD3008. An open-label, long-term extension safety study of esketamine nasal spray in treatment-resistant depression safety and sustenance of esketamine treatment response with repeated doses at intervals determined by symptom severity - SUSTAIN-3 (phase III) [CONFIDENTIAL internal sponsor's report]. Raritan (NJ): Janssen Research & Development 2019 May 21.<br>3. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry 2018;75:139-48. | Study design |
| 4. Clinical Study Report: 54135419SUI3001. A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety 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 adult subjects assessed to be at imminent risk for suicide - ASPIRE I (phase III) [CONFIDENTIAL internal sponsor's report]. Raritan (NJ): Janssen Research & Development 2019 Aug 27.<br>5. Clinical Study Report: 54135419SUI3002. A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety 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 adult subjects assessed to be at imminent risk for suicide - ASPIRE II (phase III) [CONFIDENTIAL internal sponsor's report]. Raritan (NJ): Janssen Research & Development 2019 Aug 29.<br>6. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry 2018;175:620-30. | Population |

# Appendix 3: Detailed Outcome Data

## Table 49: Newly Initiated Oral Antidepressant in Induction Studies

| Study antidepressant,[a] n (%) | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 to 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| Duloxetine | 49 (43) | 43 (38) | 44 (39) | 60 (53) | 61 (56) | 25 (35) | 23 (35) |
| Escitalopram | 26 (23) | 23 (20) | 24 (21) | 21 (18) | 17 (16) | 25 (35) | 25 (39) |
| Sertraline | 24 (21) | 24 (21) | 25 (22) | 16 (14) | 16 (15) | 15 (21) | 10 (15) |
| Venlafaxine XR | 16 (14) | 24 (21) | 20 (18) | 17 (15) | 15 (14) | 7 (10) | 7 (11) |

ESK = esketamine; FAS = full analysis set; XR = extended release.

[a] FAS population.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 50: Newly Initiated Oral Antidepressant in Relapse Prevention Study

| TRD3003 | | Stable remitters[a] | | Stable responders[a] | |
|---|---|---|---|---|---|
| | All enrolled N = 705 | ESK 56 or 84 mg N = 90 | Placebo N = 86 | ESK 56 or 84 mg N = 62 | Placebo N = 59 |
| Study antidepressant, n (%) | | | | | |
| Duloxetine | 323 (46) | 47 (52) | 38 (44) | 27 (44) | 30 (51) |
| Escitalopram | 128 (18) | 13 (14) | 14 (16) | 17 (27) | 10 (17) |
| Sertraline | 130 (19) | 15 (17) | 14 (16) | 10 (16) | 13 (22) |
| Venlafaxine XR | 118 (17) | 15 (17) | 20 (23) | 8 (13) | 6 (10) |

ESK = esketamine; FAS = full analysis set; XR = extended release.

[a] FAS population.

Source: Clinical Study Report for Study TRD3003.[9]

## Table 51: Change From Baseline in EQ-5D-5L Index Score and EQ VAS for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Change from baseline to day 28 in EQ-5D-5L index score[a]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 113 (98) | 112 (98) | 113 (100) | 111 (97) | 105 (96) | 70 (97) | 64 (98) |
| Baseline, mean (SD) | 0.531 (0.220) | 0.502 (0.208) | 0.521 (0.216) | 0.530 (0.208) | 0.501 (0.214) | 0.581 (0.226) | 0.635 (0.228) |
| End point, mean (SD) | 0.755 (0.216) | 0.741 (0.203) | 0.703 (0.217) | 0.817 (0.178) | 0.735 (0.230) | 0.653 (0.256) | 0.657 (0.211) |
| Change from baseline, mean (SD) | 0.224 (0.248) | 0.243 (0.240) | 0.181 (0.250) | 0.288 (0.232) | 0.231 (0.251) | 0.081 (0.262) | 0.026 (0.224) |
| Difference of LS means versus placebo (95% CI) | NR | NR | NR | NR | NR | NR | NR |

| Outcome measures | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| P value (1-sided) | NR | NR | NR | NR | NR | NR | NR |
| **Change from baseline to day 28 in EQ VAS[a]** | | | | | | | |
| Number of patients contributing to the analysis (% of total N) | 113 (98) | 112 (98) | 113 (100) | 111 (97) | 105 (96) | 70 (97) | 64 (98) |
| Baseline, mean (SD) | 43.2 (20.3) | 44.9 (21.9) | 45.8 (21.6) | 40.9 (20.2) | 38.4 (20.3) | 48.7 (24.1) | 50.8 (23.6) |
| End point, mean (SD) | 64.2 (23.8) | 64.1 (24.2) | 60.7 (23.7) | 69.9 (20.0) | 59.4 (23.6) | 54.3 (25.1) | 54.6 (24.9) |
| Change from baseline, mean (SD) | 20.9 (25.0) | 19.1 (26.9) | 14.9 (27.2) | 29.1 (26.3) | 20.9 (26.6) | 6.2 (22.8) | 4.4 (20.6) |
| Difference of LS means versus placebo (95% CI) | NR | NR | NR | NR | NR | NR | NR |
| P value (1-sided) | NR | NR | NR | NR | NR | NR | NR |

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; ESK = esketamine; FAS = full analysis set; LS = least squares; NR = not reported; SD = standard deviation.

[a] FAS population.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 52: Change From Baseline in EQ-5D-5L Index Score and EQ VAS for Relapse Prevention Study

| TRD3003 | Stable remitters | | Stable responders | |
|---|---|---|---|---|
| | ESK N = 90 | Placebo N = 86 | ESK N = 62 | Placebo N = 59 |
| **Change from baseline to end point in EQ-5D-5L index score[a]** | | | | |
| Number of patients contributing to the analysis (% of total N) | 88 (98) | 86 (100) | 61 (98) | 58 (98) |
| Baseline, mean (SD) | 0.925 (0.044) | 0.918 (0.042) | 0.877 (0.066) | 0.875 (0.080) |
| End point, mean (SD) | 0.857 (0.128) | 0.822 (0.144) | 0.855 (0.088) | 0.802 (0.129) |
| Change from baseline, mean (SD) | -–0.067 (0.118) | –0.096 (0.148) | –0.023 (0.075) | –0.073 (0.138) |
| Difference of LS means versus placebo (95% CI) | NR | NR | NR | NR |
| P value (2-sided) | NR | NR | NR | NR |
| **Change from baseline to end point in EQ VAS[a]** | | | | |
| Number of patients contributing to the analysis (% of total N) | 88 (98) | 86 (100) | 61 (98) | 58 (98) |
| Baseline, mean (SD) | 88.4 (9.2) | 86.6 (9.8) | 77.0 (17.4) | 79.1 (14.3) |
| End point, mean (SD) | 77.9 (20.8) | 70.6 (21.5) | 76.0 (17.7) | 65.4 (19.0) |
| Change from baseline, mean (SD) | –10.4 (20.3) | –16.1 (21.8) | –1.3 (15.6) | –13.8 (19.8) |
| Difference of LS means versus placebo (95% CI) | NR | NR | NR | NR |
| P value (2-sided) | NR | NR | NR | NR |

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; ESK = esketamine; FAS = full analysis set; LS = least squares; NR = not reported; SD = standard deviation.

[a] FAS-remitters or FAS-responders population in maintenance phase.

Source: Clinical Study Report for Study TRD3003.[9]

## Table 53: Response and Remission Outcomes for Induction Studies

| Outcome measures | TRD3001 | | | TRD3002 | | TRD3005 | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 114 | Placebo N = 113 | ESK 56 or 84 mg N = 114 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Response (≥ 50% improvement in MADRS score) at day 28[a]** | | | | | | | |
| N | 115 | 113 | 113 | 112 | 109 | 71 | 64 |
| n (%) | 61 (53) | 54 (48) | 42 (37) | 71 (63) | 54 (50) | 17 (24) | 8 (13) |
| P value | NR | NR | NR | NR | NR | NR | NR |
| **Remission (MADRS score ≤ 12 points) at day 28 [a]** | | | | | | | |
| N | 115 | 113 | 113 | 112 | 109 | 71 | 64 |
| n (%) | 40 (35) | 40 (35) | 33 (29) | 54 (48) | 33 (30) | 11 (15) | 4 (6) |
| P value | NR | NR | NR | NR | NR | NR | NR |

ESK = esketamine; FAS = full analysis set; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; NR = not reported.

[a] FAS population with LOCF for missing data.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 54: Sensitivity Analysis for Time to Relapse in Study TRD3003

| Sensitivity analyses | Patients who relapsed | | | |
|---|---|---|---|---|
| | ESK, n (%) | Placebo, n (%) | HR (95% CI) | P value (2-sided) |
| **FAS-remitters** | | | | |
| Unweighted log-rank test and Cox proportional hazards model[a] | 24 (27) | 39 (45) | 0.46 (0.27 to 0.77) | 0.003 |
| Tipping point analysis[b] | NR | NR | NR | Tipping point not reached for delta values up to 50 |
| Post hoc<br>Censoring 3 patients with a change in dissociation (CADSS scores) in patients switched to placebo | 24 (27) | 36 (42) | 0.50 (0.30 to 0.84) | 0.008 |
| Post hoc<br>Censoring 7 patients with a change in dissociation (CADSS score and dissociation adverse effects) after switch to placebo | NR | NR | 0.56 (0.33 to 0.95) | 0.030 |
| Post hoc<br>Censoring patients with early relapses after randomization: | | | | |
| 1 week | 0 | 0 | 0.47 (0.28 to 0.78) | NR |
| 2 weeks | 0 | 6 (15) | 0.54 (0.32 to 0.91) | NR |
| 3 weeks | 1 (4) | 13 (33) | 0.64 (0.37 to 1.12) | NR |
| 4 weeks | 4 (17) | 19 (49) | 0.71 (0.38 to 1.31) | NR |

CADSS = Clinician Administered Dissociative States Scale; CI = confidence interval; ESK = esketamine; FAS = full analysis set; HR = hazard ratio; NOD = Notice of Deficiency; NR = not reported.

[a] Treatment as a factor in Cox proportional hazards model.

[b] Applied increasing relapse hazard (delta) to 8 ESK patients who discontinued early. Delta values were increased from 1 (i.e., censoring is ignorable) up to the tipping point when the results were no longer significant.

Source: Clinical Study Report for Study TRD3003.[9] Janssen response to NOD.[25]

## Table 55: Timing of Adverse Events in the Induction Studies

| Adverse events | TRD3001[a] | | | TRD3002[a] | | TRD3005[a] | |
|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 115 | ESK 84 mg N = 116 | Placebo N = 113 | ESK 56 or 84 mg N = 115 | Placebo N = 109 | ESK 28 to 84 mg N = 72 | Placebo N = 65 |
| **Treatment-emergent adverse events on intranasal dosing days** | | | | | | | |
| Total number of adverse events | 1,282 | 1,285 | 438 | 1,518 | 323 | 340 | 149 |
| Number of events on dosing days (%) | 1,144 (89) | 1,149 (89) | 312 (71) | 1,400 (92) | 212 (66) | 297 (87) | 96 (64) |
| Number of events resolved on same day (%)[b] | 1,047 (92) | 1,079 (94) | 254 (81) | 1,312 (94) | 180 (85) | 255 (86) | 56 (58) |

ESK = esketamine

[a] Safety set.

[b] Denominator for calculating percentages was the number of events on dosing days.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] and Study TRD3005.[7]

## Table 56: Summary of Harms for Transferred-Entry Patients on Placebo in Study TRD3003

| | Optimization phase | Maintenance phase | Follow-up phase |
|---|---|---|---|
| TRD3003[a] | Placebo n = 86 | Placebo n = 54 | Placebo n = 64 |
| **Patients with ≥ 1 adverse event** | | | |
| n (%) | 53 (62) | 37 (69) | 5 (8) |
| Most common adverse events[b], n (%) | | | |
| Viral upper respiratory tract infection | NR | 13 (24) | 0 |
| Dysgeusia | 8 (9) | 8 (15) | NR |
| Headache | 16 (19) | 12 (22) | 0 |
| **Patients with ≥ 1 SAE** | | | |
| n (%) | 0 | 1 (2) | 0 |
| Description | NA | Clavicle fracture | NA |
| **Death** | | | |
| n (%) | 0 | 0 | 0 |
| **Patients who stopped intranasal study drug due to adverse events** | | | |
| n (%) | 0 | 2 (4) | 0 |
| Description | NA | Blood pressure increased, rash, nail infection | NA |
| **Patients who stopped oral antidepressant due to adverse events** | | | |
| n (%) | 0 | 1 (2) | 0 |
| Description | NA | Rash, nail infection | NA |
| **Notable harms** | | | |
| Suicidality, n (%) | 1 (1) | 0 | 0 |
| TEAE suggestive of abuse, n (%) | NR | NR | 1 (2) |

NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Safety population.

[b] Frequency of 10% or greater.

Source: Clinical Study Report for Study TRD3003.[9]

## Table 57: Summary of Adverse Events for Follow-Up Phase of Included Studies

| TRD3003[a] | TRD3001 | | | TRD3002 | | TRD3005 | | TRD3003 |
|---|---|---|---|---|---|---|---|---|
| | ESK 56 mg N = 47 | ESK 84 mg N = 52 | Placebo N = 69 | ESK N = 34 | Placebo N = 52 | ESK N = 12 | Placebo N = 3 | ESK N = 481 |
| **Patients with ≥ 1 adverse event** | | | | | | | | |
| n (%) | 14 (30) | 15 (29) | 26 (38) | 9 (27) | 12 (23) | 1 (8) | 1 (33) | 53 (11) |
| **Patients with ≥ 1 SAE** | | | | | | | | |
| Follow-up phase, n (%) | 2 (4) | 2 (4) | 1 (1) | 1 (3) | 0 | 0 | 0 | 3 (0.6) |
| Description | depression | Insomnia, anxiety, depression | Suicidal ideation | Cerebral hemorrhage | — | — | — | Chest pain, intervertebral disc protrusion, depression, and mania |
| **Death** | | | | | | | | |
| n (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Patients who stopped oral antidepressant due to adverse events** | | | | | | | | |
| n (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Notable harms** | | | | | | | | |
| Suicidality, n (%) | 0 | 1 (2) | 3 (4) | 0 | 0 | 0 | 0 | 3 (0.6) |
| TEAE suggestive of abuse, n (%) | 0 | 1 (2) | 1 (1) | 1 (3) | 2 (4) | 0 | 0 | 1 (0.2) |

ESK = esketamine; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Safety population.

Source: Clinical Study Reports for Study TRD3001,[5] Study TRD3002,[6] Study TRD3005,[7] and Study TRD3003.[9]

# Appendix 4: Description and Appraisal of Outcome Measures

## Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MCID):

- MADRS total score
  - response and remission (defined by MADRS score)
  - relapse (defined as MADRS ≥ 22 in patients who had previously achieved remission or response, or hospitalization for worsening depression)
- SDS
- EQ-5D-5L (index score and VAS)
- PHQ-9 total score
- C-SSRS.

## Findings

### Table 58: Summary of Outcome Measures and Their Measurement Properties

| Outcome measure | Type | Conclusions about measurement properties | MCID |
|---|---|---|---|
| MADRS | MADRS assesses depressive symptomology, particularly change in patients treated with antidepressants. This scale is clinician-rated and consists of 10 items. Each item is rated on a scale of 0 to 6, resulting in a maximum total score of 60 points, in which higher scores are indicative of greater depressive symptomology. | Reliability and validity have been demonstrated in patients with MDD | ≥ 2 points |
| SDS | The SDS is a short, 3-item self-reported measure developed to assess the functional impact and associated disability in patients with psychiatric disorders. Each of the items is scored on a scale of 1 to 10; higher scores indicate more severe impairment. The items may also be summed into a total measure of global impairment, ranging from 0 to 30 points. | Reliability and validity have been evaluated in patients with psychiatric disorders including MDD | Unspecified |
| EQ-5D-5L | EQ-5D-5L is a generic, preference-based measure of HRQoL. | Reliability and validity have been demonstrated in patients with MDD | Canadian population: 0.037 for the health state index score |
| PHQ-9 | The PHQ-9 is a 9-item self-reported measure of depressive symptoms. Each item is rated on a scale of 0 to 3, resulting in a maximum total score of 27 points, in which higher scores indicating | Reliability and validity as a screening tool for depressive disorder as well as grading depressive symptom severity | Unspecified |

| Outcome measure | Type | Conclusions about measurement properties | MCID |
|---|---|---|---|
| | greater severity of depressive symptoms. | have been demonstrated in patients with MDD | |
| C-SSRS | The C-SSRS is an interview-based measure of suicidal ideation and behaviour with 4 subscales (ideation severity, ideation intensity, behaviour, and lethality). The items on each subscale are rated on 3- to 6-point ordinal scales or a nominal scale. Higher total score indicates a higher level of suicidality. | Validity of this scale has been demonstrated in adolescents with MDD | Unspecified |

C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HRQoL = health-related quality of life; MADRS = Montgomery-Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9; SDS = Sheehan Disability Scale.

### Montgomery-Åsberg Depression Rating Scale

The MADRS is a clinician-rated, 10-item scale used to measure depression severity and detect changes due to antidepressant treatment.[51,52] It is commonly used in antidepressant efficacy trials.[53] The 10 items included in the MADRS are[51]:

- apparent sadness
- reported sadness
- inner tension
- reduced sleep
- reduced appetite
- concentration difficulties
- lassitude
- inability to feel
- pessimistic thoughts
- suicidal thoughts.

Each item is rated on a 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms) scale, resulting in a maximum total score of 60 points, in which higher scores are indicative of greater depressive symptomology.[51] The MADRS scoring instructions indicate that a total score ranging from 0 to 6 indicates that the patient is in the reference range (no depression), 7 to 19 indicates “mild depression,” 20 to 34 indicates “moderate depression,” and a scores of 35 and greater indicate “severe depression.”[54] There is evidence to support that an improvement of 2 points or more on the MADRS is considered clinically relevant.[55,56]

The psychometric properties of the MADRS scale have been evaluated in numerous studies and compared to those of other scales, such as the 17-item Hamilton Depression Rating Scale (HAM-D17). The MADRS has high internal consistency, and slightly higher than that of the HAM-D17.[57] The clinician inter-rater reliability of this scale was also acceptable on individual items as well as the total score.[58] With respect to its content validity, most of the items are highly related to the core concept of depression. However,

similar to the HAM-D17, not all of the core criteria symptoms used in the *DSM-5* are assessed by the MADRS and therefore neither scale is completely adequate to define the severity of depression or remission.[57] There is a high degree of correlation between scores of the MADRS and other measures, such as the HAM-D17 and the 6-item Hamilton Depression Rating Scale, thereby showing good convergent validity.[57,59,60] The MADRS has also shown high ability to discriminate between various levels of depression severity.[57] Studies have repeatedly found the MADRS to have greater sensitivity to treatment-related change compared to the HAM-D17,[58,60-62] however at least 1 study involving patients with MDD found its sensitivity to be lower than that of the HAM-D17.[63] This high capability of the MADRS to detect change in patients' conditions over time may be related to its more uniform structure compared to the HAM-D17.[64] Overall, the MADRS has been found to have sound psychometric properties and be at least comparable to, if not somewhat exceeding, the HAM-D17 on certain psychometric aspects.

Response to treatment is usually defined as at least 50% reduction of the MADRS total score from baseline.[37] No consensus has emerged regarding a cut-off value on the MADRS for defining remission in clinical trials.[40] Criterion scores to identify patients who have experienced remission have ranged from 6 through 12 in various trials.[37,38] However, 1 recent study which set out to establish an empirically based cut-off for remission concluded that, based on a narrow definition of remission, the optimal MADRS cut-off was 4 points or less. On the basis of a less conservative definition of remission, the recommended cut-off was 9 points or less.[40] There is evidence to support that a MADRS score of less than 10 is a valid cut point for remission.[39]

### Sheehan Disability Scale

The SDS is a short, 3-item self-reported measure developed to assess the functional impact and associated disability in patients with psychiatric disorders.[65,66]

The 3 items assess disruption of work or school, social life, and family life or home responsibilities. Each item is scored on a 1 to 10 scale, where 0 indicates no impairment, 1 to 3 mild impairment, 4 to 6 moderate impairment, 7 to 9 marked impairment, and 10 extreme impairment. Scores exceeding 5 points on any of the items are indicative of functional impairment and heightened risk of mental disorder.[65] The items may also be summed into a total measure of global impairment, ranging from 0 to 30 points.[65] The SDS also has 1 item on days lost from school or work and 1 item on days when underproductive. There is some evidence that the SDS is a sensitive measure of disability for patients with psychiatric disorders in primary care. The sensitivity and specificity of SDS in patients with any of the 6 mental disorders (alcohol dependence, drug dependence, general anxiety disorder, MDD, obsessive-compulsive disorder, and panic disorder) were reported to be 83% and 69%, respectively.[67] One study evaluated this scale in a sample of 1,001 primary care psychiatric patients (proportion of patients with MDD was not specified in this study) and found that an higher score (≥ 5) was associated with an increased risk of psychiatric impairment.[68] Also, more than 80% of patients with a diagnosis of a mental disorder were shown to have an elevated SDS score. The internal consistency reliability of the SDS was high (coefficient alpha = 0.89).[68] An MCID of the SDS score has not been specified.

### EuroQol 5-Dimensions 5-Levels Questionnaire

The EQ-5D-5L was developed by the EuroQol Group as an improvement to the EQ-5D-3L to measure small and medium health changes and reduce ceiling effects.[31,32,69] The instrument is comprised of 5 dimensions: mobility, self-care, usual activities, pain or

discomfort, and anxiety or depression. Each dimension is rated on 5 levels: level 1 “no problems,” level 2 “slight problems,” level 3 “moderate problems,” level 4 “severe problems,” and level 5 “extreme problems” or “unable to perform.”[31,32,69] A total of 3,125 unique health states are possible, with 55,555 representing the worst health state and 11,111 representing the best state. The corresponding scoring of EQ-5D-5L health states is based on a scoring algorithm that is derived from preference data obtained from interviews using choice-based techniques (e.g., time trade-off) and discrete choice experiment tasks.[31,32,69] The lowest and highest score varies depending on the scoring algorithm used. The anchors are 0 (dead) and 1 (full health), however negative values are also allowed to represent health states that a population considers worse than death. As an example, a Canadian scoring algorithm results in a score of –0.148 for health state 55,555 (worst health state) and a score of 0.949 for health state 11,111 (best health state).[31,32,69] Another component of the EQ-5D-5L is a visual analogue scale (EQ VAS), which asks respondents to rate their health on a visual scale from 0 (worst health imaginable) to 100 (best health imaginable).[31,32,69]

Richardson et al. examined various instruments, including the EQ-5D-5L, in respondents who were healthy and who had a chronic disease (e.g., arthritis, asthma, cancer, depression, diabetes, hearing loss, and heart disease) through an online survey in Australia, Canada, Germany, Norway, the UK, and the US.[70] For discriminant validity, the mean EQ-5D-5L differed between healthy respondents and respondents with a chronic disease (0.88 in healthy and range of 0.09 to 0.29 in chronic disease). For construct validity, the EQ-5D-5L was strongly correlated with the physical component of the Short Form (36) Health Survey (average across all disease states, r = 0.66), moderately correlated with the psychosocial content of the mental component of the Short Form (36) Health Survey, the Capabilities Instrument, and the Subjective Well-Being Instrument of the UK Office of National Statistics (average across all disease states, r = 0.48), and moderately correlated with preference measures of VAS and time trade-off on own health state (average across all disease states, r = 0.43). A Spanish version of EQ-5D-5L was validated in 433 patients with MDD.[71] Reliability of this instrument was evaluated (Cronbach alpha coefficient = 0.77). Convergent validity of EQ-5D-5L was examined and the Spearman correlation coefficient between the EQ-5D-5L index and Beck Depression Inventory (BDI)-II was –0.58. In addition, patients with more severe conditions had statistically significantly lower index scores on the EQ-5D-5L ($P < 0.0001$).

McClure et al. obtained MCIDs for the EQ-5D-5L by calculating the average absolute difference between the index score of the baseline health state and the index score of all single-level transitions from the baseline state.[31,32,69] A single-level transition was defined as a change in a single dimension to the next worse/better level, while holding all other dimensions constant. Such single-level transitions across all 3,125 health states were averaged to arrive at MCIDs for various countries, by applying country-specific scoring algorithms. For Canada, transitions between levels 3 and 4 were excluded from the average to form a constant distribution of MCID values across the range of baseline scores. This analysis resulted in a Canadian-specific MCID of 0.037.[31,32,69] An MCID of the EQ-5D-5L was not identified in patients with MDD or treatment-resistant depression.

### Patient Health Questionnaire-9

The PHQ-9 is a 9-item, patient-reported scale that is used to assess depressive symptoms over the previous 2 weeks. It can be used as a tool for both depressive disorder screening as well as grading depressive symptom severity, which may be useful in measuring the

response to antidepressive treatment.[33,72] The scale scores each of the following 9 symptom domains of the MDD criteria[33]:

- little interest or pleasure in doing things
- feeling down, depressed, or hopeless
- trouble falling or staying asleep, or sleeping too much
- feeling tired or having little energy
- poor appetite or overeating
- feeling bad about yourself or that you are a failure or have let yourself or your family down
- trouble concentrating on things, such as reading the newspaper or watching televisions
- moving or speaking so slowly that other people could have noticed? Or so fidgety or restless that you have been moving a lot more than usual?
- thoughts that you would be better off dead, or thoughts of hurting yourself in some way.

Each item is rated on a 4-point scale, where 0 indicates "not at all," 1 indicates "several days," 2 indicates "more than half the days," and 3 indicates "nearly every day." The patient's responses are summed to provide a total score ranging from 0 to 27 with higher scores indicating greater severity of depressive symptoms.[72] In the pivotal study (TRANSFORM-2), by using the PHQ-9 score, the severity of depression was defined as: none to minimal (0 to 4), mild (5 to 9), moderate (10 to 14), moderately severe (15 to 19), and severe (20 to 27).[6]

The validity and reliability of PHQ-9 as a screening tool for depression have been evaluated in patients with different underlying diseases, such as multiple sclerosis, migraine, and cardiovascular disease. The suggested cut-off point for MDD screening ranged from 7 to 11.[73-76] In a sample of a Canadian working population (N = 4,289), with a threshold of 10, PHQ-9 had a sensitivity of 51.6% and specificity of 92.6% among the study population, indicating a relatively high level of discrimination.[77] Different versions of PHQ-9 have been validated in various countries. In 782 Chinese patients with acute coronary syndrome, the reliability and criterion validity of PHQ-9 used as a screening tool for MDD were assessed. The results showed that the diagnostic accuracy of PHQ-9 was moderate with area under receiver operating characteristics curve of 0.842 (95% CI, 0.806 to 0.894), and the optimal cut-off points of PHQ-9 for screening MDD was 10. Sensitivity and specificity in this population were 86.9% and 84.7%, respectively.[76] The validity of the PHQ-9 as a brief measure of depression severity was examined in approximately 3,000 primary care patients and 3,000 obstetrics and gynecology patients in the US.[33] Criterion validity of this scale was demonstrated in a subset of 580 primary care patients who underwent an interview by a mental health professional. A patient with MDD was 6 times more likely than a patient without MDD to have a PHQ-9 score of 9 or greater and 13.6 times more likely to have a score of 15 or greater. Construct validity was established by the association between PHQ-9 scores and functional status (measured with SF-20), disability days, and symptom-related difficulty. When PHQ-9 depression severity increased, there was a substantial decrease in SF-20 scores and increases in symptom-related difficulty, sick days, and health care utilization. In the same study, external validity was achieved by replicating the findings from the 3,000 primary care patients in a second sample of 3,000 obstetrics and gynecology patients. In Argentina, validation and calibration of the PHQ-9 was performed in a sample of adult ambulatory care patients (N = 169) with different degrees of severity of depression.[78]

For the diagnosis of MDD, a PHQ-9 score of 8 or greater was associated with a sensitivity of 88.2% and specificity of 86.6%. The best cut-off points were 6 to 8 for mild, 9 to 14 for moderate, and 15 or greater for severe depressive symptoms, respectively. An MCID for PHQ-9 in patients with MDD or treatment-resistant depression has not been identified.

### Columbia-Suicide Severity Rating Scale

The C-SSRS is an interview-based assessment tool for evaluating suicidal ideation and behaviour.[79] It was developed to monitor changes in suicidality over time by incorporating assessments of lifetime suicidal ideation and behaviour as well as between-visit changes. The C-SSRS has 4 subscales: severity of ideation (e.g., specificity of suicidal thoughts or intent with methods or plans), intensity of ideation (e.g., frequency and duration of suicidal thoughts), behaviour (e.g., preparatory actions, suicide attempts, and non-suicidal injurious behaviour), and lethality (assessment of actual suicide attempts — actual lethality is rated on a 6-point ordinal scale, and if actual lethality is 0, potential lethality of attempts is rated on a 3-point ordinal scale). The items on the ideation and lethality subscales are rated on 3- to 6-point ordinal scales, and the behaviour subscale uses a nominal scale. A higher total score indicates a higher level of suicidality.

The psychometric properties of the C-SSRS were assessed in 3 studies that were presented in 1 publication. Study 1 included adolescents who had previously attempted suicide, Study 2 involved adolescents with a diagnosis of MDD, and Study 3 was conducted in adult patients who presented to the emergency department for psychiatric reasons.[79] The intensity of ideation subscale demonstrated moderate to high internal consistency in all 3 studies. In support of convergent validity, the suicidal ideation and behaviour subscales on the C-SSRS correlated moderately to strongly with the corresponding suicide-related items on the MADRS and BDI, as well as with the Scale for Suicide Ideation and the Columbia-Suicide History Form in studies 1 and 3. Further analysis in studies 1 and 2 showed that the change in the severity and intensity of ideation subscale scores over time significantly corresponded with Scale for Suicide Ideation or Suicidal Ideation Questionnaire–Junior score changes. Similarly, the classification of suicidal behaviours on the C-SSRS over time in Study 1 demonstrated moderate to full agreement with the classification of the same behaviour using the Columbia Suicide History Form. The divergent validity of the C-SSRS severity and intensity of ideation subscales was analyzed in Study 1, and a weak to moderate correlation between these subscales and somatic depression items on the BDI and the MADRS was observed; however, this study population did not include adults with MDD.[79]

An MCID was not reported for the C-SSRS; however, predictive validity was examined in 2 studies. For each increase in C-SSRS level of lifetime suicidal ideation by 1 SD in an adolescent population, the odds of attempting suicide during the 24-week study increased by 45%.[79] A validation study of the electronic version of the C-SSRS evaluated an existing set of assessments extracted from multiple studies in which the majority (91%) of total patients had MDD, and demonstrated that patients who reported severe lifetime suicidal ideation or a history of suicidal behaviour at baseline were up to 9 times more likely to report suicidal behaviour during their study participation.[80]

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