Janssen Research & Development, LLC

Advisory Committee Briefing Document

Esketamine Nasal Spray for Patients with Treatment-resistant Depression

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GUIDE FOR REVIEWERS

This briefing document provides 3 levels of review with increasing levels of detail:

- The Executive Overview (Section 1, starting on page 11) provides a narrative summarizing the disease, need for novel treatments, key development program characteristics for esketamine nasal spray, study results, and conclusions. References are made to the respective supporting sections in the core document.
- The core document (Section 2 to Section 11, starting on page 30) includes detailed summaries and discussion in support of the Executive Overview.
- The appendices (starting on page 180) provide additional or more detailed information to complement brief descriptions provided in sections of the core document (e.g., demographic and baseline characteristics of the study populations, additional efficacy analyses in the Phase 3 studies, statistical methods). These appendices are referenced in the core document when relevant.

This review structure allows review at varying levels of detail; however, reviewers who read at multiple levels will necessarily encounter repetition of key material across the levels.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	antidepressant
ADR	adverse drug reaction
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANCOVA	analysis of covariance
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
C_{max}	maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CI	confidence interval
CIOMS	Council for International Organization of Medical Sciences
CYP	cytochrome P450
DEA	Drug Enforcement Administration
ECG	electrocardiogram
FDA	Food and Drug Administration
GABA	γ-amino butyric acid
ICH	International Conference on Harmonization
IM	intramuscular
IND	Investigational New Drug
IV	intravenous
LOCF	last observation carried forward
LS	least squares
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MMRM	mixed-effects model using repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NDA	New Drug Application
NMDA	N-methyl-D-aspartate
OATP	organic anion transport polypeptide
PHQ-9	9-Item Patient Health Questionnaire
P-gp	P-glycoprotein
PWC-20	20-Item Physician Withdrawal Checklist
QTc	corrected QT interval
QTcF	QT interval corrected by Fridericia's equation
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance System
REMS	Risk Evaluation and Mitigation Strategy
SDLP	standard deviation of the lateral position
SDS	Sheehan Disability Scale
SE	standard error
SIGMA	structured interview guide for the Montgomery-Asberg Depression Rating Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
US	United States
USPI	United States Prescribing Information

1. EXECUTIVE OVERVIEW

1.1. Introduction

Esketamine nasal spray is a novel product developed by Janssen Research & Development (the Sponsor) for the indication of treatment-resistant depression (TRD). While several definitions of TRD are used in clinical practice, world health authorities, including the Food and Drug Administration (FDA) and the European Medicines Agency, define patients with TRD as individuals with major depressive disorder (MDD) who have not responded to at least 2 different antidepressant treatments given at an adequate dose for an adequate duration in the current episode of depression. This definition is used in the Sponsor's clinical development program for esketamine nasal spray.

The TRD population suffers disproportionately from the morbidity and mortality associated with depression, and many patients do not experience relief from depressive symptoms after treatment with existing antidepressant medications.

Several small clinical studies and case reports in patients with major depression have suggested that intravenous (IV) ketamine, which directly interacts with glutamatergic receptors in the brain, has antidepressant activity observed within hours to days after administration.[9,27,65,118] however, there has been no comprehensive assessment of its short- and long-term efficacy, tolerability, and safety in patients with depression.

The Sponsor developed esketamine (the S-enantiomer of racemic ketamine) specifically for the treatment of depression. In 2013, esketamine nasal spray was granted Breakthrough Therapy Designation for the TRD development program, which was designed in consultation with the FDA. A crucial difference in the design of this program relative to traditional oral antidepressant drug development programs was FDA's requirement for both short-term and maintenance studies. Unlike oral antidepressants, which typically have the same dosing regimen for short-term and long-term use, for esketamine it was uncertain whether long-term treatment would be necessary as it was hypothesized that the antidepressant effect following short-term esketamine treatment could be maintained with an oral antidepressant alone. Alternatively, some patients might require a reduced esketamine dosing frequency to maintain the antidepressant effect following short-term treatment.

The safety and efficacy of esketamine nasal spray are supported by 19 Phase 1, 4 Phase 2 and 5 Phase 3 clinical studies. The totality of evidence from these studies demonstrates that esketamine provides clinically meaningful, rapid, and sustained improvement in depressive symptoms for this population. The efficacy results, combined with a well-characterized safety profile and comprehensive risk mitigation program, highlight the potential for esketamine to improve the treatment landscape for adult patients suffering from TRD.

Unmet Medical Need

Major depressive disorder is recognized as a leading cause of disability globally.[116] Despite the availability of numerous antidepressant therapies, approximately one-third of patients with MDD

do not experience adequate relief of depressive symptoms after treatment with multiple therapies[88] and are considered to have TRD.

Treatment-resistant depression has a significant impact on the lives of individual patients and their families. The disease limits the quality and length of life for affected patients. Those suffering from TRD have a 7-fold higher suicide rate,[38] lower remission rates,[88] pronounced functional impairment, and a substantially lower quality of life,[28] as well as higher medical and mental healthcare costs,[3] compared to patients with MDD who respond to antidepressant treatment.

For the majority of patients with TRD, treatment with existing antidepressant medications fails to result in remission from depressive symptoms. Current approaches include trials of therapies based on modulating the monoaminergic system that often do not provide adequate symptom relief, electroconvulsive therapy, which has considerable limitations in patient acceptability and access, or experimental therapies such as deep brain stimulation, which recently did not show significant benefit in clinical trials.[31]

Furthermore, even when patients with TRD do respond or remit during trials of new pharmacotherapeutic regimens, the durability of their response/remission is less than that observed in patients with MDD who do not meet the TRD criteria. For example, in the largest study to examine this issue, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the relapse rates for patients with TRD (who did not respond to treatment steps 1 and 2 but did respond to treatments step 3 or 4) were much higher than the rates for those with MDD who had not demonstrated treatment resistance (i.e., who responded to treatment steps 1 or 2).[88] Thus, there is a substantial need to develop innovative treatments for the rapid and sustained relief of depressive symptoms in patients with TRD.

Mechanism of Action

Systems that regulate synaptic connectivity, including the glutamate system, have become promising areas of research in the search for novel antidepressant agents after several small studies suggested that IV ketamine has rapid antidepressant activity at low doses that did not induce anesthesia. [9,27,65,118] Ketamine is currently approved in the US for inducing and maintaining anesthesia via IV infusion or intramuscular (IM) injection; however, ketamine is not indicated for use in MDD, including TRD.

Ketamine is a racemic mixture of 2 enantiomers: esketamine (S-ketamine) and arketamine (R-ketamine). While ketamine, esketamine, and arketamine are glutamate receptor modulators – more specifically, N-methyl-D-aspartate (NMDA) receptor antagonists – esketamine has 1.5- to 4-fold greater potency at the NMDA receptor than either ketamine or arketamine.[4,35,50,68]

By blocking NMDA receptors, ketamine and esketamine are hypothesized to increase neurotrophic signaling that restores synaptic function. Pharmacology data provide evidence that esketamine and ketamine inhibit NMDA receptors in the dose range shown to elicit antidepressant effects in clinical studies. Unlike most of the existing therapies, esketamine and ketamine do not directly affect the function of receptors and/or transporters of serotonin,

norepinephrine, γ-amino butyric acid (GABA), or opioid peptide systems.[13,19,22,34,39,40,41,45,46,50,53,62,68,79,92,100,117] See Section 2.2 for further information.

Proposed Product Use

The Sponsor conducted a systematic program to evaluate the efficacy and safety of esketamine nasal spray for the following proposed indication:

> *treatment-resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode)*

Esketamine will be flexibly dosed; the recommended doses are 56 and 84 mg. During the first 4 weeks of treatment (induction phase), the recommended dosing frequency is twice weekly, and subsequently during the maintenance phase, the dosing frequency is reduced to once weekly or once every other week. Esketamine nasal spray will be administered by the patient under the supervision of a healthcare professional and should be administered in conjunction with an oral antidepressant.

Clinical Development Program

The Sponsor's New Drug Application (NDA) contains data from 19 Phase 1, 4 Phase 2 and 5 Phase 3 clinical studies, which are summarized in this document.

To measure the severity of depressive symptoms and changes in severity with treatment, the Sponsor used the Montgomery-Asberg Depression Rating Scale (MADRS) as the primary assessment of efficacy in the clinical development program. The MADRS is a clinician-reported outcome tool widely used for primary outcome measures in MDD clinical trials[69] and accepted by regulatory agencies.[23,110] The scale consists of 10 items corresponding to the core symptoms of depression: apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 to 6 for a total possible score of 60; higher scores represent a more severe condition. In the Sponsor's clinical development program, the severity of depressive symptoms based on MADRS total score was defined as follows: no symptoms: ≤12; mild depression: 13-27; moderate depression: 28-34; severe depression: ≥35. Individuals with a MADRS total score of 12 or less were considered to be in remission, and those with more than 50% improvement from baseline in MADRS total score were considered to have responded to treatment. (see Section 7.1 for additional information).

To provide context for review of the data presented in the remainder of the document, several features of the Phase 3 clinical study design merit comment:

- Requirement to demonstrate both short-term efficacy and long-term maintenance of effect: For typical antidepressants (e.g., selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors), FDA generally requires two adequate and well-controlled (pivotal) short-term Phase 3 studies which reach statistical significance for initial approval; a long-term maintenance of effect study is usually a postmarketing commitment. Numerous short-term studies with esketamine and ketamine alike have demonstrated rapid onset of efficacy in patients with MDD and TRD. As discussed with FDA during design of the Phase 3 clinical program, a fundamental question to be answered in the program was whether and how the antidepressant effect may be sustained to treat a chronic relapsing illness. This specific aim necessitated conducting a maintenance study to determine if continued esketamine administration was needed to sustain improvement during long-term care or if the initial response to esketamine instead could be maintained with an oral antidepressant alone after discontinuation of esketamine. In addition, if long-term esketamine use was necessary to sustain improvement, a second critical aim involved establishing a dose and minimum dosing frequency that could sustain the antidepressant effects during maintenance treatment.

  Given the importance of maintenance of effect data with this novel treatment, FDA stated that one positive, adequate and well-controlled short-term study and one positive, adequate and well-controlled maintenance of effect study (along with the requisite safety data to meet International Conference on Harmonization requirements) would be sufficient to support an NDA submission. Thus, the 2 pivotal Phase 3 studies in the clinical development program which reached statistical significance and form the foundation of the NDA were: (1) TRANSFORM-2, the short-term flexible-dose study and (2) SUSTAIN-1, the maintenance of effect study (Section 2.3.2). Supportive evidence of the efficacy and safety of esketamine from the other completed Phase 3 studies and from additional Phase 2 studies that reached statistical significance is also presented.

- Co-administration of esketamine with a newly-initiated oral antidepressant: The Sponsor and FDA agreed that nasally-administered study medication (esketamine or placebo) was to be given concurrently with a newly-initiated oral antidepressant (AD), referred to as new AD control, in the Phase 3 studies. Therefore, these studies did not use either an inactive comparator (i.e., placebo) only design or a classical adjunctive (add-on) design. Instead, the new oral AD was incorporated into both study arms to determine whether, among patients with confirmed stable remission/stable response to initial esketamine + oral AD therapy, treatment with esketamine could be stopped and longer-term maintenance achieved with the oral AD alone. The use of a newly-initiated oral AD (instead of one to which patients had previously not responded) was thought to provide patients a greater likelihood of achieving sustained improvement following discontinuation of esketamine. Furthermore, initiating a new AD, instead of continuing a failed medication to which the patient had demonstrated no clinically meaningful response, ensured that all patients in the Phase 3 studies received a clinically optimized AD treatment, consistent with international clinical treatment recommendations for MDD to replace an ineffective therapy with a different agent. [2,8,21,51,77] This unique aspect of the program is important to consider when interpreting the results.

- Blinding: Several measures were implemented in the Phase 3 studies to achieve and maintain blinding:

  - Placebo nasal spray: The control treatment in all Phase 3 studies included a placebo nasal spray. A bittering agent was added to the placebo solution to facilitate blinding by simulating the taste of the esketamine solution.
  - Blinded, remote, independent assessment of efficacy: As esketamine has known transient dissociative effects (i.e., distortion of time and space, illusions, derealization, and depersonalization) that are difficult to blind and potentially could bias the research staff who observe these effects, the MADRS was performed prior to nasal spray dosing throughout the double-blind studies over the telephone by independent, blinded raters using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA); see Appendix 1.

- Dedicated study in older patients: Patients ≥65 years are generally included as part of Phase 3 study populations for typical antidepressant programs. However, the Sponsor conducted a dedicated short-term study in patients ≥65 to evaluate the efficacy and safety of esketamine in this vulnerable population.

Further details about the regulatory history of the product and the features of the clinical development program are provided in Sections 2.3.1 and 2.3.2.

1.2. Overview of Nonclinical Assessment

Results from nonclinical studies related to cardiovascular safety, general toxicity, neurotoxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity did not reveal particular safety concerns (Section 3). Nonclinical pharmacokinetics, distribution and metabolism were investigated as well. Although developmental neurotoxicity effects with intranasal esketamine were not demonstrated in animals, as a precaution the use of esketamine nasal spray during pregnancy is not recommended considering there are known developmental neurotoxicity findings for racemic ketamine in animals.

1.3. Overview of Clinical Pharmacology

Esketamine was selected for development over racemic ketamine because its higher potency towards the NMDA receptor allows for lower doses of esketamine to be administered, thus reducing the volumes of solution required for delivery from a nasal spray device improving overall tolerability of the nasal spray. The intranasal route of administration offers a non-invasive and more convenient dosing option for patients and physicians relative to IV administration. The physiology of the nasal mucosa facilitates rapid and appreciable absorption of esketamine. Furthermore, nasal absorption bypasses "first-pass" metabolism by the gut and liver and decreases the likelihood that esketamine will be affected by other coadministered drugs which alter the activity of hepatic cytochrome P450 (CYP) enzymes.

Pharmacokinetic and pharmacodynamic information relevant for esketamine nasal spray treatment were obtained after a single dose and twice-weekly administration in 19 Phase 1 studies, 3 Phase 2 studies, and 3 Phase 3 studies (Section 4). Results from these studies indicated that no adjustment of the esketamine dose is needed for body weight, gender, level of hepatic impairment, level of renal impairment, or presence of symptoms of allergic rhinitis.

Importantly, given the polypharmacy that characterizes the treatment regimens for MDD and TRD patients, no clinically relevant drug-drug interactions were observed. Adjustment of the nasal esketamine dose is not needed for patients being treated with an inhibitor of hepatic enzymes CYP2B6 or CYP3A, inducer of hepatic enzymes CYP3A and CYP2B6, intranasal corticosteroid, or intranasal decongestant. In addition, the pharmacokinetics of nasal esketamine is similar in patients with MDD being treated with an oral antidepressant and healthy participants.

1.4. Overview of Phase 2 Clinical Studies

Dose Information from Phase 2 Studies with IV Esketamine and Ketamine

Two initial Phase 2 studies using subanesthetic doses of IV formulations of esketamine (TRD2001) and ketamine (TRD2002) were conducted in patients with TRD to guide selection of dose and dosing frequency for the subsequent Phase 2 dose-response study of esketamine nasal spray.

- Study TRD2001 demonstrated that IV esketamine (0.2 and 0.4 mg/kg) provided rapid relief of depressive symptoms in patients with TRD. As there were no additional benefits for patients who received the higher dose, the circulating levels of esketamine at the 0.20 mg/kg dose were selected as the exposure target for further development of intranasally administered esketamine (Section 5.1).
- As single dose studies with IV ketamine suggested that weekly dosing may not be sufficient to maintain the antidepressant effects,[78,118] Study TRD2002 assessed whether IV ketamine administered at higher frequencies could sustain the antidepressant effects in patients with TRD. Administration of IV ketamine (0.5 mg/kg) either two or three times weekly similarly maintained antidepressant effects over 15 days; therefore, the lower dosing frequency (twice weekly) was selected for subsequent studies (Section 5.1).

Results from Phase 1 studies suggested that plasma esketamine concentrations produced by the 84-mg dose of intranasally administered esketamine would reliably achieve or exceed the concentrations produced by the 0.2-mg/kg infusion of IV esketamine. A range of doses of esketamine nasal spray was selected (i.e., 28, 56, and 84 mg) for subsequent Phase 2 studies to evaluate the dose-response relationship with respect to MADRS total score and other endpoints.

Phase 2 Dose-response Study with Esketamine Nasal Spray in Patients with TRD

The Phase 2 dose-response study SYNAPSE assessed 14-, 28-, 56-, and 84-mg doses of esketamine administered twice weekly. The doses of 28 to 84 mg were selected based on the results from previous Phase 2 and Phase 1 studies suggesting these doses would have antidepressant effects in patients with TRD. The 14-mg dose was included to evaluate if this dose could determine a minimally effective dose of esketamine. The change from baseline in the MADRS total score after 1 week of treatment was used to measure changes in depressive symptoms.

Improvements in depressive symptoms after 1 week of treatment in the 28-, 56-, and 84 mg esketamine dose groups were significantly greater than the improvement in the placebo group.

The 28-mg dose elicited the least improvement and appeared less able to sustain the improvements. The esketamine 14 mg dose was not efficacious after 1 week of treatment. Therefore, the 56-mg dose was considered the lowest efficacious dose.

Further information about this study is provided in Section 5.2.1.

Phase 2 Study with Esketamine Nasal Spray in Patients with MDD at Imminent Risk for Suicide

The Phase 2 study PERSEVERE in patients with MDD at imminent risk for suicide, a population related to TRD, was included in the NDA to provide further evidence for the rapid antidepressant effects of treatment with 84 mg of esketamine nasal spray. This study evaluated the efficacy of esketamine (84 mg) compared with placebo in improving the symptoms of MDD (including suicidal ideation) in patients who presented to an emergency room or other permitted setting and were assessed to be at imminent risk for suicide. As this proof-of-concept study was conducted in the context of a psychiatric emergency, the 84-mg dose was selected to provide patients the greatest opportunity for rapid onset of efficacy with the option to reduce the dose to 56 mg for tolerability.

Nasal spray study medication was administered twice weekly in addition to standard of care treatment (initiated or optimized antidepressant treatment and inpatient hospitalization). The primary efficacy endpoint was improvement in depressive symptoms (assessed by change in MADRS total score) from baseline to 4 hours after the initial dose of nasal spray.

A significantly greater improvement in MADRS total score was observed in the esketamine + standard of care group compared with the placebo + standard of care group at 4 hours after the first dose of study treatment and at Day 2, approximately 24 hours after the first dose. Further information is provided in Section 5.2.2.

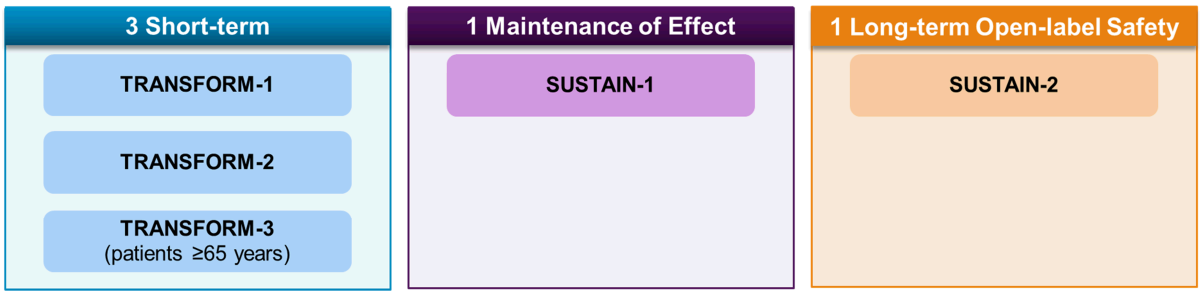
1.5. Overview of Phase 3 Study Design and Population

Five Phase 3 studies with esketamine nasal spray in adults with TRD were completed in the clinical development program (Figure 1).

- The efficacy and safety of esketamine, given concurrently with a newly-initiated oral AD were evaluated in 3 double-blind, controlled, short-term Phase 3 studies:
  - TRANSFORM-1 and 2 were conducted in patients 18 to 64 years of age.
  - TRANSFORM-3 was conducted only in patients ≥65 years of age, a population often underrepresented in clinical studies for treatments of MDD and rarely evaluated as the only population in a study with MDD patients.
- A fourth double-blind randomized withdrawal study, SUSTAIN-1, compared continued esketamine treatment with discontinuation of esketamine in delaying relapse among adults with TRD who had achieved stable remission or stable response after 16 weeks of treatment with esketamine plus an oral AD.

- A fifth open-label Phase 3 study, SUSTAIN-2 was designed to assess long-term safety and tolerability in adults with TRD.

Figure 1: Completed Phase 3 Studies in the TRD Clinical Development Program



Patients who participated in the 5 completed Phase 3 studies were eligible to continue treatment in an open-label safety extension study, SUSTAIN-3, which is currently ongoing.

All completed Phase 3 studies included a screening phase to assess eligibility and a 4-week induction phase with:

- Double-blind study treatment in the short-term studies (TRANSFORM-1, 2, and 3)
- Open-label study treatment in the long-term studies (SUSTAIN-1 and 2)

In SUSTAIN-1 and 2, optimization and maintenance phases followed the induction phase.

Study Treatments

- Esketamine nasal spray was administered at doses of 28 mg (patients ≥65 years only), 56 mg, or 84 mg. The 28-mg dose was used only for patients ≥65 years as a starting dose for improved tolerability and as an option for those not tolerating higher doses.
- Doses of esketamine nasal spray were administered intermittently: twice weekly during the induction phase with the dosing frequency subsequently reduced to once weekly or once every 2 weeks based on efficacy in the optimization and maintenance phases of the longer-term studies SUSTAIN 1 and 2.
- Nasally-administered study medication (esketamine or placebo) was given concurrently with a newly-initiated oral AD, dosed daily to the maximum dose recommended in the label for the oral AD.

Short-term Double-blind Studies

The designs for the three Phase 3 short-term double-blind studies (TRANSFORM-1, 2, and 3) were nearly identical, differing mainly in dosing regimen and age of the population. Mean baseline MADRS total scores ranged from 35.2 to 37.6 (MADRS total score ≥35 signals severe depression).

Patients who entered the double-blind induction phase discontinued their current AD medication and received treatment with a randomly assigned nasal spray study medication (esketamine or placebo, twice weekly) plus a new oral AD for 4 weeks.

Maintenance of Effect Study

The Phase 3 study SUSTAIN-1 used a randomized withdrawal design to assess the time to relapse in patients who had achieved stable remission (primary endpoint) or stable response (secondary endpoint) after 16 weeks of treatment with esketamine + oral AD. The time to relapse was compared between patients randomized to continue treatment with esketamine and those randomized to discontinue esketamine. The study was terminated when a sufficient number of relapses had occurred as determined by the Independent Data Monitoring Committee during an interim analysis.

Patients could have entered SUSTAIN-1 directly or transferred after participating in one of the short-term studies TRANSFORM-1 or 2. See Section 6.3 for further details.

Long-term Safety Study

The Phase 3 long-term, uncontrolled, open-label study SUSTAIN-2 was designed primarily to obtain longer-term data on safety. Special attention was given to addressing concerns in the literature about potential impaired cognition and symptoms of interstitial cystitis associated with high doses and chronic use of ketamine. The evaluation of long-term efficacy was a secondary objective.

The maximum duration of a patient's participation was 60 weeks. Patients could have entered SUSTAIN-2 directly or transferred after participating in the short-term study TRANSFORM-3. After achieving the required number of patients exposed to esketamine, the study was terminated.

1.6. Overview of Clinical Efficacy

Short-term Double-blind Phase 3 Studies

Statistical Analysis of the Primary Efficacy Endpoint

Key features of the statistical analysis for the short-term double-blind studies are described below, in Section 7.2, and Appendix 13.

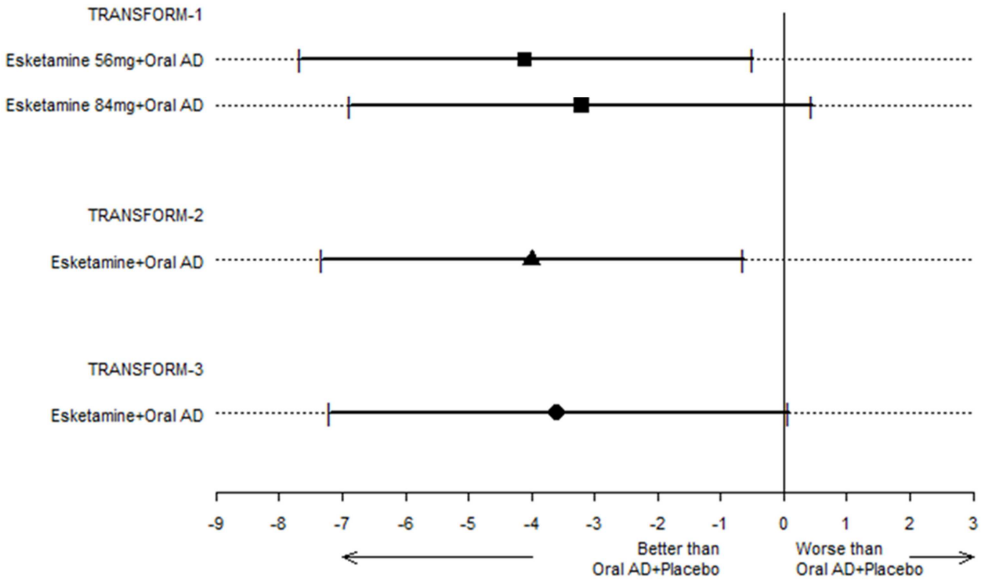
- The primary analysis set for all efficacy analyses in the short-term double-blind studies included all randomized patients who received at least 1 dose of nasal study medication and 1 dose of oral AD medication during the double-blind induction phase (referred to as the full analysis set).
- The primary efficacy variable, change from baseline in MADRS total score at Day 28, was analyzed based on a mixed-effects model using repeated measures (MMRM) on observed case data (based on an assumption of uninformative missingness).
- In TRANSFORM-1, for the primary endpoint, testing of the esketamine 56 mg dose group was conducted at the 2-sided 0.0425 level only if the 84-mg dose group was significant at the 2-sided 0.05 level.
- In TRANSFORM-2 and 3, testing of the primary endpoint was conducted using a 2-sided significance level of 0.05.

- TRANSFORM-1 and 3 included an interim analysis to re-estimate the sample size needed to achieve the desired power while maintaining control of the overall type I error rate or to stop the study for futility.

Primary Efficacy Endpoint: Change in MADRS Total Score from Baseline to Day 28

The improvements in depressive symptoms after 4 weeks of esketamine treatment were consistent across all 3 short-term Phase 3 studies (Figure 2), with statistically significant improvements demonstrated in the flexible-dose study TRANSFORM-2 (2-sided p=0.020). The mean treatment group difference for the primary endpoint ranged from -3.2 to -4.1 across studies, dose regimens, and analyses. These treatment differences are at least as large as the median treatment differences reported in controlled clinical studies of currently marketed antidepressants in patients with an inadequate response to previous AD therapy (e.g., quetiapine and aripiprazole) or in active comparator-controlled studies of the olanzapine-fluoxetine combination (Symbyax); see Appendix 5.

Figure 2: MADRS Total Score: Least-squares Mean Difference by MMRM (Observed Case) of Esketamine + Oral AD versus Oral AD + Placebo in Change From Baseline to Day 28 in TRANSFORM-1, 2, and 3 (Full Analysis Set)

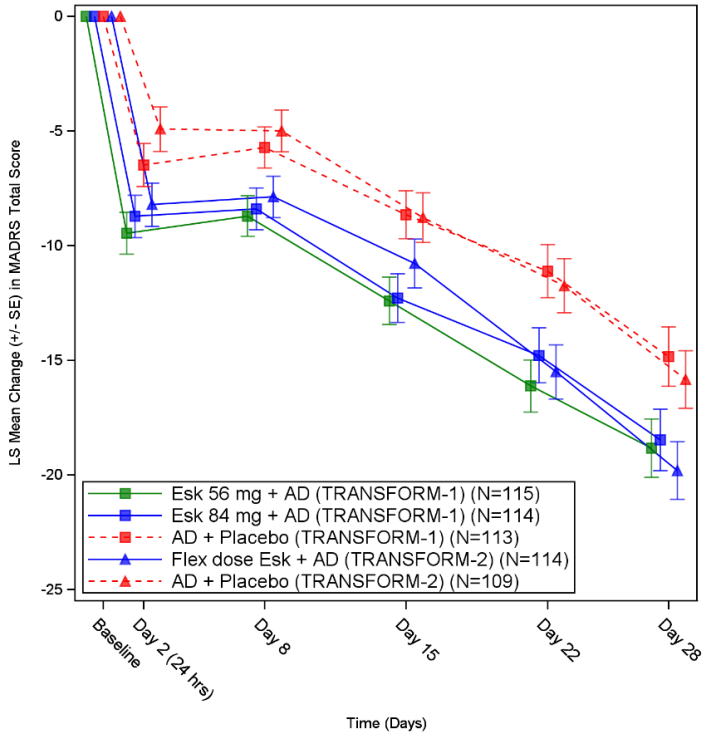


AD: antidepressant; LS: least-squares; MADRS: Montgomery-Asberg Depression Rating Scale; MMRM: mixed-effects model using repeated measures
Note: The graph shows the difference in LS means (with 95% CIs) for TRANSFORM-2, and the median unbiased estimates (with 95% CIs) of the differences between esketamine + oral AD and oral AD + placebo for TRANSFORM-1 and TRANSFORM-3. The LS means and median unbiased estimates are obtained from MMRM.

Change in MADRS Total Score Over Time in TRANSFORM-1 and 2

As shown in Figure 3, in TRANSFORM-1 and 2, the least squares mean changes in the MADRS total score over time showed a numerically larger improvement in clinician-rated depression symptoms relative to the oral AD + placebo group as early as 24 hours after the first dose of esketamine + oral AD (i.e., Day 2). This difference persisted in subsequent weeks until the full antidepressant effect was achieved at the end of the 4-week induction phase.

Figure 3: Least Squares Mean Changes (±SE) in MADRS Total Score Over Time Observed Case MMRM Double-blind Induction Phase (TRANSFORM-1 and 2: Full Analysis Set)



AD = antidepressant; Esk = esketamine; SE = standard error; LS = least-squares; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures
LS Mean and SE were based on MMRM fitted separately for each study with change from baseline as the response variable and the fixed effect model terms for treatment, day, region or country, class of oral antidepressant, and treatment-by-day, and baseline value as a covariate. Negative change in score indicates improvement.

Response and Remission Rates

To understand how the difference in MADRS total score is clinically meaningful, it is helpful to assess rates of response (substantial clinical improvement, defined as ≥50% improvement from baseline in depressive symptoms as measured by MADRS total score in the Phase 3 short-term studies) and rates of remission (substantial improvement leading to near absence of disease symptoms, defined as MADRS total score ≤12). At Day 28, response rates were 53% to 54% in both dose groups in TRANSFORM-1 versus 39% for oral AD + placebo, and 69% in the esketamine + oral AD group in TRANSFORM-2 versus 52% for oral AD + placebo. For patients 65 and older in TRANSFORM-3, the response rate at Day 28 was 27% in the esketamine + oral AD group versus 13% for oral AD + placebo. In the esketamine + oral AD groups, remission rates at Day 28 among patients 18-64 years of age were 36% to 39% in both dose groups of TRANSFORM-1 and 53% in TRANSFORM-2 versus 31% for the oral AD + placebo groups in both studies. For patients ≥65 years of age in TRANSFORM-3, remission rates were 17% in the esketamine + oral AD group versus 7% in the AD + placebo group. See further discussion in Section 7.3.1.1.

Maintenance of Effect Study

Statistical Analysis of the Primary Efficacy Endpoint

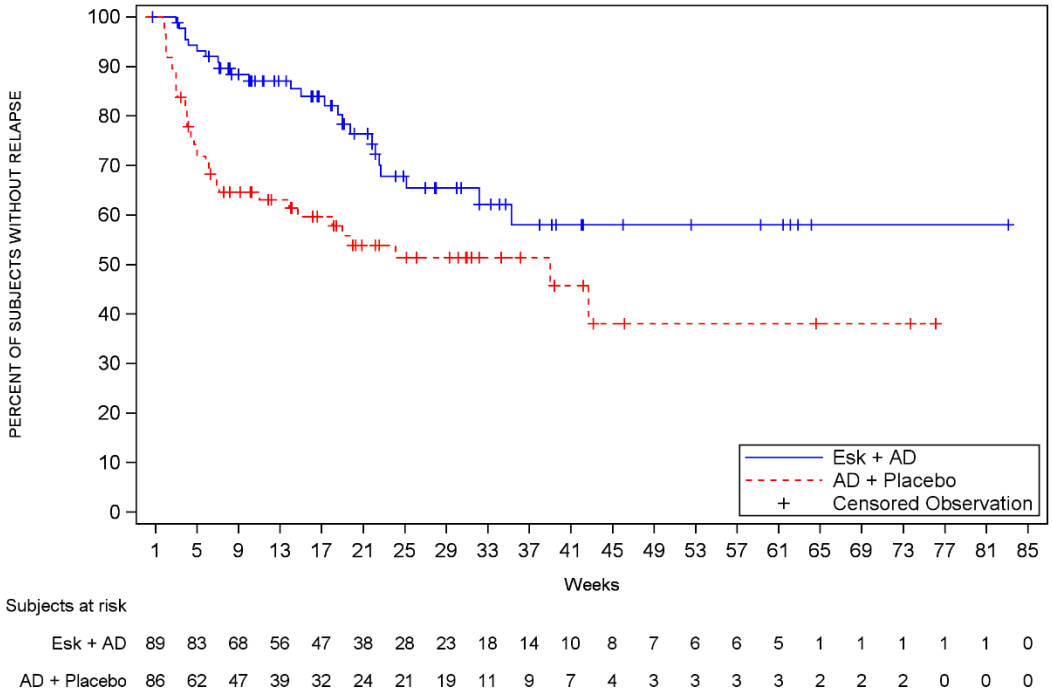
Key features of the statistical analysis in SUSTAIN-1 are described below, in Section 7.2 and Appendix 13. The analysis set used for analysis of the primary endpoint included all randomized patients who were in stable remission at the end of the optimization phase and who received at least 1 dose of nasal study medication and 1 dose of oral AD during the maintenance phase (the full [stable remitter] analysis set). The cumulative distribution function of the time to first relapse during the maintenance phase for esketamine-treated patients who achieved stable remission at the end of the optimization phase was estimated by the Kaplan-Meier method; time to first relapse was summarized and treatments were compared using the weighted log-rank test. The weighted estimate of the hazard ratio and its 95% confidence interval (CI) was based on the technique described in Wassmer.[114] SUSTAIN-1 was designed with an interim analysis that allowed early termination of the maintenance phase for efficacy or to re-estimate the sample size (i.e., required number of relapses in stable remitters).

Primary Efficacy Endpoint: Time to Relapse

In the full (stable remitters) analysis set, relapse events occurred during the maintenance phase for 26.7% of patients randomized to continue esketamine + oral AD treatment and 45.3% of patients randomized to discontinue esketamine and receive oral AD + placebo treatment. The estimated hazard ratio of esketamine + oral AD relative to oral AD + placebo based on weighted estimates was 0.49 (95% CI: 0.29; 0.84) (Section 7.3.2.1).

Kaplan-Meier curves of the time to relapse in the full (stable remitters) analysis set are presented for the 2 treatment groups in Figure 4. Based on the weighted combination log-rank test, the difference between treatment groups for the time to relapse was statistically significant (2-sided p=0.003).

Figure 4: Cumulative Proportion (Kaplan-Meier Estimates) of Stable Remitter Patients Who Remained Relapse Free During the Maintenance Phase of SUSTAIN-1



AD = antidepressant; Esk = esketamine.
Note: The data represent the full (stable remitters) analysis set, which included 175 stable remitters and 1 stable responder (who was incorrectly randomized as a stable remitter).

1.7. Overview of Clinical Safety

The safety assessment is based on data from the 6 completed Phase 2 and 3 studies in patients with TRD (SYNAPSE; TRANSFORM-1, 2 and 3; SUSTAIN-1 and 2), the ongoing Phase 3 open-label safety extension study in patients with TRD (SUSTAIN-3) through a clinical cutoff date of 04 March 2018, and the completed Phase 2 study in the related population of patients with MDD at imminent risk for suicide (PERSEVERE).

Extent of Exposure in Phase 2 and 3 Clinical Studies

- A total of 1861 unique patients were treated with esketamine (1045 patient-years of exposure) in the completed and ongoing Phase 2 and 3 TRD clinical studies as of the clinical cutoff date of 4 March 2018 (see Section 8.2):
  - In the 6 completed Phase 2 and 3 TRD clinical studies 1,708 patients were exposed to esketamine nasal spray (611 patient-years of exposure).
  - In the ongoing long-term, open-label, Phase 3 extension study SUSTAIN-3, 1,092 patients were exposed to esketamine nasal spray (434 patient-years of exposure); of these, 153 patients were not previously exposed to esketamine in any of the completed Phase 3 studies.

- During the Phase 2 and 3 double-blind studies/study phases, exposure to esketamine nasal spray totaled 122 patient-years, and exposure to placebo nasal spray totaled 100 patient-years.

In the completed Phase 3 clinical studies:

- 479 patients were treated with esketamine nasal spray for ≥180 days
- 178 were treated with esketamine nasal spray for ≥350 days
- 194 patients were ≥65 years of age; 25 patients were ≥75 years of age

Overview of Adverse Events

- The most commonly observed adverse drug reactions (ADRs, defined as adverse events reasonably associated with the use of esketamine) in TRD patients treated with esketamine + oral AD (with incidence ≥10% and greater than in oral AD + placebo group) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting; see Section 8.3.2 for further information.
- Most (94.9%) treatment-emergent adverse events (TEAEs, defined as adverse events that were first reported or worsened in severity after starting study treatment) with esketamine in the Phase 2 and 3 TRD studies were mild to moderate in severity.
- Most TEAEs in esketamine-treated patients occurred shortly after dosing, were transient, and resolved on the same day. In the esketamine + oral AD groups in the short-term studies (TRANSFORM-1, 2, and 3), over 86% of all TEAEs occurred on nasal spray dosing days and of those events, over 85% also resolved the same day.
- There were no new safety concerns identified with long-term repeated, intermittent weekly or every-other-week administration of esketamine doses (28, 56, or 84 mg) over a duration of up to 1 year in the uncontrolled, open-label safety study SUSTAIN-2.
- The TEAE profile for patients ≥65 years of age was generally consistent with that observed in patients <65 years of age. In the long-term safety study SUSTAIN-2, a slowing of reaction time in the absence of any other change in cognitive performance was observed in patients ≥65 years of age (see discussion below and Section 8.8); however, the observation could not be attributed to study medication and the clinical relevance and consequences have not been established.
- In the fixed-dose study TRANSFORM-1, the overall rates of TEAEs and severe TEAEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, and most TEAEs across both dose groups were mild or moderate in severity, occurred on the day of dosing, and resolved the same day. TEAEs of dissociation occurred at a higher rate (6.4% higher) in the esketamine 84 mg group than the 56 mg group, and severe TEAEs of dissociation and nausea occurred at a higher rate (2.9% higher for both dissociation and nausea) in the esketamine 84 mg group.
- A total of 5 deaths occurred in the completed and ongoing Phase 2 and 3 clinical studies in patients with TRD as of the clinical cutoff date of 4 March 2018 (1861 unique patients treated with esketamine; 1045 patient-years of exposure; see Section 8.2 for additional information about exposure):

  - Completed double-blind studies/study phases: One death (multiple injuries sustained in a road traffic accident) occurred among esketamine-treated patients during the double-blind phases of the completed Phase 2 and 3 studies (122 patient-years of exposure). No death occurred in the oral AD + placebo groups of these studies (100 patient-years of exposure).
  - Completed and ongoing open-label studies/study phases: There were 3 deaths (2 completed suicides and 1 case of acute cardiac and respiratory failure) among patients treated with esketamine + oral AD during the open-label studies/study phases (923 patient-years of exposure).
  - Follow-up phases: There was 1 death (completed suicide) during the follow-up phases of these studies when the patient was not receiving nasally-administered study medication.
  - All 5 deaths were assessed by the investigator and the Sponsor as not related to esketamine treatment.
  - Further details and discussion of mortality rates observed in other studies of the TRD population are provided in Section 8.3.4.1.
- Across the completed Phase 3 studies/study phases in patients with TRD, the incidence of serious adverse events ranged from 0.9% to 6.9% in the esketamine + oral AD treatment groups and from 0.5% to 3.1% in the oral AD + placebo groups.
- Across the completed Phase 3 studies/study phases, the incidence of TEAEs leading to discontinuation of study medication ranged from 1.1% to 9.5% in the esketamine + oral AD treatment groups and from 1.4% to 3.1% in the oral AD + placebo groups.

Safety Topics of Interest

Suicidal Ideation and Behavior: Evaluation of Columbia-Suicide Severity Rating Scale (C-SSRS) scores and TEAEs of suicidal ideation and behavior in the Phase 2 and 3 clinical studies in patients with TRD did not suggest that esketamine is associated with increased risk of suicidal ideation and behavior (Section 8.4). The TRD studies included patients who have suicidal ideation without intent; patients with depression who have suicidal intent were included in the Phase 2 study PERSEVERE (see Sections 1.4 and 5.2.2) as well as in ongoing Phase 3 studies to assess esketamine for use in patients with MDD at imminent risk for suicide. Most patients stayed within the same suicidality category based on C-SSRS score throughout the Phase 3 studies. For the subgroup with no suicidal ideation or behavior at baseline, the percentage who reported suicidal ideation at any time postbaseline in the controlled Phase 3 studies/study phases was similar for the esketamine + oral AD (ranging from 2.4% to 13.8%) and oral AD + placebo groups (ranging from 4.5% to 16.9%). Among patients in the Phase 3 studies, 10 patients reported suicidal behavior postbaseline based on the C-SSRS; all of these patients had a lifetime history of suicidal ideation or suicidal behavior, and 5 of these patients had suicidal ideation at baseline (see Section 8.4 for further details). There were 3 cases of completed suicide in the Phase 2 and 3 studies in patients with TRD (see above and Section 8.3.4.1). In the controlled Phase 3 studies, the overall incidence of suicidality-related TEAEs (preferred terms are provided in Appendix 11) was similar for the esketamine + oral AD (0% to 2.0%) and oral AD + placebo

groups (0% to 0.9%); in the uncontrolled, open-label long-term study SUSTAIN-2, 5.5% reported suicidality-related TEAEs.

Dissociation: Consistent with the observation of peak plasma esketamine levels at approximately 40 minutes after dose administration, dissociative/perceptual changes captured using the Clinician Administered Dissociative States Scale (CADSS) had an onset shortly after the start of the dose, peaked by 40 minutes after dose administration, and typically resolved within 1.5 hours (Section 8.5). Peak mean CADSS scores attenuated with repeated dosing. Reported TEAEs associated with these symptoms were primarily transient; across Phase 3 studies >98% of TEAEs of dissociation reported on the day of administration resolved on the same day. Most events of dissociation were mild or moderate in severity; severe events were reported for <6% of patients in each Phase 3 study. There were no serious adverse events of dissociation. Across the Phase 3 studies, 7 patients discontinued esketamine due to a TEAE of dissociation.

Effects on Blood Pressure: Transient increases in systolic and diastolic blood pressure were observed following administration of esketamine nasal spray, with maximum elevations in the clinical studies observed within 40 minutes of dosing (consistent with peak plasma elevations) and values returning to, or close to, pretreatment levels by 1.5 hours after dose administration (Section 8.9.1). The largest mean of the maximum blood pressure increases across dosing days compared to predose values in the short-term Phase 3 studies were:

- Systolic blood pressure: 13.3 to 16.0 mm Hg in the esketamine + oral AD groups and 6.1 to 11.1 mm Hg in the oral AD + placebo groups
- Diastolic blood pressure: 8.7 to 9.5 mm Hg in the esketamine + oral AD groups and 4.9 to 6.8 mm Hg in the oral AD + placebo groups

Changes in blood pressure observed in the 56 mg and 84 mg esketamine dose groups did not demonstrate a dose-response relationship. A similar pattern for transient increases in blood pressure were observed in patients ≥65 years. In the long-term safety study SUSTAIN-2, there were no cumulative effects of the changes in blood pressure and the pattern of transient blood pressure increases remained consistent over time for patients 18-64 years and those ≥65 years. TEAEs related to increased blood pressure were reported at higher frequencies following treatment with esketamine + oral AD (6.6% to 13.9% [patients ≥65 years in TRANSFORM-3]) compared to oral AD + placebo (0.9% to 6.2% [patients ≥65 years in TRANSFORM-3]) in the controlled Phase 3 studies/study phases. In the open-label long-term safety study SUSTAIN-2, TEAEs related to increased blood pressure were reported for 13.0% of patients receiving esketamine + oral AD. In the Phase 3 studies, there were 4 patients with a severe TEAE related to increased blood pressure (1 case of hypertensive crisis and 3 cases of blood pressure increased). Two patients experienced a serious adverse event related to increased blood pressure (1 case of hypertensive crisis and 1 case of blood pressure increased). See Section 8.9.2 for further details.

Sedation and Somnolence: Based on the pattern of responses on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) in the Phase 2 and 3 studies, sedative effects of esketamine were generally mild, had an onset shortly after the nasal spray dosing peaking at 30 to 45 minutes postdose, and typically resolved by 1 to 1.5 hours postdose. The reported TEAE data for sedation and somnolence were consistent with MOAA/S findings. Across the Phase 2 and 3 TRD studies, TEAEs of somnolence or sedation were primarily mild or moderate in intensity and nonserious. In the Phase 3 studies, there were 12 patients with a severe event of somnolence, and 8 patients with a severe event of sedation. One patient experienced a serious TEAE of sedation. Four patients discontinued esketamine due to TEAEs of somnolence and/or sedation (somnolence: 1 patient; sedation: 2 patients; both somnolence and sedation: 1 patient). Most (>95%) reported TEAEs of somnolence or sedation occurred on the day of dosing in the short-term and long-term Phase 3 studies/study phases and of these, ≥96% resolved spontaneously the same day. See Section 8.7 for further information.

Effects on Cognition: In the short-term Phase 3 studies, 4 weeks of treatment with esketamine + oral AD did not influence any aspect of cognition studied in patients 18-64 years of age with TRD and was not associated with any systematic changes in cognition in patients ≥65 years of age. In the long-term open-label safety study SUSTAIN-2, overall group mean performance on multiple cognitive domains including visual learning and memory, as well as spatial memory/executive function, either improved or remained stable postbaseline in adult patients. In the subset of patients ≥65 years of age from this open-label study, a slowing of reaction time was observed starting at Week 20 and through the end of the study; however, this appeared to represent an isolated observation related to processing speed and not a broad attentional impairment. Performance on all other cognitive tests remained stable in patients ≥65 years of age in this study. See Section 8.8 for further information.

Respiratory Rate and Oxygen Saturation: Treatment with esketamine nasal spray had no clinically meaningful effects on respiratory rate or oxygen saturation as measured by pulse oximetry. There were no cases of respiratory depression or TEAEs that required cardiopulmonary resuscitation or other medical intervention reported in any esketamine-treated patient in the Phase 2 or 3 studies in TRD.

Interstitial Cystitis: There were no cases of interstitial cystitis (including ulcerative cystitis) in any of the clinical trials with esketamine.

1.8. Overview of Abuse Potential

While the potential for abuse, misuse, and diversion exists for esketamine due to its similar pharmacologic profile to ketamine, no evidence of abuse, misuse or overdose was observed in the esketamine development program with a TRD population (note, patients with moderate to severe substance use disorder were excluded from the studies), and possible diversion was minimal (<0.1% clinical supply kits unaccounted for in the Phase 3 studies). In addition, the potential for overdose, respiratory depression, and death with esketamine is low, given the underlying properties of the compound. Abuse potential will be mitigated by the controlled distribution program with direct distribution of medication to sites of care and administration

under the supervision of a healthcare professional. To mitigate the risk of diversion, esketamine nasal spray will not be available at retail pharmacies or shipped directly to patients.

Esketamine and ketamine show qualitatively similar pharmacological binding profiles, suggesting the 2 drugs are similar in terms of abuse potential, and all evidence taken together, including results from the human abuse potential study (Section 9.2.1), indicates that esketamine is appropriately characterized as a Schedule III substance in the US (Section 9). The incidence rate of recreational ketamine abuse in the US is relatively low compared with other hallucinogens and more widely abused substances, and this low rate has persisted despite the long history of ketamine use as an anesthetic and a recent increase in the number of clinics providing off-label IV ketamine to treat patients with major depression.

To mitigate the risk for abuse and misuse of esketamine nasal spray, there will be a comprehensive set of measures in place, including the proposed Risk Evaluation and Mitigation Strategy (REMS; see description below), administration only at the site of care under the supervision of a healthcare professional, product labeling, an extensive educational and training program and resources, together with several features of the single-use disposable nasal spray device, which was designed to mitigate the risks of abuse and misuse of esketamine.

1.9. Overview of Risk Mitigation Strategies

There will be a comprehensive program in place to address the potential for misuse and abuse of esketamine and to mitigate the risk of administration of esketamine without monitoring (Section 10). To mitigate the potential for misuse and abuse, the Sponsor will implement several measures as outlined in the proposed REMS, including a certification requirement for outpatient healthcare settings and pharmacies that dispense esketamine, a controlled distribution program in which esketamine will only be available to hospitals and REMS-certified outpatient healthcare settings and pharmacies (not to retail pharmacies), and a requirement for the Sponsor to disseminate REMS communication materials (e.g., Dear Healthcare Professional Letter and esketamine REMS Fact Sheet), to inform healthcare professionals about the REMS program and to outline the risks and safe use of esketamine. Furthermore, a suspicious order monitoring program will be implemented to detect unusual orders or patterns suggestive of inappropriate prescribing or diversion.

The company will conduct surveillance through both routine pharmacovigilance for signal detection of events related to abuse or misuse of esketamine and will engage an external company, Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS®), to monitor for signals of increased ketamine or esketamine abuse, misuse or diversion.

Esketamine is not to be dispensed to patients to take home; it will be self-administered under the supervision of healthcare professionals with an observation period after dose administration to monitor for adverse reactions and blood pressure changes as described in the proposed product label. Patients are to be released only after they are considered clinically stable and their blood pressure has stabilized. To mitigate the risk of administration without appropriate monitoring per

the proposed product label, the proposed REMS includes measures to ensure that all relevant staff are educated about monitoring patients for treatment-emergent transient dissociative and blood pressure changes associated with esketamine administration. Furthermore, there will be an educational program in place for patients and healthcare professionals to provide appropriate precautions for abuse potential as well as to inform them of how esketamine is safely administered and the risks of adverse reactions.

1.10. Benefit-risk Conclusions

Approximately one-third of patients with major depression are not adequately treated with currently available medications, despite the availability of many AD agents. There is a significant unmet medical need for a novel TRD treatment. In the US, only a single pharmacotherapy for TRD is approved (olanzapine/fluoxetine combination, Symbyax), and its use is limited by tolerability. For patients who have a partial response to their current treatment, augmentation with a second agent (e.g., aripiprazole, quetiapine, brexpiprazole) may be an option; however, the tolerability of these agents also has limitations. The currently available non-pharmacological treatment options for TRD referred to in guidelines on the treatment of depression (e.g., electroconvulsive therapy and deep brain stimulation) have considerable limitations in terms of efficacy and/or tolerability and acceptability to patients.

The totality of evidence supports a positive benefit-risk balance for esketamine nasal spray as a new treatment for adults with TRD. In the context of the high medical need and poor quality of life for TRD patients, 5 to 21 additional patients remitting or 14 to 17 additional patients responding per 100 treated (Section 11.5), with symptom reduction starting to manifest in some patients within days, is a considerable benefit that outweighs the adverse reactions, predominantly dissociation, vertigo and dizziness. In view of the elevated morbidity and mortality associated with TRD, the benefit seen with continued maintenance treatment of 19 to 32 fewer relapses per 100 patients (who have achieved stable remission or response; Section 11.5) over long-term therapy also outweighs the few severe common adverse reactions. The single death across the 4 controlled Phase 3 studies, three deaths in the uncontrolled open-label safety studies, and one death in the follow-up phase of the Phase 2 dose-response study SYNAPSE were not considered related to treatment by the study investigator, and the cumulative exposure to esketamine across studies was much larger than that to placebo. Notably, the all-cause mortality rate in a study of TRD patients in the Medicare system[38] was higher than that observed in the clinical studies with esketamine in TRD patients (see Section 8.3.4.1).

The safety experience with esketamine indicated that most of the adverse reactions seen with the drug, including those of common events such as dissociative symptoms, dizziness/vertigo, increased blood pressure, and sedation, occurred shortly after dosing while the patient was under the supervision of a healthcare professional, were transient, and resolved the same day. In addition, certain adverse reactions such as dissociation, dizziness/vertigo, and nausea/vomiting tended to lessen in frequency with continued dosing. The benefits of esketamine outweigh the risks of the infrequent severe or treatment-limiting side effects in the TRD population. While the potential for abuse exists with esketamine, a comprehensive set of risk mitigation initiatives,

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including a proposed REMS and controlled distribution program as well as surveillance measures, are planned to address the potential for abuse and misuse.

With a comprehensive risk mitigation program, which includes education about dosing under the supervision of a healthcare professional, esketamine has the potential to improve the treatment landscape for TRD, based on the rapid and durable efficacy observed in clinical studies. Esketamine is therefore anticipated to address a major public health interest and has the potential to provide important benefits in establishing a new standard of care for achieving meaningful clinical response and remission among adults with TRD.

2. INTRODUCTION

Depression is a widespread public health concern and a leading cause of disability worldwide. Despite the availability of many antidepressant therapies, a large number of patients with depression do not experience relief of depressive symptoms after treatment. Esketamine nasal spray is a novel product developed for patients with treatment-resistant depression.

This briefing document presents data from studies conducted by Janssen Research & Development LLC (the Sponsor) related to the efficacy and safety of a novel nasal spray formulation of esketamine (S-ketamine, the S-enantiomer of ketamine) for the following proposed indication:

> *treatment-resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode)*

The proposed dosage recommendations for esketamine nasal spray are shown in the following table. Dose adjustments should be made based on efficacy and tolerability to the previous dosing in the induction or maintenance phase. Esketamine nasal spray should be administered in conjunction with an oral antidepressant.

Dosage Recommendations for Esketamine Nasal Spray

Induction Phase	Maintenance Phase
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly**
Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment	Periodically reexamine the need for continued treatment.

* For patients ≥65 years Day 1 starting dose is 28 mg.
** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

Esketamine nasal spray is designed to be administered by the patient under the supervision of a healthcare professional. The drug solution is packaged in a single-use nasal spray device, which holds a total volume of 0.2 mL of solution (equivalent to 32.3 mg of esketamine hydrochloride or 28 mg of esketamine base). When actuated, each device dispenses 2 individual sprays (one in

each nostril) delivering a 28-mg dose of esketamine. One, 2, or 3 nasal spray devices will be used to provide the doses of 28 mg, 56 mg or 84 mg, respectively, with a 5-minute rest between use of each device.

In the remainder of the document, esketamine nasal spray is referred to as esketamine unless it is important to specify the route of administration for clarity.

2.1. Unmet Medical Need

Major depressive disorder (MDD) is recognized as a leading cause of disability globally. In 2017, it was estimated that over 17 million adults in the US had a major depressive episode in the past year.[105] The goal of treatment for people suffering from depression is symptom control, namely reduction in symptoms (response) or complete alleviation (remission). Early response to treatment of depression is important to reduce the burden and suffering of patients, improve functioning, and reduce the risk of suicide. In addition, early response to treatment increases patient engagement and compliance with treatment.[88] Sustained symptom improvement is an important therapeutic outcome for patients.[103]

Although numerous antidepressant therapies are available, a subset of patients with MDD are not adequately treated. First-line therapies mainly include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). A major limitation of these medications is that patients generally do not begin to experience relief of depressive symptoms until 3 to 4 weeks after they have started treatment and may continue to suffer from functional impairment and be at risk of suicide. Moreover, as demonstrated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest study of stepwise, sequential treatment with antidepressants in real world settings, only about two-thirds of patients with MDD achieve remission after the first or second course of treatment using currently approved drugs.[88] Importantly, more than 80% of patients who needed a third step of treatment during the STAR*D study did not achieve relief of depressive symptoms, and for the minority of these patients who achieved relief, approximately 70% experienced relapse within 6 months.[88] The lack of effective alternatives for patients who do not experience relief of depressive symptoms after treatment with multiple antidepressant agents limits guidance on how to treat these patients.[2,26]

While several definitions of treatment-resistant depression (TRD) are used in clinical practice, world health authorities, including the Food and Drug Administration (FDA) and the European Medicines Agency, define TRD patients as individuals with MDD who have not responded to at least 2 different antidepressant treatments given at an adequate dose for an adequate duration in the current episode of depression. This definition is used in the Sponsor's clinical development program for esketamine nasal spray. Those suffering from TRD contribute disproportionately to the morbidity and mortality associated with depression. They have a 7-fold higher suicide rate, lower remission rates, pronounced functional impairment, a substantially lower quality of life as well as higher medical and mental healthcare costs, compared to patients with MDD who respond to antidepressant treatment.[3,28,38,88] In addition, TRD in older adults (65 years and older) is associated with decreased quality of life, functional decline, increased hospitalization, decreased productivity, and increased caregiver burden.[10]

Treatment-resistant depression has a significant impact on the lives of individual patients and their families. The disease limits the quality and length of life for affected patients. For the majority of patients with TRD, treatment with existing antidepressant medications fails to result in remission from depressive symptoms.

In the US, only a single FDA-approved pharmacotherapy for TRD is available (olanzapine/fluoxetine combination [Symbyax]), and its use is limited by tolerability, especially due to potential side effects of olanzapine.[24] For patients who have a partial response to their current treatment, augmentation with a second agent (e.g., aripiprazole, quetiapine or brexpiprazole) may be an option; however, the tolerability of these agents also has limitations.[49]

The currently available non-pharmacological treatment options for TRD referred to in guidelines on the treatment of depression (electroconvulsive therapy, deep brain stimulation, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and vagus nerve stimulation) have considerable limitations in terms of efficacy and acceptability to patients.[2,21,75,76,77] While electroconvulsive therapy is reported to be effective in TRD,[21] it is associated with significant adverse effects including memory loss, seizures, cardiovascular complications and general complications associated with anesthesia. Recent controlled trials with deep brain stimulation have failed to show efficacy.[31] The availability of transcranial direct current stimulation and repetitive transcranial magnetic stimulation is limited, and evidence to support benefit in patients who are unresponsive to more than 3 or 4 antidepressant treatments is currently lacking.[21] Vagus nerve stimulation also has limited evidence of efficacy in patients with TRD.[2,77]

The current approaches are sequential trials of therapies that frequently fail to provide adequate improvement of depressive symptoms. Thus, there is a substantial need to develop innovative treatments for the rapid and sustained relief of depressive symptoms in adult patients with TRD.

2.2. Mechanism of Action

Systems that regulate synaptic connectivity, including the glutamate system, have become promising areas of research in the search for novel antidepressant agents. Several small clinical studies and case reports in patients with major depression have suggested that intravenous (IV) ketamine, which directly interacts with glutamatergic receptors in the brain, has antidepressant activity observed within hours to days after administration.[9,27,65,118] Ketamine is currently approved in the US, Europe and many other countries for inducing and maintaining anesthesia via IV infusion or intramuscular (IM) injection; however, ketamine is not indicated for use in MDD, including TRD. In published clinical studies with IV ketamine, antidepressant effects were observed after administration of low doses (0.5 mg/kg infused over 40 minutes in most studies) that did not induce anesthesia (i.e., subanesthetic doses).[9,27,65,118]

Ketamine is a racemic mixture of 2 enantiomers: esketamine (S-ketamine), the S-enantiomer, and arketamine (R-ketamine), the R-enantiomer. While ketamine, esketamine, and arketamine are considered to be glutamate receptor modulators, or more specifically, N-methyl-D-aspartate (NMDA) receptor antagonists, the strength of the interaction between esketamine and the

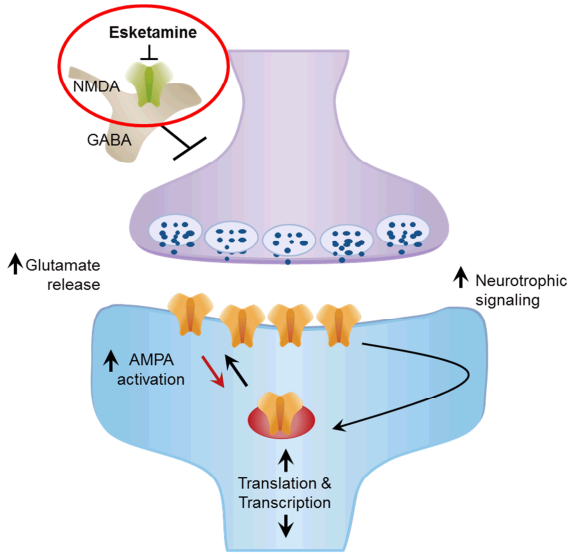
NMDA receptor is greater than that between ketamine and the NMDA receptor (approximately 1.5- to 2.8-fold greater)[35,50,68] and that between arketamine and the NMDA receptor (approximately 4-fold greater;[35, 68] the Sponsor's pharmacology studies). In other words, esketamine has greater potency at the NMDA receptor than either ketamine or arketamine.

Building on previous studies suggesting IV ketamine has substantial antidepressant effects, the Sponsor initiated a systematic program to develop esketamine as a nasal spray for the treatment of depressive symptoms in patients with TRD. Esketamine was selected for development over racemic ketamine because of its higher potency towards the NMDA receptor, which allows for lower doses of esketamine to be administered, thus reducing the volumes of fluid required for delivery from a nasal spray device. Relative to IV administration, the intranasal route of administration not only offers a non-invasive and more convenient dosing option for patients and physicians but is associated with a reduced likelihood of dosing errors since esketamine is administered as a multiple of a fixed dosage unit (28 mg for esketamine), which is prepackaged in a single-use container. Further, the physiology of the nasal mucosa facilitates rapid and appreciable absorption via the intranasal route.[106] Esketamine that is absorbed through the nasal mucosa bypasses first-pass metabolism by the gut and liver and is not likely to interact with other coadministered drugs such as those which alter activity of hepatic cytochrome P450 enzymes.

Esketamine nasal spray has the potential to address the critical unmet medical need for patients with depression due to its novel mechanism of action (Figure 5). Putative etiological contributors of depression, including stress and other conditions, are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behavior.[33,64] By blocking NMDA receptors, administration of ketamine and esketamine results in increased glutamate release, which leads to increased α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor activation, which in turn increases release of various neurotrophic factors; in preclinical chronic stress models, this cascade restores synaptic function and structure in brain regions involved in regulating emotional behavior and processing.[43] Since postmortem studies of patients with MDD manifest evidence of atrophy and altered function in the same regions, ketamine and esketamine are hypothesized to directly address the pathophysiology of depression by modulating the glutamate system to restore synaptic function.

Figure 5: Proposed Mechanism of Action for Esketamine

- **NMDA receptor antagonism facilitates release of glutamate -> AMPA receptor activation**
- **AMPA receptor activation increases signaling of neurotrophic factors, which is associated with long term antidepressant effects**



AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA=γ-amino butyric acid; NMDA=N-methyl-D-aspartate
Art adapted from Sanacora and Schatzberg, *Neuropsychopharmacology* (2015)[91]

Notably, this evidence from nonclinical studies specifically demonstrates that single doses of ketamine can increase the density of synapses in animals that have been subjected to chronic stress,[20,58,59] and these synaptic changes persist for a week or more after a single administration of ketamine.[20,33,59] These results appear consistent with the clinical observation in patients with MDD that the antidepressant effects of ketamine and esketamine persist for several days after a single dose, and that intermittent dose administration can maintain the antidepressant effects.

Pharmacology data provide evidence that in the dose range shown to elicit antidepressant effects in clinical studies, esketamine and ketamine inhibit NMDA receptor, but do not directly affect the function of receptors and/or transporters of serotonin, norepinephrine, acetylcholine, γ-amino butyric acid (GABA), melatonin, or opioid peptide systems, nor do they directly affect sodium or potassium channels.[13,19,22,34,39,40,41,45,46,50,53,62,68,79,92,100,117] Using information from nonclinical pharmacology experiments and translational modeling with human plasma levels, approximately 30% NMDA receptor occupancy is predicted to be attained in the human brain at the peak plasma esketamine concentration after 84 mg nasal esketamine.

2.3. Development Program for Esketamine Nasal Spray

While a number of small clinical studies have suggested that subanesthetic doses of IV ketamine can provide rapid improvement of symptoms of depression, there has been no comprehensive assessment of its short- and long-term efficacy, tolerability, and safety for patients with depression. The Sponsor initiated a systematic program to develop esketamine (which has higher potency at the NMDA receptor than ketamine) using a non-invasive route of administration with the goal of evaluating the efficacy and safety of esketamine nasal spray for induction and maintenance treatment of patients with TRD. In addition, a large development program is ongoing to assess esketamine nasal spray for use in the associated serious and potentially fatal

condition involving patients with MDD at imminent risk for suicide. The Sponsor's recent New Drug Application (NDA) and this document contain data evaluating the efficacy and safety of esketamine nasal spray for the treatment of TRD in adults, defined as adults with MDD who have not responded to at least 2 different antidepressants of adequate dose and duration to treat the current depressive episode. Results from the studies described in Table 1 were included in the NDA.

Table 1: Clinical Studies Included in NDA Evaluating Esketamine Nasal Spray for Patients with TRD

Study Phase	Study Population	Study Medication (Route of Administration)	Number of Studies
Phase 1	Healthy participants, special populations, and patients with MDD	Esketamine (intranasal, IV, oral) and ketamine (IV)	19
Phase 2	Patients with TRD	Esketamine (IV) and ketamine (IV)	2
	Patients with TRD	Esketamine (intranasal)	1
	Patients with MDD at imminent risk for suicide	Esketamine (intranasal)	1
Phase 3	Patients with TRD	Esketamine (intranasal)	5

IV=intravenous; MDD=major depressive disorder; NDA=New Drug Application; TRD=treatment-resistant depression

To measure the severity of depressive symptoms and changes in severity with treatment, the Sponsor used the Montgomery-Asberg Depression Rating Scale (MADRS) as the primary assessment of efficacy in the clinical development program. The MADRS is a clinician-reported outcome tool widely used for primary outcome measures in MDD clinical trials.[69] The scale consists of 10 items corresponding to the core symptoms of depression: apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 to 6 for a total possible score of 60; higher scores represent a more severe condition. In the Sponsor's clinical development program, the severity of depressive symptoms based on MADRS total score was defined as follows: no symptoms: ≤12; mild depression: 13-27; moderate depression: 28-34; severe depression: ≥35. Individuals with a MADRS total score of 12 or less were considered to be in remission, and those with more than 50% improvement from baseline in MADRS total score were considered to have responded to treatment (see Section 7.1 for additional information).

2.3.1. Regulatory History

On 18 May 2012, the Sponsor submitted an Investigational New Drug (IND) application (114,345) to develop esketamine nasal spray for the treatment of patients with TRD. In a submission dated 16 September 2013, JRD requested Breakthrough Therapy Designation for this development program; FDA granted the designation on 7 November 2013.

The development program was designed and conducted in consultation with FDA. Since 2012, the Sponsor met with the Division ten times under IND 114,345 regarding the TRD development program. In addition to the eight face-to-face meetings (1 Type A, 4 Type B, 3 Breakthrough Therapy Designation Guidance) and two meetings via teleconference (1 Breakthrough Therapy

Designation Guidance, 1 Nonclinical Guidance), there were numerous written correspondences with the Agency.

Important decisions and agreements reached with the Division pertinent to the product's development program include:

- The definition of treatment-resistant depression
- The design of the short-term efficacy studies including the need to initiate a new conventional, oral antidepressant treatment at the start of esketamine treatment and the length of the induction phase (4 weeks)
- The requirement for maintenance of effect study data in the NDA to inform clinicians on how best to use the product after an initial response is achieved
- The primary endpoint (the difference in MADRS score from baseline to the end of 4 weeks) and key secondary endpoints (onset of clinical response, Sheehan Disability Scale, 9-item Patient Health Questionnaire)
- The safety assessments incorporated in the Phase 3 studies
- The need for and design of a human abuse potential study
- The need for and design of neurotoxicity studies in the rat
- The Sponsor's strategy related to development of the intranasal device, and manufacturing and control of the active pharmaceutical ingredient and drug product
- An agreed initial Pediatric Study Plan granting a full waiver of pediatric studies in TRD
- Agreement on coding of adverse events from Phase 3 studies
- Agreement on the content and format of the NDA to support filing the application (including one positive short-term study and a positive maintenance of effect study)

In addition to submission of the final study protocols to the IND, statistical analysis plans for the pivotal Phase 3 studies and the supportive Phase 2 studies were submitted as drafts for the Division's review and then as final prior to database lock with FDA's comments incorporated, where applicable.

2.3.2. Features of the Development Program

To provide context for review of the data presented in the remainder of the document, it is important to note several features of the Phase 3 clinical study design and to review a high-level summary of the results from the Phase 2 and 3 clinical studies.

For typical antidepressants (e.g., SSRIs and SNRIs), FDA generally requires 2 adequate and well-controlled (pivotal) short-term Phase 3 studies which reach statistical significance for initial approval; a long-term maintenance of effect study is usually a postmarketing commitment. Numerous short-term studies with esketamine and ketamine alike have demonstrated rapid onset of efficacy in patients with MDD and TRD. As discussed with FDA during design of the Phase 3 clinical program, a fundamental question to be answered in the program was whether and how the antidepressant effect may be sustained to treat a chronic relapsing illness. This specific aim

necessitated conducting a maintenance study to determine if continued esketamine administration was needed to sustain improvement during long-term care or if the initial response to esketamine instead could be maintained with an oral antidepressant alone after discontinuation of esketamine. In addition, if long-term esketamine use was necessary to sustain improvement, a second critical aim involved establishing a dose and minimum dosing frequency that could sustain the antidepressant effects during maintenance treatment.

Given the importance of maintenance of effect data with this novel treatment, FDA stated that one positive, adequate and well-controlled short-term study and one positive, adequate and well-controlled maintenance of effect study (along with the requisite safety data to meet International Conference on Harmonization [ICH] requirements) would be sufficient to support an NDA submission. Thus, the 2 pivotal studies in the clinical development program which reached statistical significance and form the foundation of the NDA were: (1) TRANSFORM-2, the short-term flexible-dose study and (2) SUSTAIN-1, the maintenance of effect study (Table 2). Supportive evidence of the efficacy and safety of esketamine from the other completed Phase 3 studies and from additional Phase 2 studies that reached statistical significance is also presented.

Table 2: Summary of Results for the Primary Efficacy Endpoints in the Phase 2 and 3 Studies

Study Phase	Study Description, Study Drug (Population)	Study Name/Study Abbreviation	Primary Endpoint 2-sided p-value
Studies Meeting Primary Endpoint			
Phase 3	Short-term, flexible-dose, esketamine nasal spray (18-64 years with TRD)	**TRANSFORM-2 (Pivotal)**	$p = 0.020$
Phase 3	Maintenance of effect, esketamine nasal spray (18-64 years with TRD)	**SUSTAIN-1 (Pivotal)**	$p = 0.003$
Phase 2	Short-term, fixed-dose, intravenous esketamine (18-64 years with TRD)	TRD2001	$p \leq 0.003$
Phase 2	Short-term, fixed-dose, intravenous racemic ketamine (18-64 years with TRD)	TRD2002	$p < 0.001$
Phase 2	Short-term, fixed-dose, esketamine nasal spray (20-64 years with TRD)	SYNAPSE (Panel A)	$p = 0.043$ (28 mg) $p = 0.002$ (56 mg) $p < 0.001$ (84 mg)
Phase 2	Short-term, fixed-dose, esketamine nasal spray (18-64 years with MDD at imminent risk for suicide)	PERSEVERE	$p = 0.015$
Studies Not Meeting Primary Endpoint			
Phase 3	Short-term, fixed-dose, esketamine nasal spray (18-64 years with TRD)	TRANSFORM-1 (Pivotal)	$p = 0.088$
Phase 3	Short-term, flexible-dose, esketamine nasal spray (≥65 years with TRD)	TRANSFORM-3 (Pivotal)	$p = 0.059$

TRD=treatment-resistant depression

Further, the Sponsor and FDA agreed that nasally-administered study medication (esketamine or placebo) was to be given concurrently with a newly-initiated oral AD (referred to as new AD control) in the Phase 3 studies. Therefore, the Phase 3 short-term studies used neither an inactive comparator (i.e., placebo) only design nor a classical adjunctive (add-on) design. While this is unusual, a new oral AD was initiated at the outset of treatment for 2 main reasons:

- As esketamine was not intended to be used as monotherapy, an important question to be asked in the Phase 3 program was whether, among patients with confirmed stable remission/stable response to initial esketamine + oral AD therapy, treatment with esketamine could be stopped and longer-term maintenance achieved with the oral AD alone. The use of a newly-initiated oral AD (instead of one to which patients had previously not responded) was thought to provide patients a greater likelihood of achieving sustained improvement following discontinuation of esketamine.
- Initiating a new AD, instead of continuing a failed medication to which the patient had demonstrated no clinically meaningful response, ensured that all patients in the Phase 3 studies received a clinically optimized AD treatment, consistent with international clinical treatment recommendations for MDD to replace an ineffective therapy with a different agent.[2,8,21,51,77]

Additionally, as esketamine has known transient dissociative effects (i.e., distortion of time and space, illusions, derealization, and depersonalization) that are difficult to blind and potentially could bias the research staff who observe these effects, the MADRS assessment was performed prior to nasal spray dose administration throughout the double-blind studies over the telephone by independent, blinded raters using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA), provided in Appendix 1.[115] The MADRS assessment is usually performed during a face-to-face interview; however, a study of the reliability of the SIGMA supported the equivalence of remote administration of the MADRS using the SIGMA by telephone to face-to-face interviews.[115]

3. NONCLINICAL ASSESSMENT

In addition to a comprehensive clinical program for esketamine nasal spray, the Sponsor conducted an extensive nonclinical program. Results from nonclinical studies related to cardiovascular safety, general toxicity, neurotoxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity and pharmacokinetics, distribution and metabolism are briefly discussed below.

3.1. Safety Pharmacology

An in vitro nonclinical safety pharmacology study showed that esketamine has no relevant effect on the human-ether-à-go-go-related gene (hERG) channel-mediated potassium current. Following single IV dosing of esketamine to dogs, transient increases in heart rate, blood pressure and respiration rate were noted at esketamine exposures resembling those achieved in humans at 84 mg. The nonclinical cardiovascular changes are in line with the clinical experience of ketamine and esketamine. No cardiovascular safety issues were observed upon electrocardiographic monitoring in the 3- and 9-month repeat-dose toxicity studies with intranasally administered esketamine in dogs, where esketamine maximum plasma concentration (C_{max})- and area under the concentration-time curve (AUC)-related safety margins of 4-7 and 0.9-1.5, respectively, were obtained.

Investigations on the potential effects of intranasal esketamine on the function of the central nervous system including neurobehavioral and neurological examinations in the 6-month and 9-month repeat-dose toxicity studies in rats and dogs, respectively, as well as functional assays in

the pre- and postnatal developmental toxicity study in rats, did not reveal any adverse effects at exposures relevant to the clinical use of intranasal esketamine.

3.2. Toxicology

Esketamine was evaluated in repeat-dose toxicity studies of 3- and 6-month duration in rats and of 3- and 9-month duration in dogs following once daily intranasal administration up to 9 mg/day in rats (corresponding to approximately 27 mg/kg/day) and 72 mg/day in dogs (corresponding to approximately 10 mg/kg/day), respectively. In addition, intermittent dose administration and reversibility of potential effects were evaluated in the 3-month rat and dog studies. In rats and dogs, clinical signs included decreased/increased general activity, ataxia, and salivation. In general, these signs showed evidence of a dose relationship and accommodation with continued dosing and were considered related to the pharmacological action of esketamine. After up to 6 months of intranasal dosing of esketamine in rats and 9 months in dogs, no adverse effects were noted. Consequently, the No-Observed-Adverse-Effect Level was 9 mg/day in rats and 72 mg/day in dogs. These No-Observed-Adverse-Effect Levels represented the maximum feasible dose levels for long-term studies with intranasal instillation in rats and dogs. No notable treatment-related lesions were observed in the nasal cavity or any peripheral organ including the brain, liver, and urinary bladder, which are known to be target organs of toxicity for parenterally administered racemic ketamine.

The Sponsor's nonclinical toxicology program for esketamine further included single-dose and 14-day repeat-dose neurotoxicity studies in rats; a rat fertility and early embryonic developmental toxicity study; a rat pre- and postnatal developmental toxicity study; in vitro and in vivo genotoxicity studies, and 6- and 24-month carcinogenicity studies in transgenic mice and rats, respectively.

Studies described in the literature have shown that high dose levels of racemic ketamine can induce neurotoxicity in adult, adolescent, and juvenile animals as evidenced by histopathological brain lesions and functional sequelae. However, the precise thresholds for dose and duration of exposure causing neurotoxicity in animals remain to be established, and the relevance to humans of ketamine's neurotoxic action in animals as detected by brain histopathology and functional changes of the central nervous system is unknown. Prolonged administration of large doses of ketamine has been reported to induce cortical atrophy and white matter abnormalities in the brains of adult human ketamine abusers examined by magnetic resonance imaging.[60,61,87,113]

In specific single and 14-day repeat-dose neurotoxicity studies with intranasal esketamine in rats, no brain lesions were found at dose levels up to the maximum feasible dose or maximum tolerated dose. The total esketamine plasma exposures (AUC) were up to 86-fold (single-dose rat study) or 11-fold (14-day rat study) higher than those achieved in humans at 84 mg. Furthermore, in the 6-month rat and 9-month dog repeat-dose toxicity studies, in which chronic daily dosing of intranasal esketamine started in adolescence, no evidence of neurotoxicity was found as assessed by examinations of brain histopathology in both species, neurobehavioral endpoints in the rat, and neurological assessments in the dog. Similarly, no evidence of neurotoxicity based on brain histopathology was noted in the 3-month rat and dog studies with

intranasal instillation of esketamine. The total esketamine plasma exposures (AUC) in the rat and dog repeat-dose toxicity studies over 3 months in duration were similar to those in humans at 84 mg. Overall, the risk of neurotoxicity associated with esketamine nasal spray to adult patients with TRD is considered low.

No adverse effects on fertility and reproductive capacity and performance were found in a rat fertility and early embryonic development study and the 6-month rat toxicity study, where a reproductive phase was included. Both studies were conducted with intranasally administered esketamine (up to 9 mg/day).

Developmental (neuro)toxicity was investigated in a pre- and postnatal developmental toxicity study, where pregnant rats received intranasal esketamine (up to 9 mg/day) from implantation to weaning. This treatment window covered the period of organogenesis during pregnancy as well as early postnatal development in the lactation phase. In addition to a general developmental toxicity assessment, the brains of the parent generation and the born offspring were examined histopathologically. Neurobehavioral testing was performed in the born offspring. In this study, no findings of concern were noted. Rat and rabbit embryo-fetal developmental toxicity studies, where the parent animals were treated with intranasal racemic ketamine during pregnancy (i.e., the period of organogenesis) and the offspring was examined prior to birth, did not reveal evidence of developmental toxicity either. However, racemic ketamine administered intravenously at high anesthetic dose levels to pregnant animals is known to cause brain abnormalities and nervous system functional impairment in the offspring. Although developmental neurotoxicity effects with intranasal esketamine were not demonstrated in animals, as a precaution the use of esketamine nasal spray during pregnancy is not recommended considering there are known developmental neurotoxicity findings for racemic ketamine in animals.

A series of in vitro and in vivo genotoxicity studies was performed with esketamine and ketamine. The in vitro micronucleus test with esketamine showed genotoxic potential in the presence of metabolic activation. The bacterial reverse (Ames) mutation test with ketamine showed no evidence of mutagenicity. The in vitro mouse lymphoma study with ketamine did show effects in the presence of metabolic activation. Two in vivo genotoxicity studies, i.e., an in vivo micronucleus test with intraperitoneal injection of ketamine in mice, and an in vivo Comet assay with IV-infused esketamine in rat liver cells, both conducted up to the maximum tolerated dose for the respective administration route, revealed no effects. The overall weight of evidence met the criteria of ICH S2 (R1) for adequate follow-up testing of in vitro genotoxicity findings and demonstrated the absence of genotoxic risk. The lack of genotoxic potential was confirmed by the observation that there were no neoplastic findings associated with esketamine administration in a 24-month intranasal rat carcinogenicity study and in a 6-month subcutaneous carcinogenicity study in transgenic (Tg.rasH2) mice.

Noresketamine, a pharmacologically active and major human plasma metabolite of esketamine, is adequately covered in at least one animal species (rat) in general toxicology and other studies

conducted with intranasal esketamine. Hence, no separate toxicology evaluation was conducted for noresketamine.

An abuse potential assessment with intranasal esketamine in animals was not conducted. A human abuse potential study was conducted to compare drug likability of intranasally administered esketamine with ketamine administered by IV infusion (Section 9.2.1); this study supersedes an abuse potential study in animals.

3.3. Pharmacokinetics in Animals and Product Metabolism

Across species, rapid absorption occurred following intranasal administration of esketamine, with peak plasma concentrations generally reached within 30 minutes. Following intranasal dosing in mice and rats, C_{max} values of esketamine and noresketamine were comparable whereas the AUC values were higher for noresketamine than for the parent. In the dog, the AUC of noresketamine was lower than that of esketamine. In mice, rats, and dogs no major gender differences in AUC were noted.

The tissue distribution of esketamine is characterized by a fast equilibrium between plasma and well-perfused tissues (including the brain) leading to a rapid tissue uptake. Total brain concentrations of esketamine were 4-fold (rat) to 7-fold (human) higher compared to those in the systemic circulation. After the peak, brain levels decline rapidly, paralleling the decay in plasma. In general, the brain uptake of the more polar metabolites was less efficient than that of the parent drug.

The major in vitro biotransformation pathway of esketamine in liver microsomes and S9 fractions of mouse, rat, dog and human was N-demethylation to noresketamine, followed by hydroxylation on different positions of the cyclohexanone ring, oxidative deamination and keto-reduction.

4. CLINICAL PHARMACOLOGY

Scope of the Clinical Pharmacology Program

Pharmacokinetic and pharmacodynamic information relevant for esketamine nasal spray treatment were obtained after a single dose and twice-weekly administration in 19 Phase 1 studies, 3 Phase 2 studies (TRD2001, TRD2002, and SYNAPSE), and 3 Phase 3 studies (TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3).

Phase 1 studies were conducted in healthy younger (18-64 years) and older (≥65 years) adults of non-Asian and Asian origin, recreational polydrug users, participants with allergic rhinitis, and participants with renal or hepatic impairment. In addition, pharmacokinetic samples were collected from patients with TRD who were enrolled in Phase 2 and short-term Phase 3 studies with esketamine nasal spray.

Drug-drug interaction studies were conducted in healthy participants to evaluate potential drug-drug interactions with inhibitors and an inducer of the cytochrome P450 (CYP) enzymes responsible for esketamine metabolism. In addition, the pharmacokinetics of esketamine nasal

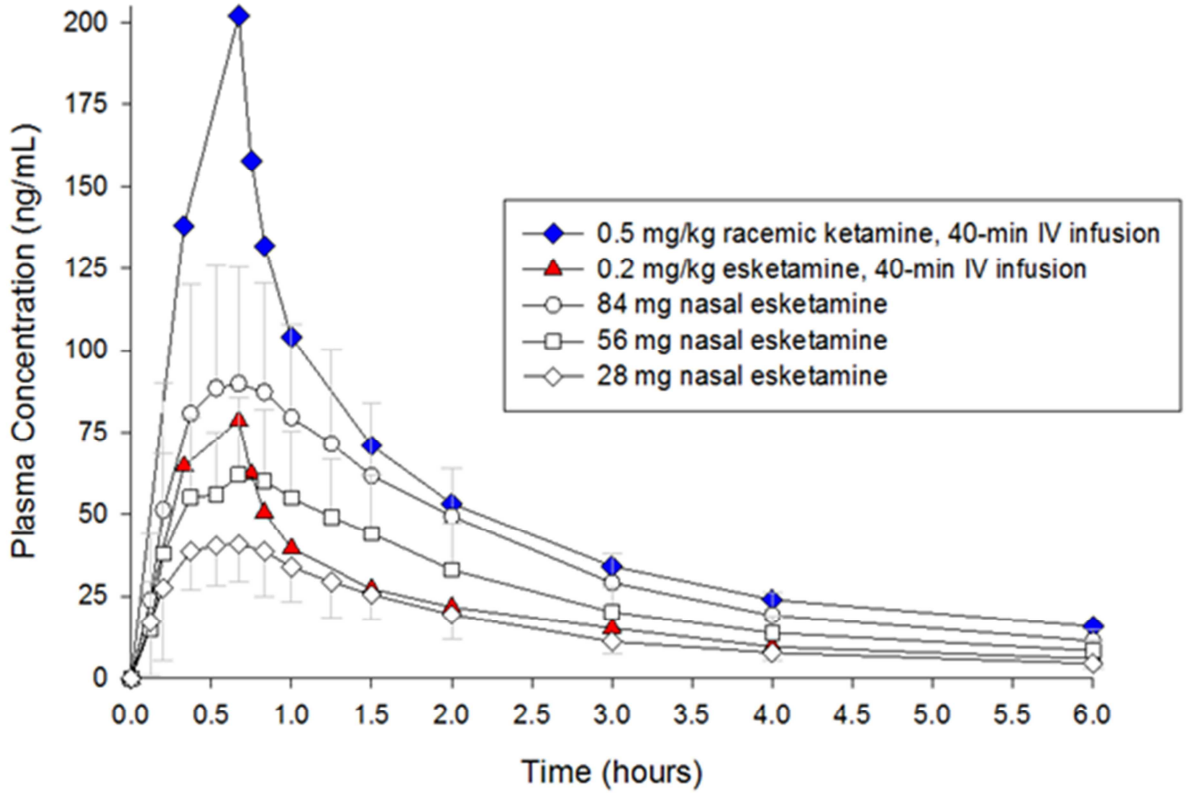
spray was evaluated in patients pretreated with a nasal corticosteroid or nasal decongestant. The effects of esketamine nasal spray on the pharmacokinetics of other coadministered drugs were also evaluated.

4.1. Pharmacokinetic Characteristics of Esketamine Nasal Spray

A summary of general clinical pharmacokinetic findings is as follows:

- The C_{max} and AUC of esketamine in plasma increased in a dose-related and nearly linear manner at clinically relevant doses of 28 mg, 56 mg, and 84 mg esketamine nasal spray (see Figure 6).
- Esketamine does not accumulate in plasma when administered intranasally twice weekly.
- After C_{max} is reached, the decline in plasma esketamine concentrations is multiphasic (Figure 6). The decline is initially rapid and characterized by a half-life of approximately 30 minutes. The subsequent, sequential half-lives are approximately 2 hours and 11 hours.
- Variability between participants in C_{max} and AUC after nasal esketamine is moderate, typically ranging from 30% to 40% (expressed as percent coefficient of variation). Variability of esketamine AUC is on the lower end of this range.

Figure 6: Mean Plasma Ketamine and Esketamine Concentration-Time Profiles Following Administration of 0.5 mg/kg Racemic Ketamine or 0.2 mg/kg Esketamine (40-minute IV infusion) in Patients with TRD and 28 mg, 56 mg, or 84 mg Esketamine Nasal Spray in Healthy Participants



IV=intravenous; TRD=treatment-resistant depression

Notes: Standard deviation bars for the IV regimens are not shown for clarity.
The plasma concentration-time profile of racemic ketamine produced by an IV regimen demonstrated to have antidepressant activity (i.e., 0.5 mg/kg given as a 40-minute infusion) in patients with major depressive disorder is provided as a reference[65]
Peak anesthetic induction blood levels of ketamine are as high as 9,000 – 25,000 ng/mL. The levels to maintain anesthesia are 2,000 – 3,000 ng/mL; patients awaken after levels are reduced to 500 – 1,000 ng/mL.[30,99]

Absorption

- Esketamine can be measured in plasma within 7 minutes following a 28-mg dose of nasal spray.
- Maximum plasma concentrations are reached 20 to 40 minutes after the last nasal spray (t_{max}).
- The mean absolute bioavailability of 84 mg esketamine nasal spray is 48%.

Distribution

- Esketamine is extensively distributed into tissues. Intravenously administered esketamine has a large volume of distribution (709 L).
- Esketamine is not highly bound to plasma proteins (i.e., <50%).

- Esketamine is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or organic anion transport proteins OATP1B1 or OATP1B3.

Metabolism and Elimination

- Esketamine is predominately (i.e., >80%) eliminated by hepatic metabolism followed by excretion of numerous metabolites into urine.
- Esketamine is predominately metabolized by hepatic CYP2B6 and CYP3A4. Other enzymes, including CYP2C19 and CYP2C9, contribute to a small extent.
- N-demethylation of esketamine to noresketamine is the initial metabolic pathway. Noresketamine is subsequently metabolized to numerous downstream metabolites.
- Based on results from nonclinical studies, the contribution of esketamine metabolites to the antidepressant activity of esketamine is expected to be minimal. Noresketamine is 3- to 6-times less potent than esketamine as a NMDA receptor antagonist, and the brain-to-plasma ratio of noresketamine is 6-times lower than that of esketamine. Other circulating metabolites are inactive as NMDA receptor antagonists.

4.2. Pharmacokinetics of Esketamine Nasal Spray in Subpopulations

The pharmacokinetics of intranasally administered esketamine is similar in patients with depression and healthy participants.

Adjustment of the nasal esketamine dose is not warranted for: (i) gender, (ii) body weight, (iii) mild or moderate hepatic impairment, (iv) mild to severe renal impairment, (v) presence of symptoms of allergic rhinitis.

For patients ≥65 years of age, the initial recommended dose of esketamine is 28 mg. Subsequent doses may be increased in increments of 28 mg up to either 56 mg or 84 mg, based on efficacy and tolerability. This dosing strategy was used in the Phase 3 studies with patients ≥65 years. A flexible dosing schedule was used to facilitate improved tolerability by gradually increasing the dose and to align with clinical practice for antidepressant medications, as many clinicians prefer to gradually increase the dose of medication and then adjust as clinically required.

4.3. Effect of Other Drugs on the Pharmacokinetics of Esketamine Nasal Spray

Esketamine that is absorbed directly into the bloodstream through the nasal mucosa is only minimally affected by changes in the activity of drug metabolizing enzymes in the liver. Adjustment of the nasal esketamine dose is not warranted in patients being treated with an: (i) inhibitor of hepatic enzymes CYP2B6 or CYP3A or (ii) inducer of hepatic enzymes CYP3A and CYP2B6.

The proposed label recommends that patients wait at least 1 hour after using an intranasal corticosteroid or decongestant before administering nasal esketamine. This recommendation is based on the results of a Phase 1 study which demonstrated the absence of clinically relevant effects on the pharmacokinetics of nasal esketamine when administered 1 hour after such intranasal drugs.

In addition, the pharmacokinetics of nasal esketamine is similar in patients with MDD being treated with an oral antidepressant and healthy participants.

4.3.1. Effect of Esketamine Nasal Spray on Other Drugs

Importantly, given the polypharmacy that characterizes the treatment regimens for MDD and TRD patients, esketamine has a low potential to alter the pharmacokinetics of other co-administered drugs based on the information below.

- Esketamine nasal spray (84 mg) administered twice per week for 2 weeks did not affect the activity of CYP2B6 enzyme activity, evaluated using oral bupropion as a probe substrate.
- Esketamine nasal spray (84 mg) administered twice per week for 2 weeks minimally induced CYP3A enzyme activity as shown by the slightly lowered mean plasma AUC_{∞} (by approximately 16%) of the probe substrate midazolam.
- Esketamine and it major circulating metabolites do not induce the hepatic CYP1A2 enzyme (in vitro study).
- Esketamine and its major circulating metabolites had a low inhibition potential for cytochrome P450 enzymes and uridine diphosphate glucuronosyltransferases (in vitro study).
- At clinically relevant doses, the administration of esketamine is not expected to inhibit the drug transporters P-gp, BCRP, multidrug and toxin extrusion transporters MATE1 and MATE2-K, OCT2, or OAT1, OAT3, OATP1B1, or OATP1B3 (in vitro study).

5. PHASE 2 CLINICAL STUDIES

Brief descriptions of the 4 Phase 2 clinical studies included in the NDA for esketamine nasal spray in patients with TRD are provided in this section (Table 3); the Phase 2 studies are referenced using the study name or the last 7 characters of the study code as shown.

Table 3: Completed Phase 2 Clinical Studies

Study Code	Study Name or Abbreviated Study Code	Study Population	Adjunctive Study Treatments
ESKETIVTRD2001	TRD2001	Adults (18-64 years) with TRD	IV esketamine (0.2 or 0.4 mg/kg) Placebo 2 times weekly
KETIVTRD2002	TRD2002	Adults (18-64 years) with TRD	IV ketamine (0.5 mg/kg) Placebo 2 or 3 times weekly
ESKETINTRD2003	SYNAPSE	Adults (20-64 years) with TRD	Esktetamine nasal spray (14, 28, 56 or 84 mg) Placebo 2 times weekly
ESKETINSUI2001	PERSEVERE	Adults (19-64 years) with MDD at imminent risk for suicide	Esktetamine nasal spray (84 mg) Placebo 2 times weekly

IV=intravenous; MDD=major depressive disorder; TRD=treatment-resistant depression

5.1. Phase 2 Studies with IV Esketamine and Ketamine in Patients with TRD

Two initial Phase 2 studies using subanesthetic doses of IV formulations of esketamine (TRD2001) and ketamine (TRD2002) were conducted to provide evidence of antidepressant activity in patients with TRD and to guide selection of dose and dosing frequency for the subsequent Phase 2 dose-response study of esketamine nasal spray (SYNAPSE; see Section 5.2.1). In both studies, IV esketamine and ketamine were adjunctive to the patient's ongoing oral antidepressant medication.

Study TRD2001 with IV Esketamine

Study TRD2001 assessed the efficacy and safety and explored the dose-response of IV esketamine infusion in patients with TRD.[97] Thirty patients were randomly assigned 1:1:1 to receive an IV infusion of 0.2 mg/kg or 0.4 mg/kg esketamine or placebo over 40 minutes on Day 1. The primary endpoint was change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (baseline) to Day 2.

The least-squares (LS) mean changes (standard error [SE]) from baseline to Day 2 in MADRS total score for both esketamine groups showed significant improvement (-16.8 [3.00] for the 0.2 mg/kg dose, 2-sided p=0.0028; -16.9 [2.61] for the 0.4 mg/kg dose, 2-sided p=0.0019) compared with placebo (-3.8 [2.97]). Esketamine showed a rapid (within 2 hours) antidepressant effect. As there were no additional benefits for patients who received the higher dose, the circulating levels of esketamine at the 0.20 mg/kg dose were selected as the target for further development of intranasally administered esketamine.

Study TRD2002 with IV Ketamine

As single dose studies with IV ketamine suggested that the duration of antidepressant effects was approximately 5 days and that weekly dosing may not be sufficient to maintain these effects, Study TRD2002 evaluated the efficacy of IV ketamine administered either two or three times per week in sustaining initial antidepressant effects in adults with TRD.[98] Patients were randomized to receive IV ketamine (0.5 mg/kg) or IV placebo, administered over 40 minutes, either two or three times per week, for up to 4 weeks. Patients who discontinued double-blind treatment after at least 2 weeks for lack of efficacy could enter an optional 2-week open-label phase to receive ketamine with the same frequency as in the double-blind phase. The primary outcome measure was change from baseline to Day 15 in MADRS total score.

In the groups receiving treatment two times weekly, the mean change in MADRS total score (SD) at Day 15 was -18.4 (12.0) for ketamine and -5.7 (10.2) for placebo (2-sided p<0.001); in the groups receiving treatment three times weekly, it was -17.7 (7.3) for ketamine and -3.1 (5.7) for placebo (2-sided p<0.001). Similar observations were noted for ketamine during the open-label phase (two times weekly, -12.2 [12.8] on Day 4; three times weekly, -14.0 [12.5] on Day 5). As administration of IV ketamine at 0.5 mg/kg either two times per week or three times per week similarly maintained antidepressant effects over 15 days, the lower dosing frequency (twice weekly) was selected for subsequent studies with esketamine nasal spray.

Dosing Information for Studies with Esketamine Nasal Spray

Studies TRD2001 and TRD2002 confirmed published observations and showed that subanesthetic doses of IV ketamine (0.5 mg/kg) and IV esketamine (0.2 and 0.4 mg/kg) provided rapid relief of depressive symptoms in patients with TRD. As the 0.20 mg/kg dose of IV esketamine provided the maximal antidepressant effect in Study TRD2001, this dose was selected as the exposure target for doses of esketamine nasal spray. Additionally, in Study TRD2002 the initial treatment effect of IV ketamine could be maintained over a period of 2 weeks with dosing either two times or three times per week; therefore, the lower frequency (twice weekly) was selected for further studies with esketamine nasal spray. Results from Phase 1 studies suggested that plasma esketamine concentrations produced by the 84-mg dose of intranasally administered esketamine would reliably achieve or exceed the concentrations produced by the 0.2-mg/kg infusion of IV esketamine (Figure 6). A range of doses of esketamine nasal spray were selected (i.e., 28, 56 and 84 mg) for subsequent Phase 2 studies to evaluate the dose-response relationship with respect to MADRS total score and other endpoints. Intranasal doses higher than 84 mg were not selected as similar efficacy was seen in patients with TRD receiving IV infusions of either 0.2 mg/kg or 0.4 mg/kg esketamine.

5.2. Phase 2 Studies with Esketamine Nasal Spray

Two Phase 2 studies with esketamine nasal spray were included in the NDA to provide supportive evidence of efficacy in patients with TRD. Results from the Phase 2 dose-response study SYNAPSE in patients with TRD were used to help guide the design of the Phase 3 clinical program in TRD, including dosing information. Results from a Phase 2 proof-of-concept study in a related population with MDD, patients at imminent risk for suicide, using esketamine nasal spray (PERSEVERE) provided further support for the rapid antidepressant activity of this medication.

5.2.1. Phase 2 Dose-response Study with Esketamine Nasal Spray in Patients with TRD (SYNAPSE)

Overview

- In Panel A (with 28-, 56-, and 84-mg doses of esketamine):
  - After 1 week of treatment with 28, 56 or 84 mg of esketamine nasal spray, TRD patients had significant improvement in depressive symptoms.
  - There was a significant dose-response relationship between esketamine dose and improvement in depressive symptoms after 1 week of treatment.
  - The 28-mg dose elicited the least improvement and appeared less able to sustain the improvements.
- In Panel B (with 14- and 56-mg doses of esketamine), the 14-mg dose of esketamine was not considered efficacious.

Study Design and Population

The Phase 2 dose-response study SYNAPSE consisted of 2 panels: Panel A, conducted in the US and Belgium and Panel B, conducted in Japan. The study evaluated the efficacy and dose response of intranasally administered esketamine compared with placebo in improving depressive symptoms in patients with TRD. Panel A studied 28-, 56-, and 84-mg doses of esketamine, while Panel B studied 14- and 56-mg doses of esketamine. As mentioned above, the doses of 28 to 84 mg were selected based on the results from previous Phase 2 and Phase 1 studies suggesting these doses would have antidepressant effects in patients with TRD. The 14-mg dose was included in Panel B to evaluate if this dose could determine a minimally effective dose of esketamine. Twice-weekly esketamine or placebo nasal spray was given adjunctively with the ongoing antidepressant treatment(s) being administered at the time of study entry.

After a screening phase of up to 4 weeks, eligible patients entered the double-blind treatment phase (Days 1-15), composed of two 1-week periods. Patients were randomized to treatment at the start of Period 1, and placebo patients who did not respond in Period 1 were rerandomized to treatment in Period 2. Those completing the double-blind phase had the option to continue in the open-label treatment phase (Panel A: Days 15 to 74 and Panel B: Days 15 to 25). Patients entered an 8-week follow-up phase after cessation of study treatment.

Panels A and B were analyzed separately for efficacy using an analysis of covariance (ANCOVA) model on last observation carried forward (LOCF) data. The change from baseline in the MADRS total score for the combined periods in the double-blind treatment phase was used to measure changes in depressive symptoms. Evidence from the results of the pairwise comparisons of each esketamine dose versus placebo and the comprehensive dose-response analysis was used in the assessment of efficacy. The rate of response, defined as ≥50% improvement from baseline in MADRS total score, was a secondary endpoint.

Adults 20 to 64 years of age with a diagnosis of MDD and history of inadequate response to 2 or more antidepressants (i.e., TRD) were screened; 67 patients were randomized in Panel A, and 41 in Panel B. The completion rate for the 2-week double-blind treatment phase was 89.6% in Panel A (60 of 67 randomized patients) and 97.6% in Panel B (40 of 41 randomized patients). Of these, 57 patients in Panel A and 39 in Panel B entered the optional open-label treatment phase.

The demographic and baseline characteristics for patients enrolled in Panels A and B are shown in Table 4. In each panel, the baseline characteristics were generally similar across treatment groups.

Table 4: Demographic Characteristics at Baseline of Patients Enrolled in Panels A and B in Phase 2 Dose-response Study SYNAPSE

	Panel A Belgium and US (N=67)	Panel B Japan (N=41)
Age, years		
Mean (SD)	44.7 (10.04)	44.5 (8.03)
Sex, n (%)		
Female	38 (56.7)	17 (41.5)
Race, n (%)		
American Indian or Alaska Native	1 (1.5)	N/A
Asian	N/A	41 (100)
Black or African American	18 (26.9)	N/A
White	48 (71.6)	N/A
Ethnicity, n (%)		
Hispanic or Latino	3 (4.5)	N/A
Not Hispanic or Latino	62 (92.5)	40 (97.6)
Unknown	2 (3.0)	1 (2.4)
Baseline MADRS Total Score		
Mean (SD)	34.1 (5.11)	28.3 (7.20)

MADRS=Montgomery-Asberg Depression Rating Scale; N/A=not applicable; SD=standard deviation; US=United States

Results

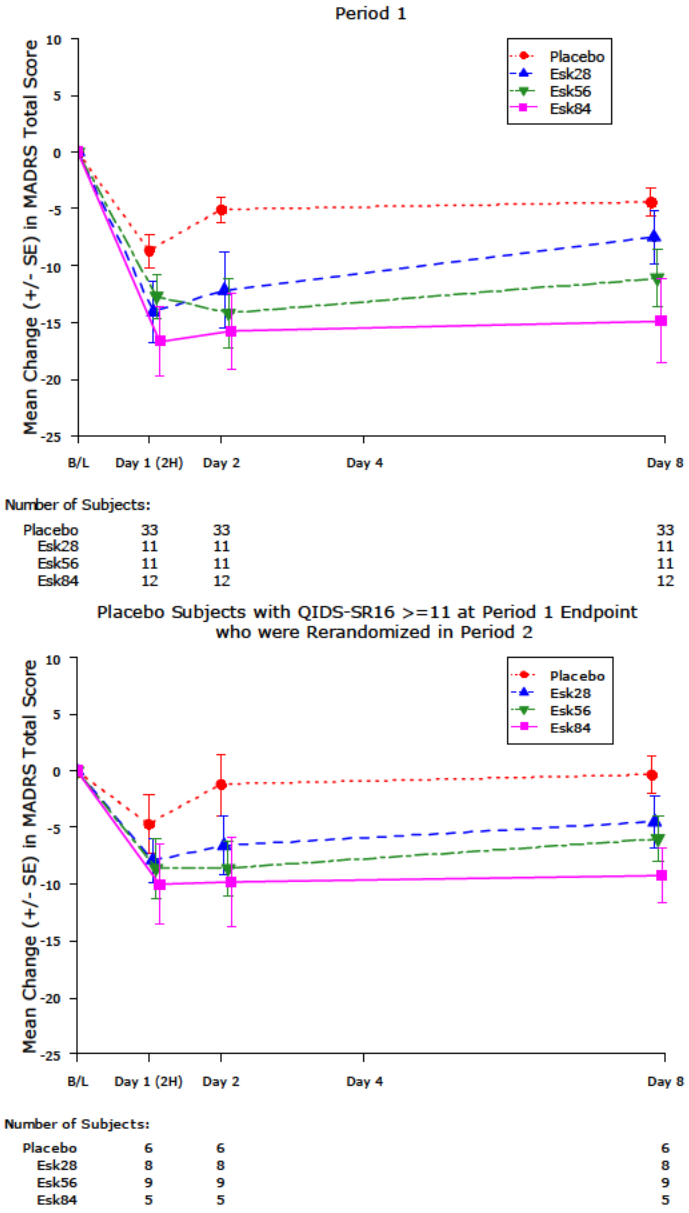
In Panel A of the adjunctive Phase 2 study SYNAPSE, improvements in MADRS total score after 1 week of treatment in all 3 esketamine dose groups were significantly greater than the improvement in the placebo group (Table 5 and Figure 7). The greatest decrease in MADRS total score was seen with the 84-mg dose, followed by the 56-mg dose; the 28-mg dose elicited the least decrease and appeared less able to sustain the decrease with twice-weekly dose administration.

Table 5: MADRS Total Score: Change from Baseline to End Point ANCOVA LOCF Analysis; Double-Blind Phase Panel A (SYNAPSE)

	Esketamine 28mg	Esketamine 56mg	Esketamine 84mg
Period 1 and Period 2 Combined			
Mean difference from Placebo (SE)	-4.2 (2.09)	-6.3 (2.07)	-9.0 (2.13)
90% CI for Mean difference from Placebo	(-7.67; -0.79)	(-9.71; -2.88)	(-12.53; -5.52)
2-sided p-value	0.043	0.002	<0.001

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; SE=standard error
A negative change in score indicates improvement.

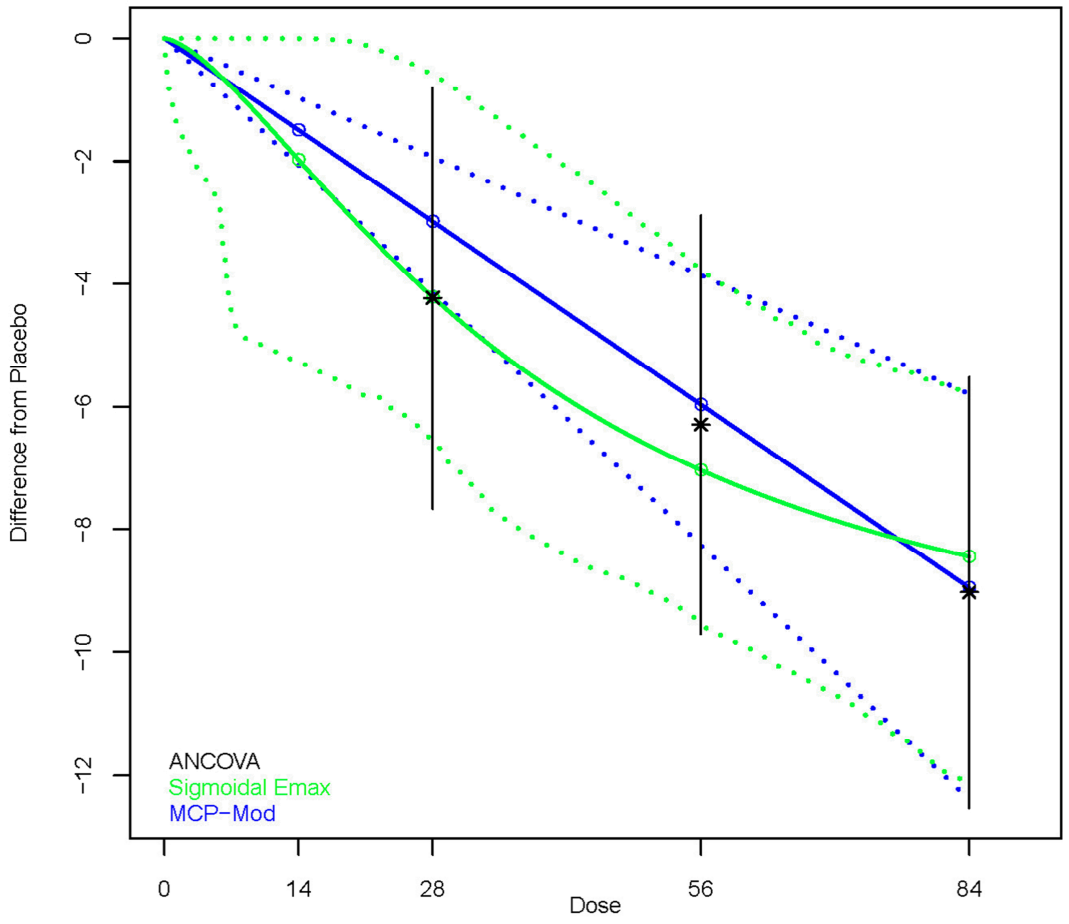
Figure 7: Mean Changes (± SE) in MADRS Total Score Over Time LOCF; Double-Blind Phase Panel A (SYNAPSE)



Esk=esketamine; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; QIDS-SR16=Quick Inventory of Depressive Symptomatology – 16-item Self Report; SE=standard error
A negative change in score indicates improvement.

Results from the dose-response analysis of data combined from both periods were statistically significant (1-sided $p<0.001$) indicating a significant dose-response relationship between esketamine dose and change in MADRS total score after 1 week of treatment (Figure 8). Analyses were performed to estimate the dose-response curves. Figure 8 shows the sigmoid E_{max} model and the linear model that was selected from the Multiple Comparisons and Modeling procedure. In addition, results from ANCOVA are presented.

Figure 8: MADRS Total Score Change from Baseline to End Point Multiple Comparisons and Modeling Procedure, Sigmoidal E_{max} and ANCOVA Treatment Effects and 90% Confidence Interval Period 1 and Period 2 Combined Panel A SYNAPSE



ANCOVA=analysis of covariance; MADRS=Montgomery-Asberg Depression Rating Scale;
MCP-Mod=Multiple Comparisons and Modeling Procedure
Note: A negative change in score indicates improvement. The solid lines are the estimated dose-response curves, and the dotted lines are the 90% confidence intervals. The asterisks (*) are estimates based on the ANCOVA analysis, and the bars are the 90% confidence intervals.

At 2 hours, 24 hours and 8 days after the first dose in Period 1, the response rate (≥50% improvement in MADRS from baseline) was higher with each esketamine dose than with placebo treatment (Table 6).

Table 6: MADRS Total Score Response Rates: ≥50% Improvement in MADRS Total Score at 2 Hours, 24 Hours and Day 8 in Period 1 (SYNAPSE)

	Placebo (N=33)	Esketamine 28mg (N=11)	Esketamine 56mg (N=11)	Esketamine 84mg (N=12)
PERIOD 1, n (%) with ≥ 50% Improvement in MADRS total score				
2 hours after the first dose	6 (18.2)	6 (54.5)	4 (36.4)	7 (58.3)
24 hours after the first dose	1 (3.0)	4 (36.4)	3 (27.3)	5 (41.7)
Day 8	2 (6.1)	1 (9.1)	2 (18.2)	5 (41.7)

MADRS=Montgomery-Asberg Depression Rating Scale

Results from Panel B during Period 1 indicated that the esketamine 14 mg dose was not efficacious; the LS mean (SE) differences from placebo in Period 1 after 1 week of treatment were:

- +1.8 (2.62) for the esketamine 14 mg group and
- -3.7 (2.81) for the esketamine 56 mg group

5.2.2. Phase 2 Study with Esketamine Nasal Spray in Patients with MDD at Imminent Risk for Suicide (PERSEVERE)

Overview

- Patients with MDD at imminent risk for suicide treated with esketamine nasal spray in addition to standard of care treatment (initiated or optimized AD treatment and inpatient hospitalization), demonstrated significantly greater improvement in depressive symptoms at 4 hours after the first dose compared with those treated with placebo + standard of care.

Study Design and Population

The Phase 2 study PERSEVERE in patients with MDD at imminent risk for suicide, a population related to TRD, was included in the NDA to provide further evidence for the rapid antidepressant effects of esketamine nasal spray. This study evaluated the efficacy of intranasally administered esketamine (84 mg) compared with placebo in reducing the symptoms of MDD (including suicidal ideation) in patients who presented to an emergency room (ER) or other permitted setting (e.g., inpatient psychiatric unit) and were assessed to be at imminent risk for suicide.[16] The study enrolled patients from sites in the US.

Results from previous Phase 2 and Phase 1 studies suggested the 28 to 84 mg doses of esketamine nasal spray would have antidepressant effects and be tolerated in patients with MDD (see Section 5.1). As this proof-of-concept study was conducted in the context of a psychiatric emergency, the 84-mg dose was selected to provide patients the greatest opportunity for rapid onset of efficacy with the option to reduce the dose to 56 mg for tolerability.

The study consisted of a screening evaluation performed within 24 hours prior to the first dose of esketamine or placebo nasal spray on Day 1, immediately followed by a 25-day double-blind treatment phase (Days 1 to 25) and a 56-day follow-up phase (Days 26 to 81). Nasal spray study medication was administered twice weekly in addition to standard of care treatment (initiated or optimized AD treatment and inpatient hospitalization).

The primary efficacy endpoint was change in MADRS total score from baseline to 4 hours after the initial dose of nasal spray, analyzed using an ANCOVA model on LOCF data, including factors for treatment (placebo, esketamine 84 mg), analysis center, antidepressant treatment (AD monotherapy or AD plus augmentation therapy), and baseline MADRS total score as a continuous covariate. Secondary efficacy endpoints included change in MADRS total score from baseline to 24 hours and to the double-blind endpoint at Day 25; the ANCOVA model described above was also used to analyze these endpoints.

Results

On Day 1 of the double-blind treatment phase, patients 19 to 64 years of age with a diagnosis of MDD without psychotic features were randomized in a 1:1 ratio to twice-weekly esketamine 84 mg or placebo nasal spray. The completion rate for the double-blind treatment phase was 72.1% (49 of 68 randomized patients).

The demographic and baseline characteristics of 66 patients who received at least 1 dose of study medication are shown in Table 7. In general, the treatment groups were similar with respect to baseline characteristics.

Table 7: Demographic Characteristics at Baseline of Patients with MDD at Imminent Risk for Suicide Enrolled in PERSEVERE (Intent to Treat Analysis Set)

	Esketamine 84 mg (N=35)	Placebo (N=31)
Age, years		
Mean (SD)	35.7 (13.40)	36.0 (12.82)
Sex, n (%)		
Female	22 (62.9%)	21 (67.7%)
Race, n (%)		
Asian	1 (2.9%)	0
Black or African American	12 (34.3%)	13 (41.9%)
White	20 (57.1%)	15 (48.4%)
Multiple	0	1 (3.2%)
Other	0	2 (6.5%)
Not Reported	2 (5.7%)	0
Ethnicity, n (%)		
Not Hispanic or Latino	31 (88.6%)	29 (93.5%)
Hispanic or Latino	4 (11.4%)	1 (3.2%)
Not Reported	0	1 (3.2%)
Baseline MADRS Total Score		
Mean (SD)	38.5 (6.17)	38.8 (7.02)

MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; SD = standard deviation

A significantly greater improvement in MADRS total score was observed in the esketamine + standard of care group compared with the placebo + standard of care group at 4 hours after the first dose of study treatment and at Day 2, approximately 24 hours after the first dose. (Table 8 and Figure 9)

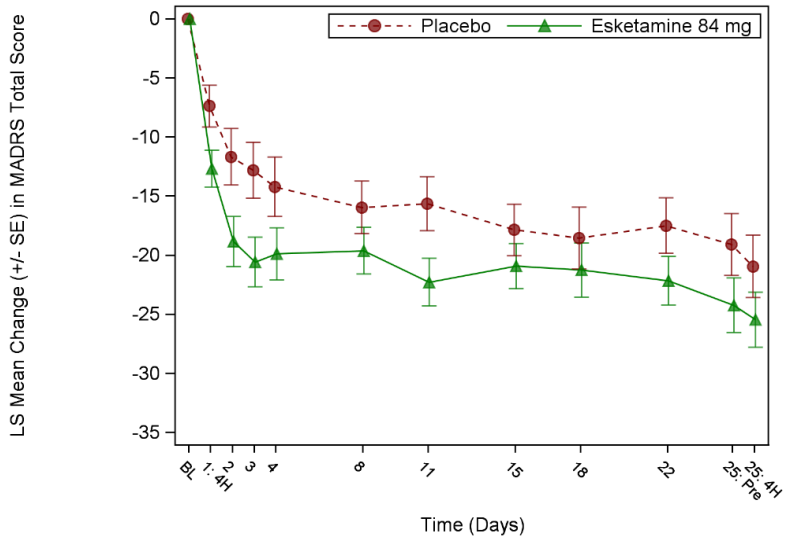
At the end point of the double-blind treatment phase (Day 25), a numerically greater improvement in the MADRS total score was observed for esketamine + standard of care compared with placebo + standard of care (Table 8 and Figure 9). Although not statistically significant, these results support continued clinical research to evaluate the benefits of esketamine over placebo after 25 days of treatment.

Table 8: Primary and Secondary Analyses of Change From Baseline in MADRS Total Score (PERSEVERE)

	Placebo (N=31)	Esketamine 84 mg (N=35)
Primary Endpoint		
Change from Baseline to Day 1: 4 hrs after first dose		
Mean (SD)	-9.1 (8.38)	-13.4 (9.03)
Difference of LS Means (SE)		-5.3 (2.10)
2-sided p-value (a)		0.015
Secondary Endpoints		
Change from Baseline to Day 2 (~24 hrs after first dose)		
Mean (SD)	-12.8 (9.77)	-19.3 (12.02)
Difference of LS Means (SE)		-7.2 (2.85)
2-sided p-value (a)		0.015
Change from Baseline to End Point		
Mean (SD)	-23.0 (10.83)	-26.4 (14.52)
Difference of LS Means (SE)		-4.5 (3.14)
2-sided p-value (a)		0.159

MADRS=Montgomery-Asberg Depression Rating Scale; SD=standard deviation; SE=standard error
(a) Based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), antidepressant therapy (AD monotherapy, AD plus augmentation therapy) and analysis center as factors, and baseline value as a covariate.
Note: Negative change in score indicates improvement.
Note: Baseline is the predose, Day 1 value.

Figure 9: Least-square Mean Changes (± SE) From Baseline for MADRS Total Score Over Time LOCF: Double- Blind Phase (PERSEVERE)



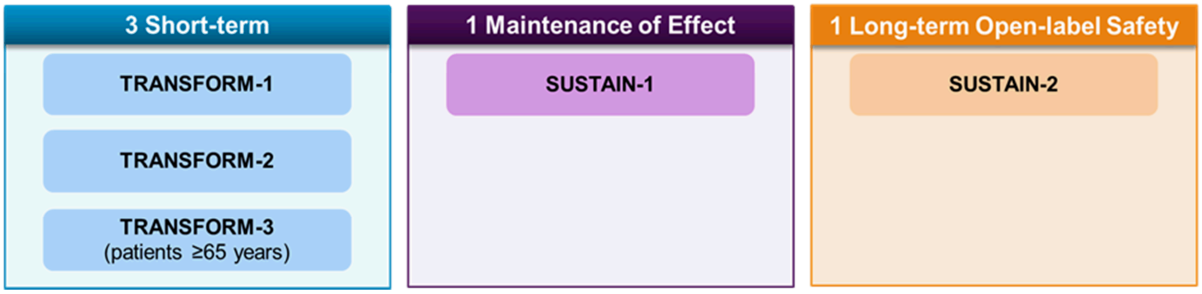
AD=antidepressant; BL=baseline; LOCF=last observation carried forward; LS=least squares; MADRS=Montgomery-Asberg Depression Rating Scale; Pre=predose; SE=standard error
N=35 in the esketamine group; N=31 in the placebo group
Note: LS Mean and SE were based on analysis of covariance (ANCOVA) model with treatment (placebo, esketamine 84 mg), antidepressant therapy. (AD monotherapy, AD plus augmentation therapy) and analysis center as factors, and baseline value as a covariate. Note: Negative change in score indicates improvement.
Note: Baseline is the predose, Day 1 value.

6. PHASE 3 STUDY DESIGN AND POPULATION

6.1. Phase 3 TRD Clinical Development Program

Five Phase 3 studies with esketamine nasal spray in patients with TRD were completed in the clinical development program (Figure 10). The efficacy and safety of esketamine, given concurrently with a newly-initiated oral antidepressant (AD), in adults with TRD was evaluated in 3 double-blind, controlled, short-term Phase 3 studies: TRANSFORM-1 and 2 were conducted in patients 18 to 64 years of age. TRANSFORM-3 was conducted only in patients ≥65 years of age, a population often underrepresented in clinical studies for treatments of MDD and rarely evaluated as the only population in a study with MDD patients. A fourth double-blind randomized withdrawal study, SUSTAIN-1, compared randomized continuation of esketamine treatment with randomized discontinuation of esketamine in delaying relapse among adults with TRD who had achieved stable remission or stable response after 16 weeks of treatment with esketamine plus an oral AD. A fifth open-label Phase 3 study, SUSTAIN-2, which did not have a comparator, was designed primarily to assess long-term safety and tolerability in adults with TRD.

Figure 10: Completed Phase 3 Studies in the TRD Clinical Development Program



TRD=treatment-resistant depression

Patients in the 5 completed Phase 3 studies were eligible to continue treatment in an open-label safety extension study, SUSTAIN-3. This study was designed to provide an opportunity for patients in whom the benefit-risk (per clinical judgment) supported treatment with esketamine to receive this medication until it is available to the patient outside of the study; until the patient no longer benefits from further treatment (per clinical judgment) or withdraws consent; or until the clinical development of esketamine for TRD is terminated. SUSTAIN-3 is currently ongoing.

The full study code, study name and description of the Phase 3 studies are shown in Table 9; in this document, the Phase 3 studies are referenced using the study names.

Table 9: Phase 3 Clinical Studies with Esketamine Nasal Spray in Patients with TRD

Study Code	Study Name	Age of TRD Population	Study Description
ESKETINTRD3001	TRANSFORM-1	18-64 years	Short-term, double-blind study (completed)
ESKETINTRD3002	TRANSFORM-2	18-64 years	Short-term, double-blind study (completed)
ESKETINTRD3005	TRANSFORM-3	≥65 years	Short-term, double-blind study (completed)
ESKETINTRD3003	SUSTAIN-1	18-64 years	Randomized withdrawal study (completed)
ESKETINTRD3004	SUSTAIN-2	≥18 years	Long-term, open-label safety study (completed)
54135419TRD3008	SUSTAIN-3	≥18 years	Long-term, open-label extension study (ongoing)

TRD=treatment-resistant depression

All completed Phase 3 studies included:

- A screening phase to assess eligibility for the induction phase with:
  - Prospective evaluation of prior oral AD treatments in the 4 double-blind studies (TRANSFORM-1, 2, and 3, and SUSTAIN-1); see Section 6.1.1
  - Retrospective evaluation of prior oral AD treatments in the open-label safety study (SUSTAIN-2); see Section 6.1.1
- 4-week induction phase with:
  - Double-blind study treatment in the short-term studies (TRANSFORM-1, 2, and 3)
  - Open-label study treatment in the long-term studies (SUSTAIN-1 and 2)

In SUSTAIN-1 and 2, optimization and maintenance phases followed the induction phase.

6.1.1. Selection of Patients with Treatment-resistant Depression

In the clinical development program for esketamine nasal spray, treatment-resistant depression was defined as a lack of clinically meaningful improvement in the current episode of depression after treatment with at least 2 different AD agents prescribed in adequate dosages for an adequate duration. Nonresponse (i.e., lack of clinically meaningful improvement) to at least 1 oral AD treatment was assessed prospectively during the screening/observation phase in all Phase 3 studies except for the long-term open-label study SUSTAIN-2, which used retrospective confirmation for all oral AD treatments.

The Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ), a validated scale to determine treatment resistance in MDD,[18] was used to document oral AD use and response (medication, dose, duration of treatment) in the current depression episode. Written documentation of the MDD diagnosis and prior AD use from medical/pharmacy records also was obtained.

Retrospective and prospective assessments of prior AD nonresponse were confirmed as follows:

- *Retrospective assessment of prior AD nonresponse in current episode of depression:* patients had documented nonresponse (≤25% improvement or lack of any clinically meaningful improvement) to the oral AD treatment taken for the current episode of depression prior to the initial screening visit for an adequate duration (at least 6 weeks) at adequate dosage, as assessed on the MGH-ATRQ and confirmed by documented medical or pharmacy records.
- *Prospective assessment of AD nonresponse:* at the initial screening visit, patients had received treatment for the current episode of depression with the oral AD for at least 2 weeks at or above the minimum therapeutic dose per the MGH-ATRQ, and they continued the medication(s) prospectively during the 4-week screening/prospective observational phase. Only patients who demonstrated (prospectively) nonresponse to the current oral AD after at least 6 weeks (≤25% improvement on MADRS total score from Week 1 to 4, together with a MADRS total score of ≥28 on Week 2 and Week 4 [≥24 for patients ≥65 years in TRANSFORM-3]), were eligible to enter the induction phase of the study. Medication adherence was documented on the Patient Adherence Questionnaire during the screening/prospective observational phase to ensure that patients took at least a minimum therapeutic dose of the current oral AD.

6.1.2. Study Treatments and Dose Selection

In each Phase 3 study, doses of esketamine nasal spray were administered intermittently: twice weekly for induction therapy, with dosing subsequently reduced to once weekly or once every 2 weeks based on efficacy in the optimization and maintenance phases of the longer-term studies SUSTAIN-1 and 2. Nasal spray study medication was given concurrently with a newly-initiated oral AD, dosed daily to the maximally tolerated dose.

Nasal Spray Study Medication

- *Nasal spray dose selection*: In the Phase 3 TRD program, esketamine nasal spray was administered at doses of 28 mg (patients ≥65 years only), 56 mg, or 84 mg. Results from the dose-response study SYNAPSE suggested that the 14 and 28 mg doses of esketamine nasal spray had insufficient efficacy in young/mid-life adults (see Section 5.2.1). The 14-mg dose was not a dose option in the Phase 3 program; however, the 28-mg dose was used only for patients ≥65 years as a starting dose for improved tolerability and as a dose option for those not tolerating higher doses.
- *Fixed and flexible nasal spray dosing*: The Phase 3 short-term double-blind study TRANSFORM-1 evaluated 2 fixed doses of esketamine (56 mg or 84 mg). Flexible dosing of esketamine was evaluated in the other Phase 3 short-term studies, TRANSFORM-2 (56 or 84 mg) and TRANSFORM-3 (28, 56, or 84 mg), and in the maintenance of effect study SUSTAIN-1 (56 or 84 mg) and long-term open-label study SUSTAIN-2 (28, 56, or 84 mg). A flexible dosing schedule was used to facilitate improved tolerability by gradually increasing the dose and to align with clinical practice, as many clinicians prefer to gradually increase the dose of AD medication and then adjust as clinically required. The fixed-dose design in TRANSFORM-1 was used to separately compare esketamine doses of 56 mg and 84 mg plus an oral AD with oral AD + placebo.
- *Frequency of nasal spray dosing*: Dosing of nasal spray study treatments (esketamine or placebo) was twice weekly during the Phase 2 study SYNAPSE and during the induction phases of the Phase 3 studies. In the longer-term Phase 3 studies (SUSTAIN-1 and 2), the frequency of nasal dosing after the induction phase was weekly for the first 4 weeks, then individualized to once weekly or every other week to achieve the lowest dosing frequency for an individual patient that could sustain initial improvements in depressive symptoms with the aim of using the lowest frequency of dosing to sustain remission. The algorithm for frequency adjustment is provided in Appendix 2.

Oral Antidepressant Study Medication

- *Oral AD treatment*: The newly assigned oral AD was dosed daily with a forced titration to the maximum dose recommended in the label. The specific oral AD administered could be selected from 2 different classes of treatments, SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine extended release). Each patient had not: (i) previously shown nonresponse to the new oral AD in the current depressive episode and/or (ii) demonstrated intolerance to the new oral AD during the patient's lifetime. These medications were representative of the 2 most commonly used classes of ADs and were consistent with the current standard of care.

As described in Section 2.3.2, nasally-administered study medication was given concurrently with a newly-initiated oral AD (new AD control); therefore, the Phase 3 short-term studies used neither an inactive comparator (i.e., placebo) only design nor a classical adjunctive (add-on) design.

6.1.3. Blinding

Several measures were implemented in the Phase 3 studies to achieve and maintain blinding:

- *Placebo nasal spray:* The control treatment in all Phase 3 studies included a placebo nasal spray. A bittering agent (denatonium benzoate) was added to the placebo solution to facilitate blinding by simulating the taste of the esketamine solution.
- *Blinded, remote, independent assessment of efficacy:* The MADRS, used to evaluate the primary endpoint for the short-term Phase 3 studies, is a structured, clinician-administered interview designed to measure depression severity (see Section 7.1). As esketamine has known transient dissociative effects (i.e., distortion of time and space, illusions, derealization, and depersonalization) that are difficult to blind and potentially could bias the research staff who observe these effects, the MADRS was performed prior to nasal spray dosing throughout the double-blind studies over the telephone by independent, blinded raters using the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA).[115] Blinded, independent raters were specifically trained not to inquire about treatment effects, and study participants were reminded not to discuss treatment effects with the MADRS raters. To enhance rating quality and reliability, and to prevent rater drift, the remote MADRS assessments were recorded and reviewed.

6.1.4. Challenges of Placebo Response in Clinical Studies with Antidepressant Medications

The mechanism underlying the placebo effect in medicine is a much-debated topic. A recent review on the mechanism of placebo responses suggested that they are mediated by expectations, associative learning processes, hope, and the quality and quantity of the patient-physician interaction.[94]

Several factors in the Phase 3 studies with esketamine nasal spray likely contributed to a significant expectation of benefit and hope for patients in these studies, presumably increasing the placebo effect in the randomized, double-blind controlled trials:

- Use of a newly-initiated AD (to which the patient had not shown a previous nonresponse) in the comparator arm (i.e., not a true placebo control);[81] therefore, every patient entering the study expected to receive a "new" treatment to which they had not previously been exposed; furthermore, there was a fixed titration schedule for the new oral AD, which leads to increased hope for response as the dose is increased
- High patient expectation of benefit due to the portrayal in the media of ketamine as a 'magical' new treatment option for depression[1,102]
- High frequency and intensity of patient-clinician interaction due to twice-weekly visits (of approximately one-half day in length) during the induction phase, which imparts a high degree of attention and care[57]
- Use of nasal spray delivery system leading to a patient expectation of 'something novel'

- Nocebo response (i.e., adverse effect following an 'inert' treatment) as noted by an increase in dissociative effects (measured by the Clinician Administered Dissociative States Scale) after placebo nasal spray administration to which a bittering agent had been added to facilitate blinding (see Section 8.5). This nocebo response increased the participants' expectation that they had received a pharmacologically active drug in the nasal spray.

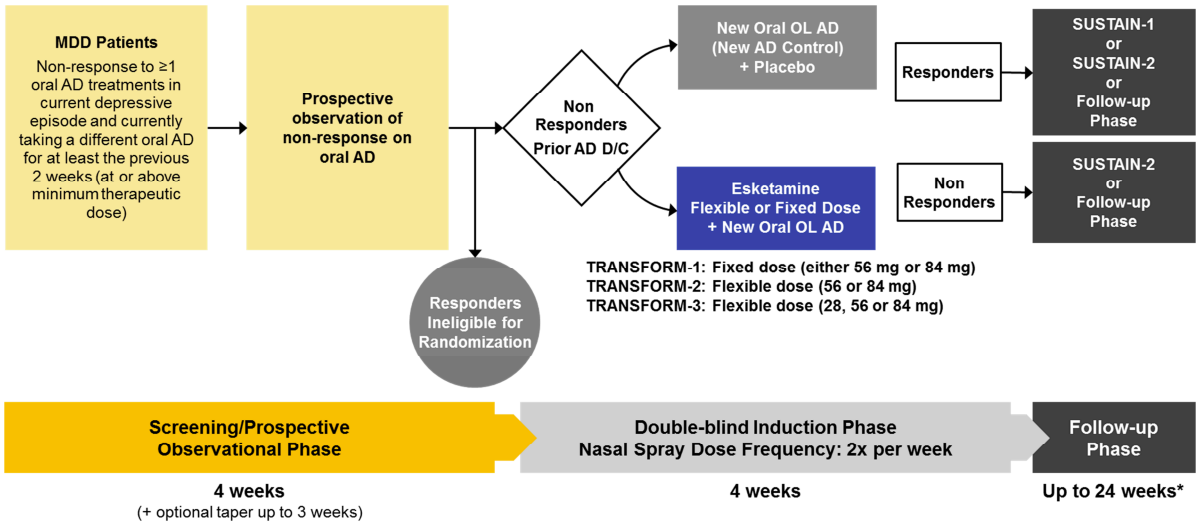
While considerable care was taken to minimize other contributors to a placebo response in the Phase 3 studies with esketamine nasal spray (e.g., efforts to select patients with TRD, efforts to minimize MADRS rater drift), expectation of benefit is difficult to control. Quantification of the impact of expectation on placebo response has been evaluated in recent studies. For example, in a comparison of overt or covert treatment with escitalopram in patients with social anxiety, patients receiving the active AD, but believing they were receiving placebo, had response rates that were 3 times lower than those receiving the identical treatment but told they were receiving active drug.[36] Similarly, in a study comparing medication + supportive care, placebo + supportive care, and supportive care alone in MDD patients, Leuchter found that expectations of medication effectiveness at enrollment predicted and increased only the placebo response.[57] Finally, the duration of placebo response typically is relatively long-lasting in trials of MDD, lasting well beyond the four week trial duration of the short-term Phase 3 TRANSFORM studies, thus reducing the effect size of the active drug versus placebo difference in antidepressant trials.[52]

6.2. Short-term Double-blind Studies

The designs for the three Phase 3 short-term double-blind studies (TRANSFORM-1, 2, and 3) were nearly identical (Figure 11), differing mainly in dosing regimen. Patients initially took part in a screening/prospective observational phase to confirm nonresponse to the current oral AD treatment regimen and determine eligibility. Patients who entered the double-blind induction phase discontinued their current (failed) AD medication and received treatment with a randomly assigned nasal spray study medication (esketamine or placebo, twice weekly) plus a new oral AD for 4 weeks.

TRANSFORM-1 was a fixed-dose study, while both TRANSFORM-2 and 3 were flexible-dose studies. In TRANSFORM-1 and 2, patients 18 to 64 years were eligible for enrollment; TRANSFORM-3 targeted patients ≥65 years with TRD. The evaluation of esketamine in TRD patients ≥65 years was important as the dosing regimen for esketamine in these patients differed from younger adults. Furthermore, the median age of the general population is increasing and patients ≥65 years are often underrepresented in clinical studies. Treatment of depression in patients ≥65 years is challenging as patients not only commonly suffer from disability, functional decline, and diminished quality of life from TRD, but also from comorbid medical conditions.[54]

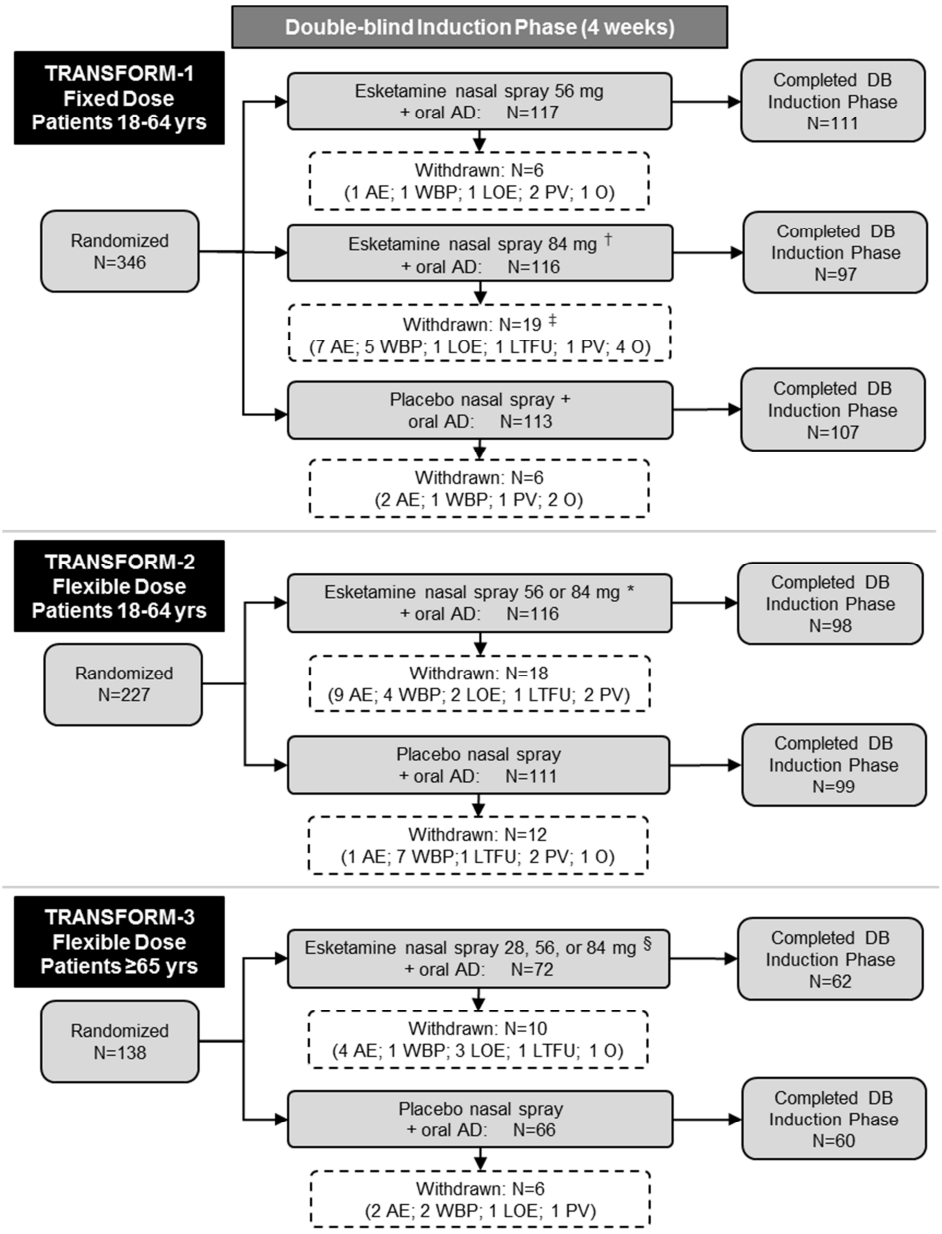
Figure 11: Short-term Phase 3 Study Diagram



AD=antidepressant; D/C=discontinued; MDD=major depressive disorder; OL=open-label
* The duration of the follow-up phase was 24 weeks in TRANSFORM-1 and 2, and 2 weeks in TRANSFORM-3.

Patient flow diagrams for the double-blind induction phases in the Phase 3 short-term studies are shown in Figure 12.

Figure 12: Patient Flow Diagram Phase 3 Short-term Studies



AD=antidepressant; AE=adverse event; DB=double-blind; LOE=lack of efficacy; LTFU=lost to follow-up; O=other reason; PV=protocol violation; WBP=withdrawal by patient

† The first esketamine dose was 56 mg for all patients in the esketamine 84 mg + oral AD group in TRANSFORM-1. The study design required a fixed titration: 56 mg on Day 1 with titration to 84 mg at subsequent treatment sessions.

‡ 11 of 19 withdrawn patients in the esketamine 84 mg + oral AD group in TRANSFORM-1 were withdrawn after only receiving the first 56-mg dose. Further information is provided in Section 8.3.3.

* All esketamine-treated patients in TRANSFORM-2 started with a 56-mg dose on Day 1. The dose could have been titrated at subsequent treatment sessions based on clinical judgment.

§ All esketamine-treated patients in TRANSFORM-3 started with a 28-mg dose on Day 1. The dose could have been titrated at subsequent treatment sessions based on clinical judgment.

Nasal spray study medication was administered twice weekly.

Oral AD study medication was administered daily according to the fixed dose titration specified in the label.

The demographic and baseline depression characteristics for patients who received at least 1 dose of nasal spray study medication and 1 dose of oral AD study medication (the full analysis set used for analysis of the primary efficacy endpoint) are shown in Table 10. Within the individual Phase 3 short-term double-blind studies in TRD, the treatment groups were balanced with respect to demographic and baseline depression characteristics.

Table 10: Demographic Characteristics at Baseline of the Double-blind Induction Phases in TRANSFORM-1, 2, and 3 (Full Analysis Set)

	TRANSFORM-1			TRANSFORM-2		TRANSFORM-3	
	Esketamine 56 mg +Oral AD (N=115)	Esketamine 84 mg +Oral AD (N=114)	Oral AD +Placebo (N=113)	Esketamine 56 or 84 mg +Oral AD (N=114)	Oral AD +Placebo (N=109)	Esketamine 28, 56 or 84 mg +Oral AD (N=72)	Oral AD +Placebo (N=65)
Age, years							
Mean (SD)	46.4 (11.18)	45.7 (11.10)	46.8 (11.36)	44.9 (12.58)	46.4 (11.14)	70.6 (4.79)	69.4 (4.15)
Age category, n (%)							
18-44 years	45 (39.1%)	48 (42.1%)	45 (39.8%)	54 (47.4%)	40 (36.7%)	N/A	N/A
45-64 years	70 (60.9%)	66 (57.9%)	68 (60.2%)	60 (52.6%)	69 (63.3%)	N/A	N/A
65-74 years	N/A	N/A	N/A	N/A	N/A	59 (81.9%)	57 (87.7%)
≥75 years	N/A	N/A	N/A	N/A	N/A	13 (18.1%)	8 (12.3%)
Sex, n (%)							
Female	81 (70.4%)	79 (69.3%)	81 (71.7%)	75 (65.8%)	63 (57.8%)	45 (62.5%)	40 (61.5%)
Race, n (%)							
American Indian or Alaskan Native	0	1 (0.9%)	0	--	--	--	--
Asian	2 (1.7%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	--	--
Black or African American	7 (6.1%)	7 (6.1%)	5 (4.4%)	6 (5.3%)	5 (4.6%)	--	--
White	91 (79.1%)	85 (74.6%)	86 (76.1%)	106 (93.0%)	102 (93.6%)	66 (91.7%)	64 (98.5%)
Other	8 (7.0%)	11 (9.6%)	10 (8.8%)	--	--	--	--
Not reported	7 (6.1%)	9 (7.9%)	9 (8.0%)	--	--	1 (1.4%)	1 (1.5%)
Multiple	0	0	1 (0.9%)	1 (0.9%)	1 (0.9%)	4 (5.6%)	0
Unknown	--	--	--	--	--	1 (1.4%)	0
Ethnicity, n (%)							
Hispanic or Latino	33 (28.7%)	27 (23.7%)	31 (27.4%)	5 (4.4%)	7 (6.4%)	10 (13.9%)	5 (7.7%)
Not Hispanic or Latino	74 (64.3%)	78 (68.4%)	71 (62.8%)	108 (94.7%)	99 (90.8%)	59 (81.9%)	59 (90.8%)
Not reported	8 (7.0%)	8 (7.0%)	11 (9.7%)	0	1 (0.9%)	2 (2.8%)	1 (1.5%)
Unknown	0	1 (0.9%)	0	1 (0.9%)	2 (1.8%)	1 (1.4%)	0
Region, n (%)							
Europe	29 (25.2%)	27 (23.7%)	29 (25.7%)	69 (60.5%)	65 (59.6%)	35 (48.6%)	24 (36.9%)
North America	52 (45.2%)	52 (45.6%)	51 (45.1%)	45 (39.5%)	44 (40.4%)	34 (47.2%)	36 (55.4%)
Other	34 (29.6%)	35 (30.7%)	33 (29.2%)	--	--	3 (4.2%)	5 (7.7%)

AD=antidepressant; N/A=not applicable; SD=standard deviation

The severity of the depressive symptomatology at the time of randomization (i.e., after treatment with at least 2 prior oral ADs) and duration of the current episode of depression further support the treatment-resistant nature of the depression experienced by patients in the Phase 3 short-term double-blind studies (Table 11).

Table 11: Psychiatric Histories at Baseline of the Double-blind Induction Phases in TRANSFORM-1, 2, and 3 (Full Analysis Set)

	TRANSFORM-1			TRANSFORM-2		TRANSFORM-3	
	Esketamine 56 mg +Oral AD (N=115)	Esketamine 84 mg +Oral AD (N=114)	Oral AD +Placebo (N=113)	Esketamine 56 or 84 mg +Oral AD (n=114)	Oral AD +Placebo (N=109)	Esketamine 28, 56 or 84 mg +Oral AD (N=72)	Oral AD +Placebo (N=65)
Age when diagnosed with MDD, years							
Mean (SD)	30.3 (12.34)	32.1 (12.86)	31.8 (12.44)	32.1 (12.53)	35.3 (13.04)	42.6 (16.18)	43.7 (16.28)
Duration of current episode, weeks							
Mean (SD)	202.8 (277.25)	212.7 (327.62)	193.1 (264.10)	111.4 (124.28)	118.0 (187.37)	163.1 (277.04)	274.1 (395.47)
Family history of depression, n (%)							
Yes	70 (60.9%)	71 (62.3%)	74 (65.5%)	51 (44.7%)	56 (51.4%)	30 (41.7%)	26 (40.0%)
MADRS total score							
Mean (SD)	37.4 (4.76)	37.8 (5.58)	37.5 (6.16)	37.0 (5.69)	37.3 (5.66)	35.5 (5.91)	34.8 (6.44)
SDS total score							
Mean (SD)*	24.0 (4.12)	24.7 (4.58)	24.4 (3.86)	24.0 (4.07)	24.2 (4.38)	21.8 (5.90)	22.9 (4.74)
PHQ-9 total score							
Mean (SD)	20.3 (4.11)	20.7 (3.58)	20.8 (3.69)	20.2 (3.63)	20.4 (3.74)	17.6 (4.99)	17.4 (6.33)

AD=antidepressant; Esk=esketamine; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; PHQ-9=9-Item Patient Health Questionnaire; SD = standard deviation; SDS=Sheehan Disability Scale

* TRANSFORM-1: Esk 56 mg + oral AD N=108, Esk 84 mg + oral AD N=107, oral AD + placebo N=105; TRANSFORM-2: Esk + oral AD N=111, oral AD + placebo N=104; TRANSFORM-3: Esk + oral AD N=45, oral AD + placebo N=44

MADRS total score (clinician-rated measure of depression severity ranging from 0 to 60) ≥35 signals severe depression

SDS total score (patient-reported measure of mental health-related functional impairment) ranges from 0 (not impaired) to 30 (extremely impaired)

PHQ-9 total score (patient-reported measure of depression severity ranging from 0 to 27) ≥20 signals severe depression

The characteristics of prior oral AD use for patients in the short-term double-blind Phase 3 studies are presented in Table 12. The most common oral AD used by patients prior to study entry was venlafaxine in TRANSFORM-1 (34.9%) and TRANSFORM-2 (40.6%) and mirtazapine in TRANSFORM-3 (30.7%).

Table 12: Characteristics of Prior Oral Antidepressant Use at Baseline in TRANSFORM-1, 2, and 3 (Full Analysis Set)

Prior Oral Antidepressants With Nonresponse (i.e., Failed Antidepressants)	TRANSFORM-1 Patients 18-64 yrs (N=342)	TRANSFORM-2 Patients 18-64 yrs (N=223)	TRANSFORM-3 Patients ≥65 yrs (N=137)
Number of specific antidepressants, n (%)			
N	342*	223†	137‡
2	167 (48.8%)	136 (61.0%)	68 (49.6%)
3 or more	167 (48.8%)	82 (36.8%)	58 (42.3%)
Number of general classes, n (%) §			
N	342	223	137
1	75 (21.9%)	49 (22.0%)	32 (23.4%)
2	208 (60.8%)	134 (60.1%)	79 (57.7%)
3 or more	59 (17.3%)	40 (17.9%)	26 (19.0%)
Duration, days			
N	329	217	108
Mean (SD)	458.5 (901.93)	374.9 (614.10)	727.1 (1202.30)

SD=standard deviation

* Of the 8 patients not summarized in the table, 4 were determined to have failed at least 2 oral antidepressants based on other data in the database; 4 had nonresponse to 1 oral antidepressant.

† The 5 patients not summarized in the table were determined to have failed at least 2 oral antidepressants based on other data in the database.

‡ Of the 11 patients not summarized in the table, 5 were determined to have failed at least 2 oral antidepressants based on other data in the database; 6 had nonresponse to 1 oral antidepressant.

§ General classes: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor (SNRI), selective serotonin reuptake inhibitor (SSRI), or other.

The new oral AD assigned to patients in the short-term Phase 3 studies is shown in Table 13.

Table 13: Oral Antidepressants Study Medication Initiated at Randomization in TRANSFORM-1, 2, and 3 (Full Analysis Set)

	TRANSFORM-1 Patients 18-64 yrs (N=342)	TRANSFORM-2 Patients 18-64 yrs (N=223)	TRANSFORM-3 Patients ≥65 yrs (N=137)
Class			
SNRI	196 (57.3%)	152 (68.2%)	61 (44.5%)
SSRI	146 (42.7%)	71 (31.8%)	76 (55.5%)
Type			
Duloxetine	136 (39.8%)	121 (54.3%)	48 (35.0%)
Escitalopram	73 (21.3%)	38 (17.0%)	50 (36.5%)
Sertraline	73 (21.3%)	32 (14.3%)	25 (18.2%)
Venlafaxine XR	60 (17.5%)	32 (14.3%)	14 (10.2%)

SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; XR=extended release

6.3. Maintenance of Effect Study

TRD is a chronic condition, with maintenance treatment recommended per treatment guidelines. As mentioned above, little is known about how the antidepressant effects of esketamine/ketamine are sustained over the long term, and no studies have described a sustained response to ketamine. However, a number of studies have assessed maintenance of the benefit from electroconvulsive therapy with continuation of pharmacotherapy in TRD and have shown that most relapses occur within 5 weeks of completion of electroconvulsive therapy.[84,89] Moreover, even in TRD patients who show responses to a new trial of antidepressant pharmacotherapy, the continuation of that pharmacotherapy shows limited ability to prevent relapse. The largest study to examine the durability of antidepressant response, the STAR*D study, showed that in participants meeting TRD criteria (based on failing at least two antidepressant treatment regimens within the current depressive episode), of those who respond to a third or fourth new antidepressant treatment, one-half relapse within 12 to 13 weeks, respectively, despite continued treatment with the treatment that induced the response.[88]

The Phase 3 study SUSTAIN-1 used a randomized withdrawal design to assess, in a blinded fashion among patients who had achieved stable remission after 16 weeks of treatment with esketamine + oral AD (end of the optimization phase), the time to relapse between patients randomized to continue treatment with esketamine and those randomized to discontinue esketamine. Stable remission was defined as a MADRS total score of ≤12 for at least 3 of the last 4 weeks of the optimization phase, with 1 excursion of a MADRS total score >12 or 1 missing MADRS assessment permitted at optimization Week 13 or 14 only.

SUSTAIN-1 also evaluated the time from randomization to relapse in the maintenance phase for patients in stable response (not in remission) at the end of the optimization phase. Stable response was defined as a ≥50% reduction in the MADRS total score from baseline for each of the last 2 weeks of the optimization phase but not meeting the definition of stable remission. Data from the stable responder group were included as it was considered that achieving a 50% or greater improvement in depression from baseline, even though stable remission had not been achieved, was a clinically meaningful outcome in TRD. Additionally, SUSTAIN-1 provided information concerning the appropriate dosing frequency for esketamine during maintenance treatment.

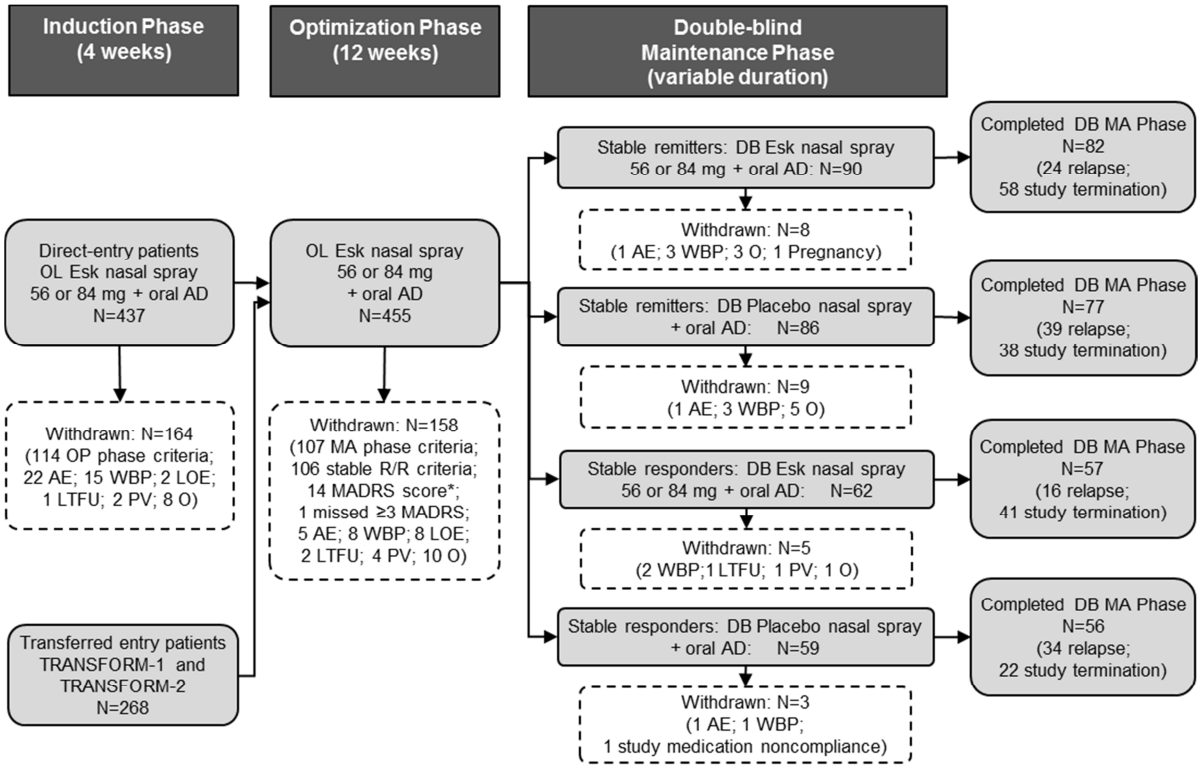
Patients could have participated in up to 5 study phases (screening/prospective observation phase, induction phase, optimization phase, double-blind maintenance phase, and posttreatment follow-up phase). A total of 705 patients enrolled in SUSTAIN-1 either directly (direct-entry patients; N=437) or after completing the double-blind induction phase of TRANSFORM-1 or 2 (transferred-entry patients; N=268). The eligibility criteria for direct-entry patients in SUSTAIN-1 were the same as those specified for TRANSFORM-1 and 2.

The study was terminated once a sufficient number of relapses had occurred as determined by the Independent Data Monitoring Committee during an interim analysis (see Section 7.2).

Figure 13 shows the number of patients who proceeded through the induction, optimization, and maintenance phases and who completed the maintenance phase. After progression through the 4-week induction and 12-week optimization phases:

- 176 esketamine-treated patients demonstrated stable remission at the end of the optimization phase, were randomized to double-blind treatment during the maintenance phase and were included in the full (stable remitters) analysis set (the primary efficacy set). One patient was a stable responder who was randomized as a stable remitter; thus, 175 were in stable remission and 1 was a stable responder.
- 121 esketamine-treated patients at the end of the optimization phase, were randomized to double-blind treatment in the maintenance phase as stable responders and were included in the full (stable responders) analysis set.
- Stable remitters and stable responders were non-overlapping groups.
- The demographic and baseline characteristics of the stable remitters and stable responders in SUSTAIN-1 were similar to those of patients enrolled in the Phase 3 short-term studies TRANSFORM-1 and 2; further details are provided in Appendix 3.

Figure 13: Patient Flow Diagram for SUSTAIN-1



AD=antidepressant; AE=adverse event; DB=double-blind; Esk=esketamine; LOE=lack of efficacy; LTFU=lost to follow-up; MA= maintenance; MADRS= Montgomery-Asberg Depression Rating Scale; O=other reason; OL=open-label; OP=optimization; PV=protocol violation; R/R=response/remission; WBP=withdrawal by patient

* MADRS total score was ≥22 for 2 consecutive visits.

The study medication dose and dosing frequency in each phase of SUSTAIN-1 are shown in Table 14.

Table 14: Study Medication Dose and Dosing Frequency in SUSTAIN-1

Study Phase	Nasal Spray Dose	Nasal Spray Dosing Frequency	Oral AD Dose (Daily)
Induction (direct-entry patients)	Esketamine 56 or 84 mg (flexible-dose)	Twice weekly	Newly-initiated oral AD, titrated to the maximum tolerated dose
Optimization	Dose unchanged from the end of the induction phase	First 4 weeks: weekly Subsequent 8 weeks: weekly or every other week based on MADRS total score (see algorithm in Appendix 2)	Oral AD dose unchanged from the end of the induction phase
Maintenance	Patients randomly assigned 1:1 to continue with esketamine (dose unchanged from end of the optimization phase) or switch to placebo	Weekly or every other week based on MADRS total score (see algorithm in Appendix 2)	Oral AD dose unchanged from the end of the optimization phase

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale

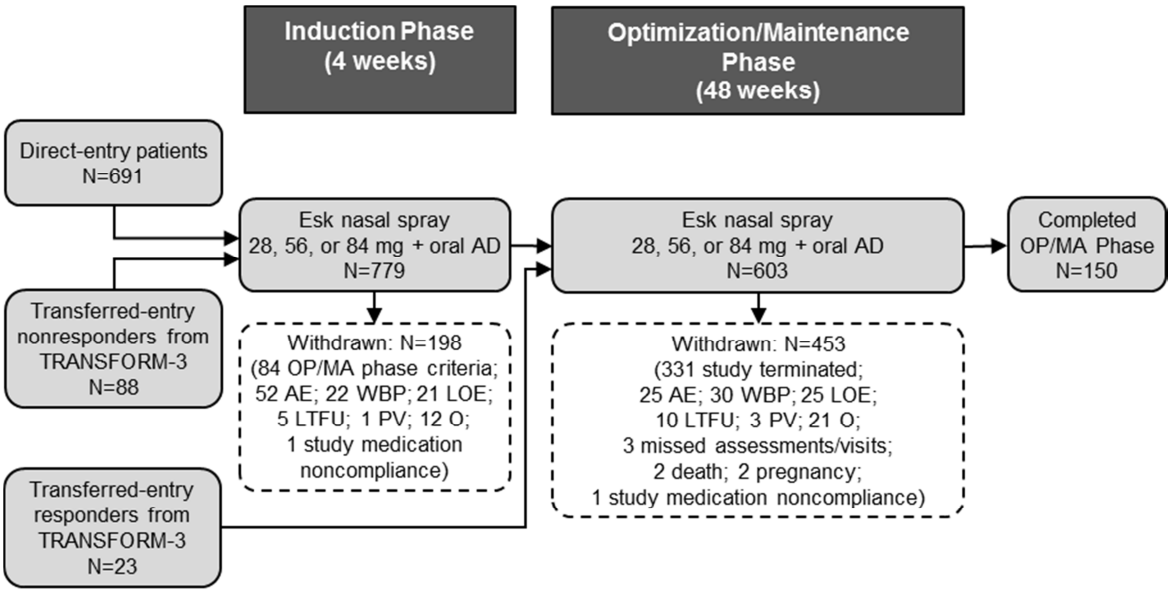
6.4. Long-term, Open-label Safety Study

The Phase 3 long-term, uncontrolled, open-label study SUSTAIN-2 was designed primarily to obtain longer-term data on safety, including the incidence, severity, and persistence of adverse events over time with esketamine + oral AD in a population with TRD. Special attention was given to addressing concerns in the literature about potential impaired cognition and symptoms of interstitial cystitis associated with high doses and chronic use of ketamine.[71] The evaluation of long-term efficacy in this population was a secondary objective, recognizing the limitations of the study's design with respect to the lack of comparator treatment and no blinding.

SUSTAIN-2 consisted of up to 4 phases (screening, induction, optimization/maintenance, and follow-up); the maximum duration of a patient's participation was 60 weeks. After achieving the required number of patients exposed to esketamine, the study was terminated, and enrollment was stopped at 802 patients (691 direct-entry patients and 111 transferred-entry patients). Figure 14 shows the number of patients who proceeded from the induction phase to the optimization/maintenance phase and who completed the optimization/maintenance phase.

The demographic and baseline characteristics of patients enrolled in SUSTAIN-2 were generally similar to those of patients enrolled in the Phase 3 short-term studies (see Appendix 4).

Figure 14: Patient Flow Diagram for SUSTAIN-2



AD=antidepressant; AE=adverse event; Esk=esketamine; LOE=lack of efficacy; LTFU=lost to follow-up; MA=maintenance; O=other reason; OP/MA=optimization/maintenance; PV=protocol violation; WBP=withdrawal by patient

The study medication dose and dosing frequency in each phase of SUSTAIN-2 are shown in Table 15.

Table 15: Study Medication Dose and Dosing Frequency in SUSTAIN-2

Study Phase	Nasal Spray Dose	Nasal Spray Dosing Frequency	Oral AD Dose (Daily)
Induction (direct-entry patients and transferred-entry nonresponders from TRANSFORM-3)	Esketamine 28 (patients ≥65 years only), 56 or 84 mg (flexible-dose)	Twice weekly	Newly-initiated oral AD (titrated to the maximum tolerated dose for direct-entry patients)
Optimization/ Maintenance	Direct-entry patients: dose unchanged from the end of the induction phase Transferred-entry responders from TRANSFORM-3: starting dose of esketamine 28 mg, with subsequent dose adjustments allowed over the next 4 weeks	First 4 weeks: weekly Subsequent 44 weeks: weekly or every other week adjusted based on the severity of depressive symptoms at weekly evaluations	Oral AD dose unchanged from the end of the induction phase

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale

7. CLINICAL EFFICACY IN THE PHASE 3 STUDIES

7.1. Efficacy Measures and Endpoints for Phase 3 TRD Studies

A summary of the primary efficacy endpoint for the 4 Phase 3 double-blind clinical studies used to evaluate the efficacy of esketamine nasal spray is shown in Table 16.

Table 16: Primary Efficacy Endpoint in Phase 3 Clinical Studies with Esketamine Nasal Spray in Patients with TRD

Study Name Age of TRD Population	Study Description	Primary Efficacy Endpoint
TRANSFORM-1 18-64 years	Short-term, double-blind fixed-dose study	Change from baseline to Day 28 in MADRS total score
TRANSFORM-2 18-64 years	Short-term, double-blind flexible-dose study	Change from baseline to Day 28 in MADRS total score
TRANSFORM-3 ≥65 years	Short-term, double-blind flexible-dose study	Change from baseline to Day 28 in MADRS total score
SUSTAIN-1 18-64 years	Randomized withdrawal study	Time from randomization to relapse among patients who achieved stable remission after 16 weeks of treatment with esketamine + oral AD

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale; TRD=treatment-resistant depression

Efficacy Measures

The MADRS was used to calculate the primary efficacy endpoint in the Phase 3 short-term double-blind studies (TRANSFORM-1, 2, and 3), as well as the secondary efficacy endpoints of onset of clinical response by Day 2 (TRANSFORM-1 and 2), response and remission rates (all Phase 3 studies), and long-term efficacy (SUSTAIN-2). The MADRS is a clinician-reported outcome tool widely used for primary outcome measures in MDD clinical trials.[69]

- The scale consists of 10 items corresponding to the core symptoms of depression (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts, and suicidal thoughts), each scored from 0 to 6, for a total possible score of 60. Higher scores represent a more severe condition. The severity of depressive symptoms based on MADRS total score was defined as follows: no symptoms: ≤12; mild depression: 13-27; moderate depression: 28-34; severe depression: ≥35.
- Remission was defined as a MADRS total score of ≤12. Although MADRS total score ≤10 is the more commonly used definition for remission,[119] a definition of ≤12 has been used in multiple published clinical studies.[51,83] In addition, the Sponsor selected a definition of MADRS total score ≤12 based on data from a Phase 0 study suggesting that remote MADRS raters score slightly higher (an average of 2 points) than face-to-face raters when patients demonstrate lower overall symptom severity (i.e., MADRS total score <15).
- Response was defined as ≥50% improvement (decrease) from baseline in MADRS total score.
- The 7-day recall period was used for the primary efficacy evaluation in TRANSFORM-1, 2, and 3. A modified recall period of 24 hours was used for the evaluation of the key secondary efficacy endpoint onset of clinical response by Day 2 (24 hours) in TRANSFORM-1 and 2.

- As detailed in Section 6.1.3, to maintain blinding, the MADRS was performed prior to nasal spray dosing throughout the double-blind studies by independent remote, blinded raters using an interview guide (SIGMA).[115] The SIGMA is provided in Appendix 1.

Secondary patient-reported outcome measures evaluated in the Phase 3 studies and discussed in this document include:

- *Sheehan Disability Scale:* a widely used patient-reported outcome to measure mental health-related disruption to occupational, social and family function.[56,96] There are 3 self-rated items regarding work, social, and family impairment, each rated on a scale from 0 (not at all) to 10 (extremely). The Sheehan Disability Scale (SDS) total score ranges from 0 to 30 where a higher score indicates greater mental health-related functional impairment; the recall period was 7-days.
- *9-Item Patient Health Questionnaire:* a patient-reported outcome measure used to assess depressive symptom domains of the nine MDD criteria and provide a complementary patient perspective to the clinician-reported MADRS. The patient's item responses are summed to provide a total score ranging from 0 to 27 with higher scores indicating greater severity of depressive symptoms. The severity of depressive symptoms based on the 9-Item Patient Health Questionnaire (PHQ-9) total score was defined as follows in the Phase 3 studies: no/minimal symptoms: 0-4; mild depression: 5-9; moderate depression: 10-14; moderately severe depression: 15-19; severe depression: 20-27.[55] The recall period is 2 weeks.

Each of these assessments was conducted before administration of nasal spray at clinic visits.

Primary and Secondary Efficacy Endpoints

Phase 3 short-term double-blind studies: In all three Phase 3 short-term studies, the predefined primary endpoint was the change from baseline (i.e., Day 1) to end of the double-blind induction phase in the MADRS total score. In TRANSFORM-1 and TRANSFORM-2, the following key secondary endpoints were prespecified to be tested in the following sequence to control the type I error rate:

- Onset of clinical response by Day 2 (defined as at least a 50% reduction from baseline in the MADRS total score with an onset by Day 2 that was maintained to Day 28; patients were allowed one excursion (nonresponse) on Days 8, 15 or 22; however, there must have been at least a 25% reduction relative to baseline in the MADRS total score)
- Change from baseline to end of the induction phase in SDS total score
- Change from baseline to end of the induction phase in PHQ-9 total score

Changes from baseline in the SDS and PHQ-9 total scores were considered other efficacy endpoints in TRANSFORM-3 (onset of clinical response by Day 2 was not assessed in this study because all patients started with the 28-mg dose of nasal spray study medication) and were not part of a testing hierarchy.

Other descriptive secondary endpoints evaluated for each of the Phase 3 short-term studies in this document are the proportion of patients who were responders (≥50% improvement from baseline in the MADRS total score) or were in remission (MADRS total score of ≤12) at the end of the double-blind induction phase.

Phase 3 maintenance of effect study: In SUSTAIN-1, the primary endpoint was prespecified as the time from randomization to relapse during the maintenance phase among patients who achieved stable remission at the end of optimization phase after 16 weeks of treatment with esketamine + oral AD. Relapse was defined as the earliest date of any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days (date of second MADRS assessment used as date of relapse in accordance with counting processes in survival analysis). The criterion for relapse based on MADRS total score was selected based on relapse criteria used in other antidepressant maintenance studies.[11]
- Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness, such as suicide attempt, completed suicide, or hospitalization for suicide prevention (start date of hospitalization or event was used as date of relapse).

For patients reported to have a clinically relevant event suggestive of a relapse of depressive illness per clinical judgment, but who were not hospitalized and MADRS criteria were not met, an independent Relapse Adjudication Committee confirmed if the event was indicative of a clinical relapse and identified the date of relapse. The above criteria are reflective of clinical worsening in patients with depression and consistent with criteria used in other trials of approved antidepressants.[11,12]

The main secondary endpoint in SUSTAIN-1 was the time from randomization to relapse in the maintenance phase for patients in stable response (not in remission) at the end of the optimization phase.

7.2. Key Features of Statistical Methods for Phase 3 TRD Studies

The section below provides information on key statistical methodology in the Phase 3 studies; further details are provided in Appendix 13.

Efficacy Analyses for Phase 3 Short-term Double-blind Studies

TRANSFORM-1 and 3 included an interim analysis to re-estimate the sample size needed to achieve the desired power while maintaining control of the overall type I error rate or to stop the study for futility. The interim analysis was conducted 4 weeks after randomizing 121 or 51 patients in TRANSFORM-1 or 3, respectively, by an independent external statistical group. The Independent Data Monitoring Committee (unblinded to the data) reviewed the results, provided the sample size for the study (based on predefined rules), and recommended to continue the study to the minimum sample size in both instances. Care was taken to ensure that the Sponsor and investigational sites remained blinded to the results of the interim analysis until the final sample size was achieved. Additional details about the interim analysis are described Appendix 13.

The primary analysis set for all efficacy analyses in TRANSFORM-1, 2, and 3 included all randomized patients who received at least 1 dose of nasal study medication and 1 dose of oral AD medication during the double-blind induction phase (referred to as the full analysis set).

In TRANSFORM-1 and 2, to control type I error across the primary (change in MADRS total score) and the 3 prespecified key secondary endpoints (tested in the following sequence: onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score) and the two dose-control comparisons (for TRANSFORM-1 only), multiplicity adjustment procedures were implemented as described in Appendix 13 and as follows:

- In TRANSFORM-1, for all 4 endpoints (primary, key secondary) testing of the esketamine 56 mg dose group was conducted at the 2-sided 0.0425 level only if the 84-mg dose group was significant at the 2-sided 0.05 level for that endpoint; testing of the endpoints was performed sequentially in the order indicated above for both dose groups only if the previous endpoint in the hierarchy was significant for both doses of esketamine. If only the 84-mg dose group was significant at the 2-sided 0.05 level for an endpoint, testing of the other endpoints down the hierarchy was conducted only for this dose group at the 2-sided 0.0075 level.
- For TRANSFORM-2, the 3 key secondary endpoints were analyzed sequentially and were considered statistically significant at the 2-sided 0.05 level only if the endpoint was individually significant and previous endpoints in the hierarchy were significant, including the primary endpoint at the 2-sided 0.05 level.

Testing of the primary endpoint in TRANSFORM-3 was done using a 2-sided significance level of 0.05.

The primary efficacy variable, change from baseline in MADRS total score at Day 28, was analyzed based on a mixed-effects model using repeated measures (MMRM) on observed case data (based on an assumption of uninformative missingness). The model specified baseline MADRS total score as a covariate, and treatment, country (TRANSFORM-2) or region (TRANSFORM-1 and 3), class of oral AD (SSRI or SNRI), day, day-by-treatment interaction as fixed effects, and a random patient effect. For TRANSFORM-1 and 3, the MMRM analysis was performed for each stage separately (Stage 1: all data on patients used for sample size re-estimation at the interim analysis; Stage 2: all data collected on the remaining patients after the interim analysis), and a weighted combination test was performed using the test statistics obtained from the 2 stages. Further discussion of the analytical approach used for evaluating the primary endpoint in TRANSFORM-1, 2, and 3, including additional sensitivity analyses, can be found in Appendix 13.

The treatment group difference (esketamine + oral AD vs oral AD + placebo) in the proportion of patients showing onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind induction phase was analyzed using a Cochran-Mantel-Haenszel (CMH) chi square test adjusting for country and class of antidepressant (SSRI or SNRI) in TRANSFORM-2. Changes from baseline at Day 28 in the SDS total score and PHQ-9 total score were analyzed using the same models as described for the primary analysis.

Efficacy Analyses for Phase 3 Maintenance of Effect Study

To minimize the duration of exposure to oral AD + placebo in patients randomized to that group in the maintenance phase in the event that esketamine + oral AD was highly effective, SUSTAIN-1 was designed with an interim analysis that allowed early termination of the maintenance phase for efficacy or to re-estimate the sample size (i.e., required number of relapses in stable remitters). Following the protocol-specified interim analysis (performed after 31 relapses from randomized stable remitters), the Independent Data Monitoring Committee recommended to continue the study and provided the total number of relapses required (59 relapse events) based on predefined rules. The Sponsor's team and sites remained blinded until the recommended total number of relapses in randomized stable remitters had occurred (for additional details about the interim analysis see Appendix 13).

The analysis set used for analysis of the primary endpoint included all randomized patients who were in stable remission at the end of the optimization phase and who received at least 1 dose of nasal study medication and 1 dose of oral AD during the maintenance phase (referred to as the full [stable remitter] analysis set). The cumulative distribution function of the time to first relapse during the maintenance phase for esketamine-treated patients who achieved stable remission at the end of the optimization phase was estimated by the Kaplan-Meier method; time to first relapse was summarized and treatments were compared using the weighted log-rank test. The weighted estimate of the hazard ratio and its 95% confidence interval (CI) was based on the technique described in Wassmer.[114] As the study was not stopped for efficacy at the interim analysis, the final efficacy analysis was performed at a significance level of 0.046 (2-sided).

For the secondary efficacy endpoint of time to relapse in stable responders (who were not stable remitters), the cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method and the treatment groups were compared using a 2-sided log-rank test for the full (stable responders) analysis set. The hazard ratio and its 95% CI was based on the Cox proportional hazards model with treatment as a factor.

7.3. Key Efficacy Results in the Phase 3 Program

As described in Section 2.3.2, FDA required inclusion of both short-term and maintenance of effect Phase 3 pivotal studies with esketamine in the original NDA. Thus, the 2 pivotal studies in the clinical development program that reached statistical significance and form the foundation of the NDA were: (1) TRANSFORM-2, the short-term flexible-dose study and (2) SUSTAIN-1, the maintenance of effect study.

7.3.1. Key Efficacy Results in the Short-term Phase 3 Studies (TRANSFORM-1, 2, and 3)

Overview

- Consistent improvements in depressive symptoms after 4 weeks of esketamine treatment were seen across the 3 short-term Phase 3 studies, with statistically significant improvements demonstrated in the flexible-dose study TRANSFORM-2 (2-sided p=0.020). The mean treatment group difference for the primary endpoint ranged from -3.2 to -4.1 across studies, dose regimens, and analyses.
- Results from the fixed-dose short-term study TRANSFORM-1 in patients 18-64 years did not achieve statistical significance; however, these results showed clinically meaningful and numerically favorable improvements in depressive symptoms after treatment with esketamine, consistent with results in TRANSFORM-2.
- Esketamine, administered concurrently with a newly-initiated oral AD, demonstrated clinically relevant and statistically significant relief of symptoms of depression in a confirmatory Phase 3 flexible-dose study in patients 18-64 years old with TRD (TRANSFORM-2; 2-sided p=0.020). Based on this study, clinical improvement with esketamine was observed as early as 24 hours and generally increased in subsequent weeks, with the full antidepressant effect observed by the end of Week 4. Results in TRANSFORM-2 were consistent with those for the placebo-controlled Phase 2 adjunctive study (SYNAPSE) in showing a rapid onset of efficacy (see Section 5.2.1).
- Although not achieving statistical significance, results of the similarly-designed study in patients ≥65 years (flexible-dose study TRANSFORM-3) with TRD showed clinically meaningful and numerically favorable improvements in depressive symptoms after treatment with esketamine, consistent with results in TRANSFORM-2.
- Consistently across studies, the results numerically favored esketamine + oral AD for the efficacy measure of onset of response by Day 2 and the patient-reported outcome measures of functioning and associated disability (based on SDS total score) and depression symptoms (based on the PHQ-9 total score) (key secondary endpoints in TRANSFORM-1 and 2), and for response and remission rates based on MADRS total scores.

Exposure

The first dose of nasal spray study medication was 56 mg for all patients 18-64 years (TRANSFORM-1 and 2) and 28 mg for patients ≥65 years in TRANSFORM-3. In the flexible-dose studies TRANSFORM-2 and 3, the dose could be increased based on the clinician's assessment of tolerability and efficacy or reduced based on assessment of tolerability. No specific criteria for increasing the dose based on the patient's antidepressant response were given.

In the flexible-dose studies TRANSFORM-2 and 3, the median final dose of esketamine nasal spray was 84 mg. On Day 25 (last nasal spray dosing session in induction phase), 66.7% (66 of 99) and 64.5% (40 of 62) of patients in the esketamine + oral AD groups in these studies, respectively, received a dose of 84 mg.

7.3.1.1. Primary Efficacy Endpoint: Change in MADRS Total Score from Baseline to Day 28

Results for the primary endpoint, change from baseline in MADRS at the end of the 4-week double-blind induction phase, as analyzed using MMRM (observed case) methods, are summarized for each of the Phase 3 short-term studies in Table 17. Across the 3 studies, treatment group differences consistently showed larger estimated improvements with esketamine + oral AD compared with oral AD + placebo (Figure 15).

- In the fixed-dose study TRANSFORM-1, while treatment effects for esketamine + oral AD were not statistically significant relative to the oral AD + placebo control, the estimated treatment differences of -4.1 for the esketamine 56 mg dose group and -3.2 for the esketamine 84 mg dose group were consistent with the treatment difference shown in TRANSFORM-2 and provide supportive evidence of a clinically meaningful benefit for both fixed dose regimens in adults with TRD (see presentation of response and remission rates below for further discussion of clinical relevance).
- In the flexible-dose study TRANSFORM-2, statistical superiority of esketamine 56-84 mg + oral AD versus oral AD + placebo in improving symptoms of depression in a TRD population after 4 weeks of treatment was shown, with a LS mean treatment difference of -4.0 (2-sided p=0.020).
- In the flexible-dose study TRANSFORM-3, while the treatment effect for esketamine + oral AD was not statistically significant relative to the oral AD + placebo control, the estimated treatment difference of -3.6 was consistent with that shown in TRANSFORM-2 and suggests a clinically meaningful benefit in the vulnerable and difficult-to-treat patients ≥65 years with TRD who were started at 28 mg and could be titrated to 56 or 84 mg as clinically appropriate (see presentation of response and remission rates below for further discussion of clinical relevance).

Table 17: MADRS Total Score: Change from Baseline to Day 28 by MMRM (Observed Case) for the Double-blind Induction Phase in TRANSFORM-1, 2, and 3 (Full Analysis Set)

	TRANSFORM-1			TRANSFORM-2		TRANSFORM-3	
	Esketamine 56 mg + Oral AD (N=115)	Esketamine 84 mg + Oral AD (N=114)	Oral AD + Placebo (N=113)	Esketamine 56 or 84 mg + Oral AD (n=114)	Oral AD +Placebo (N=109)	Esketamine 28, 56 or 84mg + Oral AD (N=72)	Oral AD +Placebo (N=65)
MMRM Analysis[a]							
Mean change from BL to Day 28	-19.0	-18.8	-14.8	-21.4	-17.0	-10.0	-6.3
Difference of LS mean[b]	-4.1	-3.2		-4.0		-3.6	
95% CI of difference[c]	-7.67; -0.49	-6.88; 0.45		-7.31; -0.64		-7.20; 0.07	
2-sided p-value[d]	N/A[e]	0.088		0.020		0.059	

AD=antidepressant; BL=baseline; CI=confidence interval; DB=double-blind; LS=least squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; N/A=not applicable; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

A negative treatment difference favors esketamine + oral AD.

[a] MMRM: Test for treatment effect is based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment, day, geographic region, class of oral AD (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. Geographic region is Country for TRANSFORM-2, and Region for TRANSFORM-1 and 3.

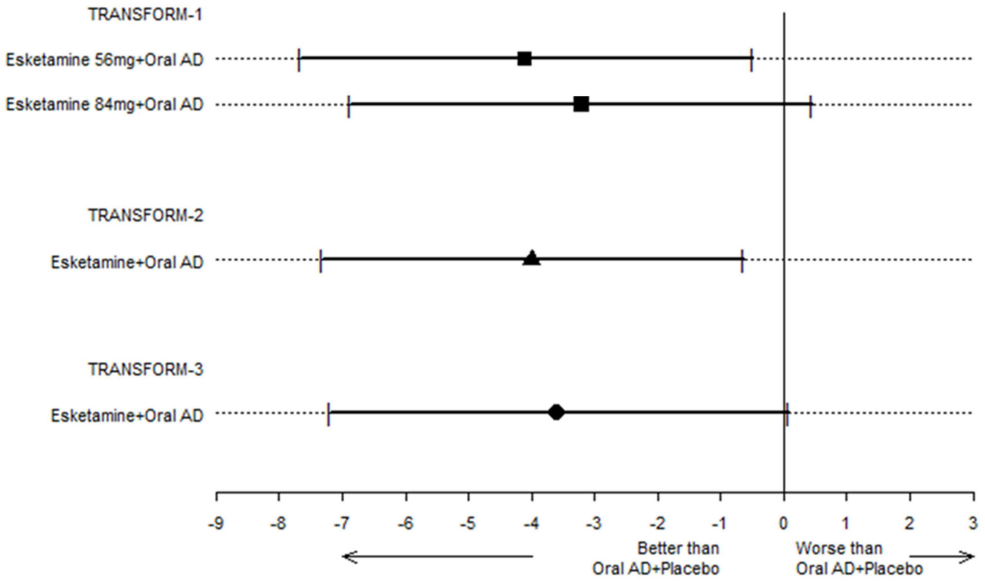
[b] For TRANSFORM-1 and 3, the difference from placebo is the median unbiased estimate, which is a weighted combination of the LS means of the difference from oral AD + placebo. For TRANSFORM-2, the difference from placebo is the LS mean difference between esketamine + oral AD and oral AD + placebo.

[c] For TRANSFORM-1 and 3, value is the 2-sided CI adjusted for sample size re-estimation (on the difference from oral AD + placebo).

[d] For TRANSFORM-1 and 3, the p-values are based on the weighted combination test statistic.

[e] Sequential testing. Because the 84 mg dose was not statistically significant, 56 mg cannot be formally evaluated for treatment difference.

Figure 15: MADRS Total Score: Least-squares Mean Difference by MMRM (Observed Case) of Esketamine + Oral AD versus Oral AD + Placebo in Change From Baseline to Day 28 in TRANSFORM-1, 2, and 3 (Full Analysis Set)



AD=antidepressant; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures
Note: The graph shows the difference in LS means (with 95% CIs) for TRANSFORM-2, and the median unbiased estimates (with 95% CIs) of the differences between esketamine + oral AD and oral AD + placebo for TRANSFORM-1 and TRANSFORM-3. The LS means and median unbiased estimates are obtained from MMRM.

The improvements in depressive symptoms after 4 weeks of esketamine treatment were consistent across all 3 short-term Phase 3 studies, with statistically significant improvements demonstrated in the flexible-dose study TRANSFORM-2. The LS mean treatment group difference for the primary endpoint ranged from -3.2 to -4.1 across studies, dose regimens, and analyses. These treatment differences are at least as large as the median treatment differences reported in controlled clinical studies of currently marketed antidepressants in patients with an inadequate response to previous AD therapy (e.g., quetiapine, and aripiprazole) or in active comparator-controlled studies of the olanzapine-fluoxetine combination (Symbyax) (see further discussion in Appendix 5). The clinical relevance of the treatment differences for change in MADRS total score is further discussed below with response and remission rates in the Phase 3 studies.

Change in MADRS Total Score Over Time

In TRANSFORM-1 and 2, the LS mean changes in the MADRS total score over time showed a numerically larger improvement in clinician-rated depression symptoms relative to the oral AD + placebo group as early as 24 hours after the first dose of esketamine + oral AD (i.e., Day 2). This difference persisted in subsequent weeks until the full antidepressant effect was achieved at the end of the 4-week induction phase (Table 18 and Figure 16).

These data confirm the rapid onset of action observed in the Phase 2 study SYNAPSE. Patients in the esketamine + oral AD group of the flexible-dose Phase 3 study TRANSFORM-2 were to start treatment with an esketamine dose of 56 mg on Day 1. The percentage receiving an esketamine dose of 84 mg was 45.8% and 63.0% on Days 4 and 8, respectively, 67.6% on Day 15 and 22, and 66.7% on Day 25 (dose to remain unchanged after Day 15). Few patients in TRANSFORM-2 who titrated to the esketamine 84 mg dose had a reduction in dose to 56 mg (n=11, 9.6%).

A numerically larger change from baseline in the MADRS total score for both doses of esketamine + oral AD compared to oral AD + placebo was observed throughout the treatment phase in the fixed-dose Phase 3 study in adults (TRANSFORM-1) (Table 18 and Figure 16).

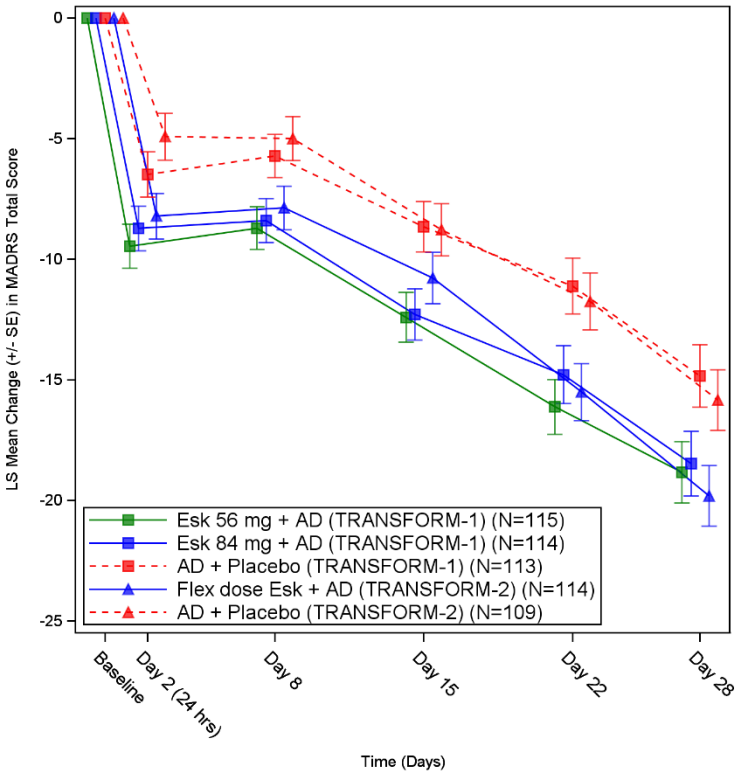
The mean change in MADRS total score over time in TRANSFORM-3 is shown in Table 18 and plotted in Figure 17.

Table 18: MADRS Total Score: Change From Baseline to Day 28 MMRM (Observed Case) Over Time; Double-blind Induction Phase (TRANSFORM-1, 2 and 3: Full Analysis Set)

	Day 2	Day 8	Day 15	Day 22	Day 28
TRANSFORM-1					
Esk 56 mg + oral AD vs oral AD + placebo					
Difference of LS means (95% CI)	-3.0	-3.0	-3.8	-5.0	-4.0
(Esk+AD minus AD+Placebo)	(-5.51; -0.45)	(-5.43; -0.54)	(-6.61; -0.90)	(-8.19; -1.84)	(-7.55; -0.43)
Esk 84 mg + oral AD vs oral AD + placebo					
Difference of LS means (95% CI)	-2.2	-2.7	-3.6	-3.7	-3.6
(Esk+AD minus AD+Placebo)	(-4.77; 0.31)	(-5.16; -0.20)	(-6.55; -0.73)	(-6.92; -0.43)	(-7.27; 0.02)
TRANSFORM-2					
Esk + oral AD vs oral AD + placebo					
Difference of LS means (95% CI)	-3.3	-2.9	-2.0	-3.8	-4.0
(Esk+AD minus AD+Placebo)	(-5.75; -0.85)	(-5.17; -0.59)	(-4.78; 0.82)	(-6.87; -0.65)	(-7.31, -0.64)
TRANSFORM-3					
Esk + oral AD vs oral AD + placebo					
Difference of LS means (95% CI)		-0.5	-0.9	-0.7	-4.0
(Esk+AD minus AD+Placebo)		(-3.02; 2.03)	(-3.74; 2.03)	(-4.02; 2.52)	(-7.71; -0.25)

AD=antidepressant; CI=confidence interval; Esk=esketamine; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures
Results are not adjusted for multiple comparisons (TRANSFORM-2) or sample size re-estimation (TRANSFORM-1 and 3).
See Appendix 13 for further details.
Note: Negative change in score indicates improvement.

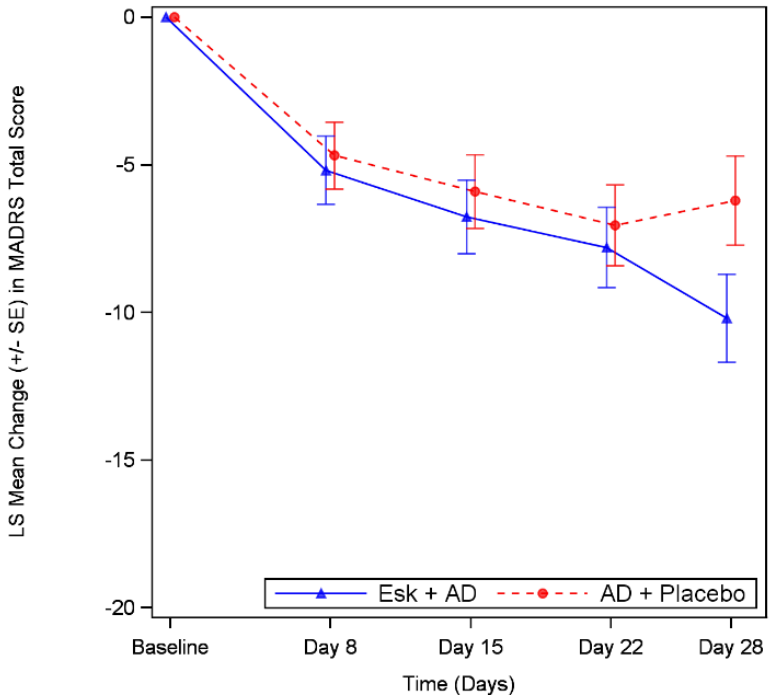
Figure 16: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM; Double-blind Induction Phase (Studies TRANSFORM-1 and 2: Full Analysis Set)



AD=antidepressant; Esk=esketamine; SE=standard error; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

LS Mean and SE were based on MMRM fitted separately for each study with change from baseline as the response variable and the fixed effect model terms for treatment (esk 56 mg + oral AD, esk 84 mg + oral AD, oral AD + placebo for TRANSFORM-1, or, esk + oral AD, oral AD + placebo for TRANSFORM-2), day, region (for TRANSFORM-1) or country (for TRANSFORM-2), class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. Negative change in score indicates improvement.

Figure 17: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)

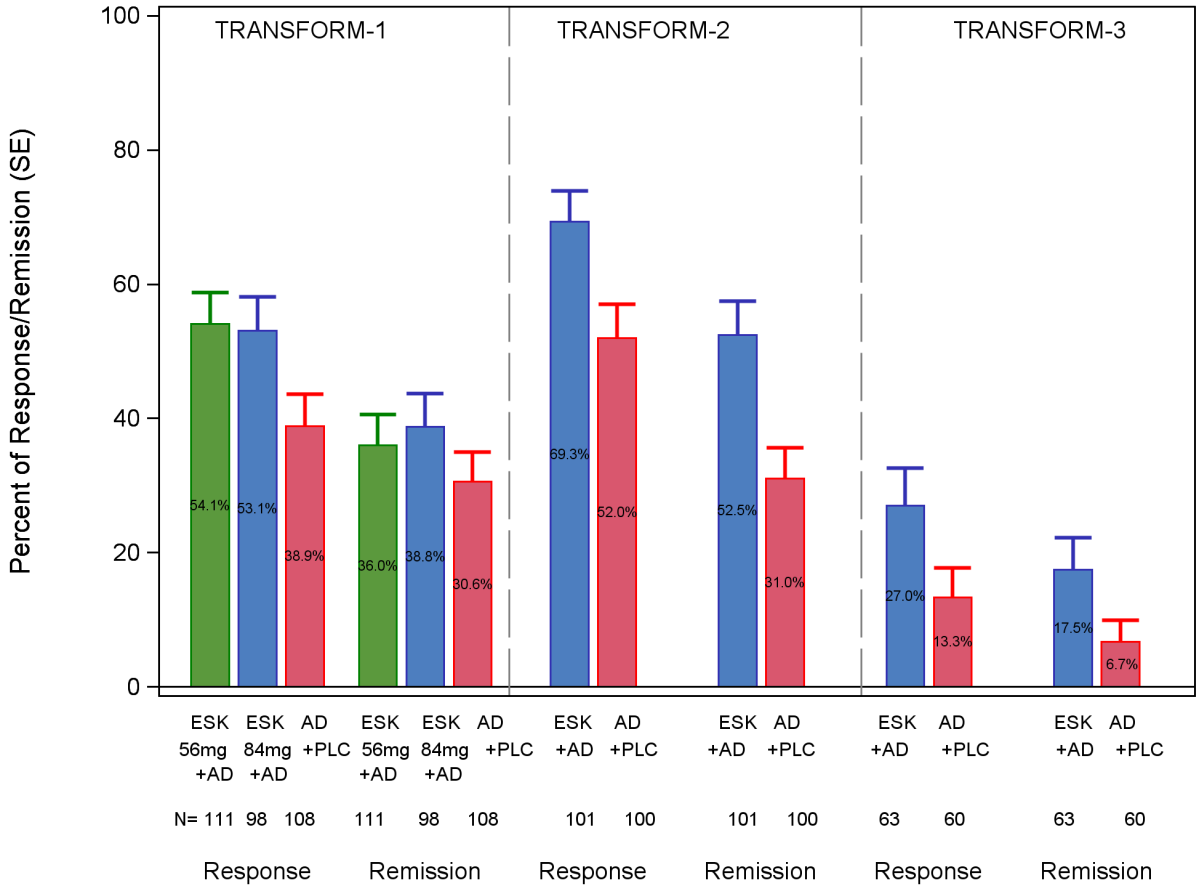


AD=antidepressant; Esk=esketamine; SE=standard error; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor
N=72 for the esketamine + oral AD group; N=65 for the oral AD + placebo group
Notes: LS Mean and SE were based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (esk + oral AD, oral AD + placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. Results are not adjusted for sample size re-estimation. Negative change in score indicates improvement.

Response and Remission Rates

To understand how the difference in MADRS total score is clinically meaningful, it is helpful to assess rates of response, which is significant clinical improvement (defined as ≥50% improvement from baseline in MADRS total score in the Phase 3 short-term studies) and rates of remission, which is significant improvement leading to near absence of disease symptoms (defined as MADRS total score ≤12 in the Phase 3 short-term studies). The percentage of responders and remitters at Day 28 in the 3 short-term studies are shown in Figure 18. In each study, remitters are also included as responders.

Figure 18: Percentage of Responders and Remitters at Day 28 (Observed Case) in the Short-term Phase 3 Studies (Full Analysis Set)



AD=antidepressant; ESK=esketamine; PLC=placebo; SE=standard error
Notes: In each study, remitters are also included as responders. N corresponds to patients with MADRS assessment at Day 28. Response defined as ≥50% improvement from baseline in MADRS total score. Remission defined as MADRS total score ≤12.

The differences between the treatment groups in response rate and remission rate show there is a clinically meaningful benefit for esketamine + oral AD. The magnitude of the difference (Figure 18) indicates the amount of benefit provided by the treatment. Estimates of the number needed to treat for response and remission are displayed in Table 19.

Table 19: Number Needed to Treat for Response and Remission at Day 28 (Observed Case) in Phase 3 Short-term Studies (Full Analysis Set)

	Number Needed to Treat		
	Flexible-dose Esketamine + Oral AD	Esketamine 56 mg + Oral AD	Esketamine 84 mg + Oral AD
TRANSFORM-1			
Response		7	8
Remission		19	13
TRANSFORM-2			
Response	6		
Remission	5		
TRANSFORM-3			
Response	8		
Remission	10		

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale
Notes: Response defined as ≥50% improvement from baseline in MADRS total score. Remission defined as MADRS total score ≤12.

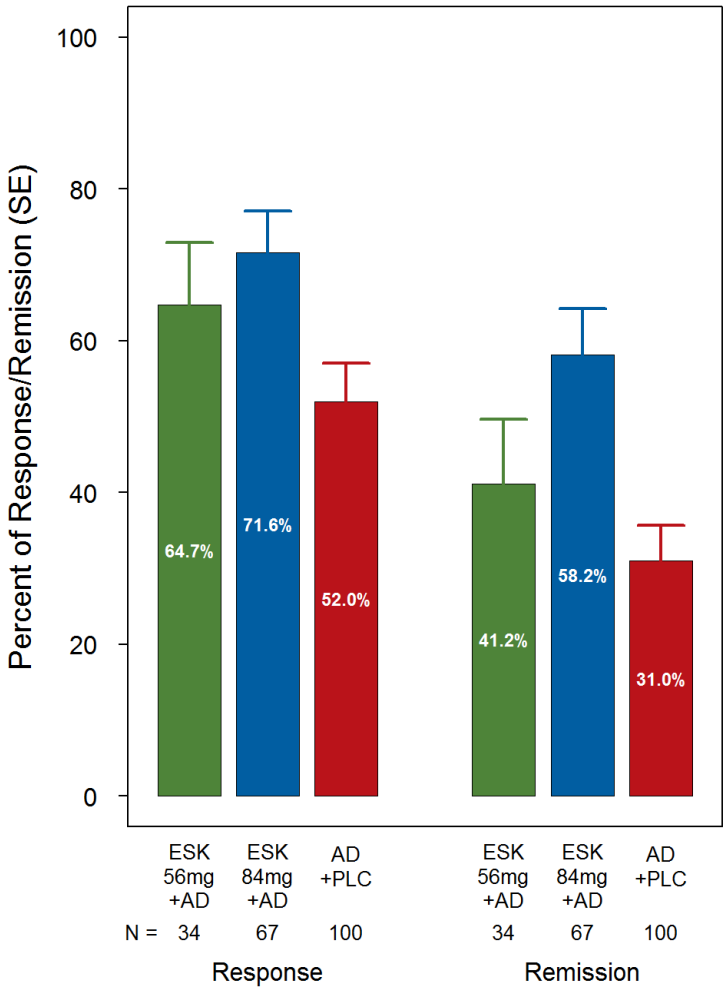
Descriptive Analysis of Response and Remission Rates by Dose After Day 15 in the Flexible-dose Study TRANSFORM-2

In the flexible-dose study TRANSFORM-2, patients received the 56-mg dose of nasal spray study medication on Day 1, and the dose could be increased based on the clinician's assessment of tolerability and efficacy or reduced based on assessment of tolerability until Day 15. After Day 15 (during the last 2 weeks of treatment), no change in dose was permitted. After Day 15, 33.0% (34 of 103) of patients received 56 mg of esketamine, and 67.0% (69 of 103) received 84 mg of esketamine.

A descriptive analysis was performed to evaluate response and remission rates for patients who received 56 mg of esketamine during the last 2 weeks of treatment and those who received 84 mg of esketamine during the last 2 weeks of treatment. Note, a limitation of this analysis is that these were not randomized groups; thus, the two populations may be different, and the conclusions may be biased due to confounding factors.

The percentage of responders and remitters at Day 28 among patients who received esketamine 56 mg + oral AD after Day 15, those who received esketamine 84 mg + oral AD after Day 15, and those who received oral AD + placebo are displayed in Figure 19. Patients who received the 84-mg dose of esketamine during the last 2 weeks of treatment in TRANSFORM-2 had numerically higher response and remission rates at Day 28 than those who received the 56-mg dose of esketamine during the last 2 weeks, suggesting that some patients benefited from increasing the dose to 84 mg.

Figure 19: Percentage of Responders and Remitters at Day 28 by the Esketamine Dose Administered After Day 15 in the Flexible-Dose Study TRANSFORM-2



AD=antidepressant; ESK=esketamine; PLC=placebo; SE=standard error
Note: N=number of patients who received each treatment after Day 15

Interim Analyses in TRANSFORM-1 and 3

The purpose of the prespecified interim analysis in TRANSFORM-1 and 3 was either to re-estimate the sample size or to stop the study due to futility as the assumptions of the expected treatment difference and variability may or may not have been upheld during the studies (further details about the interim analysis are provided in Appendix 13). The treatment differences for the primary endpoint for patients enrolled prior to the interim analysis (Stage 1) or after the interim analysis (Stage 2) also were explored for each study; see Appendix 13 for presentation of results by stage.

Subgroup Analyses of Primary Endpoint

Subgroup analyses, performed to explore the consistency of results for the primary endpoint using pooled data for TRANSFORM-1/2 (pooled to provide additional precision as some of the subgroups were small in the individual studies), showed no major differences in the results as a

function of age, gender, race, baseline MADRS total score, number of previous treatment failures in current episode, functional impairment (based on baseline SDS total score), country, region, class of newly-initiated oral AD, or oral AD class history (Appendix 6).

Subgroup analyses based on data from TRANSFORM-3 showed a difference in treatment effect for the age subgroup (Table 20 and Appendix 6). There were clinically meaningful benefits with esketamine + oral AD treatment versus oral AD + placebo for patients 65 to 74 years (Table 20 and Figure 20), but the results were not consistent for patients ≥75 years (Table 20 and Figure 21). Overall, the small sample size in the subgroup aged ≥75 years limited any meaningful conclusions. Subgroup analyses from TRANSFORM-3 showed no notable differences in treatment effects as a function of other subgroups evaluated (Appendix 6).

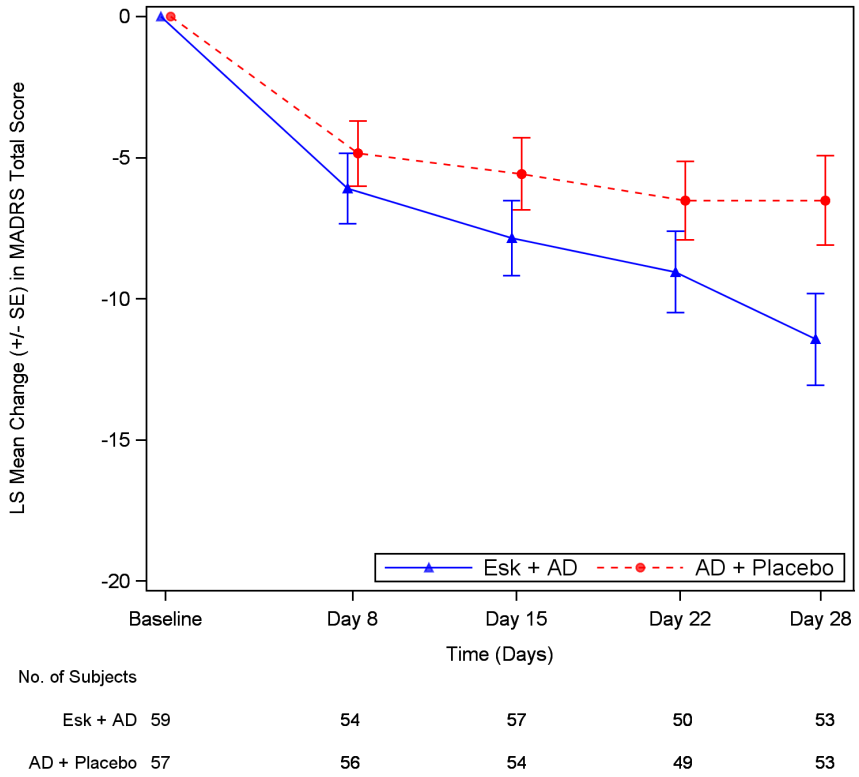
Table 20: MADRS Total Score for Patients 65 to 74 years and Patients ≥75 years: Change From Baseline to Day 28 by MMRM (Observed Case) in the Double-blind Induction Phase of TRANSFORM-3 (Full Analysis Set)

	To Day 28, by MMRM	
	Esketamine (28, 56, or 84 mg) + Oral AD (N=72)	**Oral AD + Placebo (N=65)**
Patients 65 to 74 years		
N	53	53
Mean Change, baseline to Day 28 (SD)	-10.9 (12.90)	-6.2 (9.06)
Difference (SE) [a]	-4.9 (2.04)	
95% confidence interval on difference	-8.96; -0.89	
Patients ≥75 years		
N	10	7
Mean Change, baseline to Day 28 (SD)	-5.1 (11.14)	-7.0 (7.72)
Difference (SE) [a]	-0.4 (5.02)	
95% confidence interval on difference	-10.38; 9.50	

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SD=standard error; SE=standard error

[a] The difference is the result of the least-squares means for esketamine + AD minus AD + placebo. The MMRM is based on change from baseline as the response variable and the fixed effect model terms for treatment, day, region, class of oral AD, age group, treatment-by-day, treatment-by-age group, and treatment-by-day-by-age group, and baseline value as a covariate. A negative difference favors esketamine, and the results were not adjusted for sample size re-estimation.

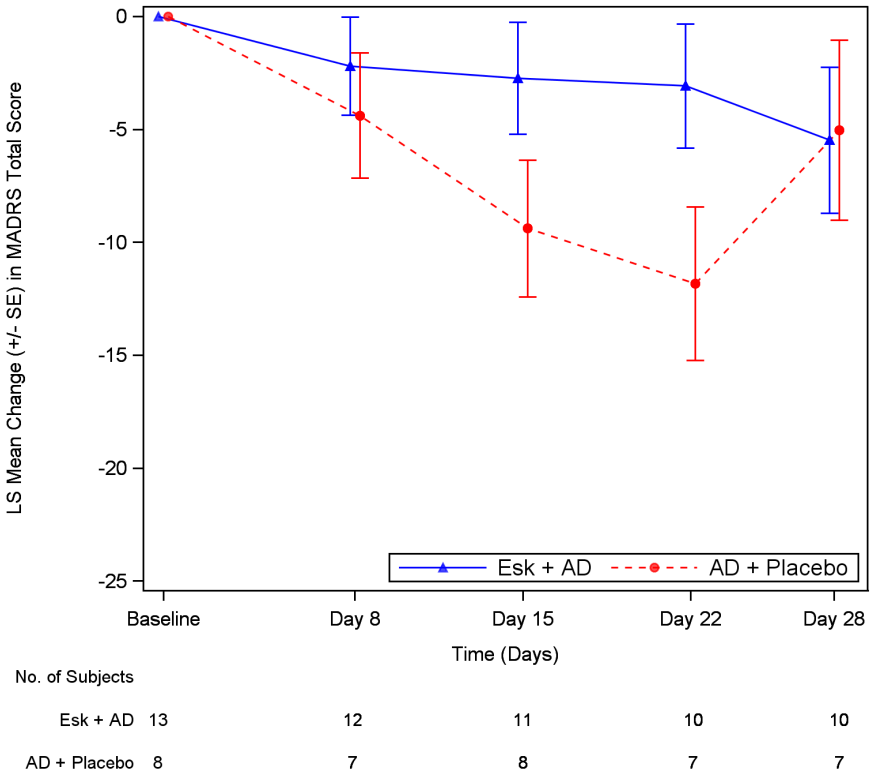
Figure 20: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM for 65-74 Age Group; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)



AD=antidepressant; Esk=esketamine; SE=standard error; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

Notes: LS Mean and SE were based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (esk + oral AD, oral AD + placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, treatment-by-age group, treatment-by-day-by-age group and baseline value as a covariate. Results are not adjusted for sample size re-estimation. Negative change in score indicates improvement.

Figure 21: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM for >=75 Age Group; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)



AD=antidepressant; Esk=esketamine; SE=standard error; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor
Note: LS Mean and SE were based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (esk + oral AD, oral AD + placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, treatment-by-age group, treatment-by-day-by-age group and baseline value as a covariate. Results are not adjusted for sample size re-estimation. Negative change in score indicates improvement.

Furthermore, since late onset depression (onset of depression after the age of 55) is considered to have different pathophysiology (significantly more magnetic resonance signal hyperintensities in the periventricular and deep white matter on magnetic resonance imaging[90]) and a higher degree of treatment resistance,[74] a post hoc analysis of change in baseline MADRS total score to Day 28 by age of onset of MDD was conducted in TRANSFORM-3. For patients with an age of onset of MDD prior to age 55, the LS mean (95% CI) treatment difference for change from baseline in MADRS total score at Day 28 between the esketamine + oral AD group (N=50) and the oral AD + placebo group (N=43) was -6.1 (-10.33; -1.81) while for patients with an age of onset of MDD after age 55 the mean (95% CI) treatment difference between esketamine + oral AD (N=13) and oral AD + placebo (N=17) was 3.1 (-4.51; 10.80).

Sensitivity Analyses of Primary Endpoint

Results of the prespecified sensitivity analysis to evaluate the robustness of the primary MMRM analysis to increasing deviations from the missing at random assumption (i.e., delta adjustment tipping point analysis) for TRANSFORM-2 showed that the study conclusions would continue to favor esketamine + oral AD over oral AD + placebo until the imputed missing changes in MADRS total scores after discontinuation for the esketamine + oral AD group would become 9.0 points worse than expected if they were missing at random.

For TRANSFORM-2, a jump to reference imputation was performed for a post hoc sensitivity analysis. Further sensitivity analyses were performed with an ANCOVA analysis of change in MADRS total score at endpoint using LOCF (pre-planned), baseline observation carried forward (post hoc) and worst observation carried forward (post hoc) methods of imputation. The ANCOVA model included factors for treatment, country, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. Comparison of the esketamine + oral AD arm versus placebo + oral AD was performed using the appropriate contrast. The results from each of these analyses were consistent with the primary MMRM analysis.

Further details about the sensitivity analyses are provided in Appendix 13.

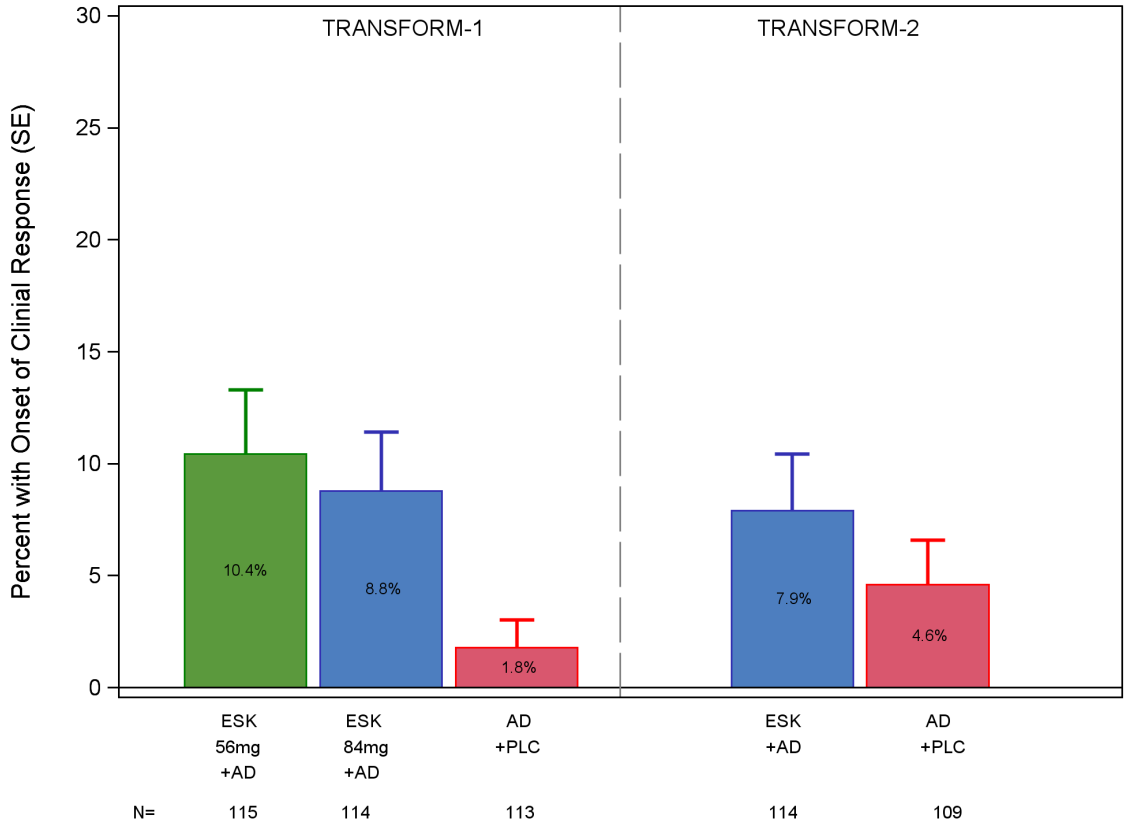
7.3.1.2. Key Secondary Efficacy Endpoints: Onset of Clinical Response and Changes from Baseline in SDS and PHQ-9 Total Scores

Three key secondary endpoints were analyzed sequentially in TRANSFORM-1 and 2 according to the prespecified hierarchy: onset of clinical response by Day 2 (24 hours), change in SDS total score, and change in PHQ-9 total score to adjust for multiplicity and control type I error (see Section 7.2 and Appendix 13).

Onset of Clinically Sustained Response by Day 2 in TRANSFORM-1 and 2

Onset of clinical response by Day 2 (proportion of patients with ≥50% improvement from baseline in MADRS total score by Day 2 that was maintained to Day 28) was numerically higher for the esketamine + oral AD groups than for the oral AD + placebo group (Figure 22). The treatment difference was not statistically significant for TRANSFORM-2 (2-sided p=0.321) and could not be tested statistically in TRANSFORM-1 as the primary endpoint in the testing hierarchy was not significant.

Figure 22: Onset of Clinically Sustained Response by Day 2 and Maintained Through Day 28 in TRANSFORM-1 and 2 (Full Analysis Set)



AD=antidepressant; ESK=esketamine; PLC=placebo; SE=standard error

Changes from Baseline in SDS and PHQ-9 Total Scores

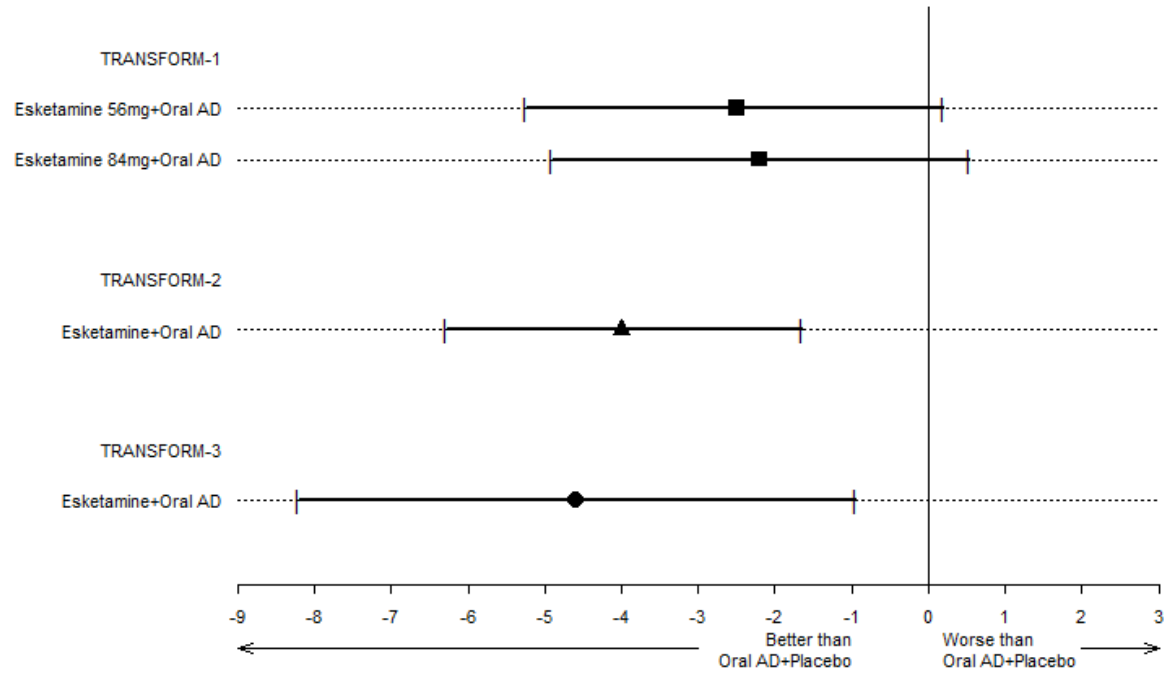
For both TRANSFORM-2 and TRANSFORM-1, the other 2 key secondary endpoints (change in SDS total score, a patient-reported measure of mental health-related functional impairment, and PHQ-9 total score, a patient-reported measure of severity of depression) in the statistical hierarchy could not be formally tested. Nevertheless, results for both patient-rated clinical measures numerically favored treatment with esketamine + oral AD, supporting the favorable evidence from the primary endpoint (MADRS) from a patient perspective. Specifically,

- Patients in the esketamine + oral AD group reported numerically greater improvements from baseline in functioning and associated disability (assessed by the SDS total score) compared with patients in the oral AD + placebo group (Figure 23).
- Patients receiving esketamine + oral AD consistently demonstrated numerically greater improvements at the end of the 4-week induction phase in the PHQ-9 total score compared with patients treated with oral AD + placebo (Figure 24).

- Among patients ≥65 years, changes from baseline in SDS and PHQ-9 total score showed numerically larger reductions (i.e., improvement) in SDS total score and PHQ-9 total score in the esketamine + oral AD group compared with the oral AD + placebo group (Figure 23 and Figure 24); however, in TRANSFORM-3, these endpoints were not part of a testing hierarchy and were not considered secondary endpoints.

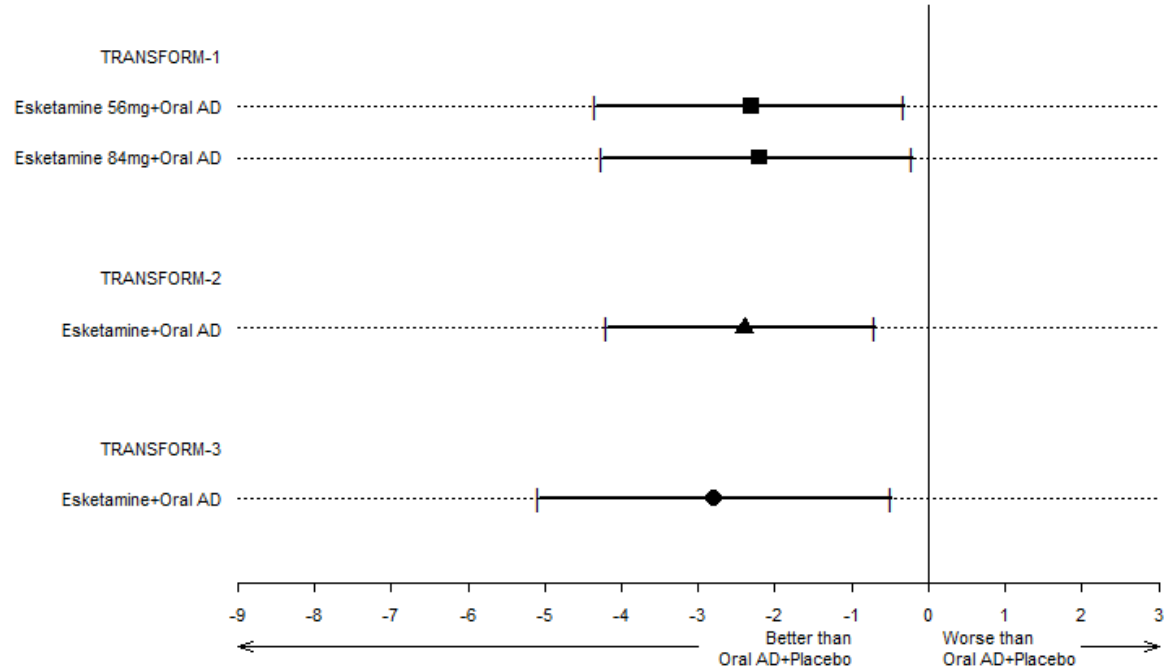
Further details about the analyses of SDS and PHQ-9 total scores are provided in Appendix 13.

Figure 23: Sheehan Disability Scale Total Score: Least-squares Mean Difference by MMRM (Observed Case) of Esketamine + Oral AD Versus Oral AD + Placebo in Change From Baseline to Day 28 (TRANSFORM-1, 2, and 3: Full Analysis Set)



AD=antidepressant; CI=confidence interval; LS=least-squares; MMRM=mixed model using repeated measures
Note: The graph shows the difference in LS means (with 95% CIs) for TRANSFORM-2 and 3, and the median unbiased estimates (with 95% CIs) of the differences between esketamine + oral AD and oral AD + placebo for TRANSFORM-1. The LS means and median unbiased estimates are obtained from MMRM.

Figure 24: Patient Health Questionnaire -9-Item: Least-squares Mean Difference by MMRM (Observed Case) of Esketamine + Oral AD Versus Oral AD + Placebo in Change From Baseline to Day 28 (TRANSFORM-1, 2, and 3: Full Analysis Set)



AD=antidepressant; CI=confidence interval; LS=least-squares; MMRM=mixed model using repeated measures
Note: The graph shows the difference in LS means (with 95% CIs) for TRANSFORM-2 and 3, and the median unbiased estimates (with 95% CIs) of the differences between esketamine + oral AD and oral AD + placebo for TRANSFORM-1. The LS means and median unbiased estimates are obtained from MMRM.

7.3.2. Efficacy Results from the Phase 3 Maintenance of Effect Study SUSTAIN-1

Overview

- In the maintenance of effect study SUSTAIN-1 (which used a randomized withdrawal design in the context of continued oral AD treatment), a statistically significantly longer time to relapse was observed with randomized continuation of esketamine treatment relative to randomized discontinuation of esketamine in adult patients with TRD who had achieved stable remission or stable response of their depression symptoms after 16 weeks of treatment with esketamine + oral AD.

Exposure

In the group of stable remitters randomized to continue treatment at the start of the double-blind maintenance phase in SUSTAIN-1, 55.6% received the 84-mg dose and 44.4% received the 56-mg dose. In the group of stable responders, 67.7% received the 84-mg dose and 32.3% received the 56-mg dose. The dosing frequency used the majority of time in the maintenance phase for patients randomized to double-blind treatment in this phase is shown in Table 21. The majority of stable remitters were maintained on an every-other-week dosing regimen.

Table 21: Dosing Frequency Used the Majority of the Time; Maintenance Phase (SUSTAIN-1)

	Stable Remitters		Stable Responders	
	Esketamine + Oral AD (N=90)	Oral AD + Placebo (N=86)	Esketamine + Oral AD (N=62)	Oral AD + Placebo (N=59)
Majority dosing frequency				
Weekly	21 (23.3%)	27 (31.4%)	34 (54.8%)	36 (61.0%)
Every other week	62 (68.9%)	48 (55.8%)	21 (33.9%)	19 (32.2%)
Weekly or every other week	7 (7.8%)	11 (12.8%)	7 (11.3%)	4 (6.8%)

AD=antidepressant
Note: Majority dosing frequency is the regimen patients were on at least 50% of the time in the Maintenance Phase.
Stable remitters and stable responders were non-overlapping groups.

Enrollment in SUSTAIN-1 was staggered over approximately 1.5 years. The double-blind maintenance phase was of variable duration and continued until the individual patient had a relapse of depressive symptoms or discontinued for any other reason, or the study ended because the required number of relapse events occurred. Exposure numbers were influenced by the study stopping at a pre-determined number of relapses based on the interim analysis. After the initial 16 weeks of treatment with esketamine + oral AD, 31.6% of patients in the combined group of stable remitters and stable responders received esketamine for >6 months and 7.9% received esketamine for >1 year in the randomized, double-blind maintenance phase (median duration, 4.2 months [range: 1 day to 21.2 months]).

7.3.2.1. Primary Efficacy Endpoint: Time to Relapse in Patients Achieving Stable Remission on Esketamine + Oral AD

In the full (stable remitters) analysis set, relapse events occurred during the maintenance phase for 26.7% of patients in the esketamine + oral AD group and 45.3% of patients in the oral AD + placebo group (number needed to treat=6; see App 12 - Table 5). As shown in Table 22, the estimated hazard ratio of esketamine + oral AD relative to oral AD + placebo based on weighted estimates was 0.49 (95% CI: 0.29; 0.84). A total of 17 patients (8 in the esketamine + oral AD group, 9 in the oral AD + placebo group) discontinued the maintenance phase for reasons other than relapse or study termination (i.e., non-administrative censoring; also see Figure 13).

Kaplan-Meier curves of the time to relapse in the full (stable remitters) analysis set are presented in Figure 25. Based on the weighted combination log-rank test, the difference between treatment groups for the time to relapse was statistically significant (2-sided p=0.003; Table 22). The median time to relapse (95% CI) was 273 (97.0; not estimable) days for the oral AD + placebo group and was not estimable for esketamine + oral AD group (this group did not reach 50% of patients relapsed based on Kaplan-Meier estimates) (Table 22).

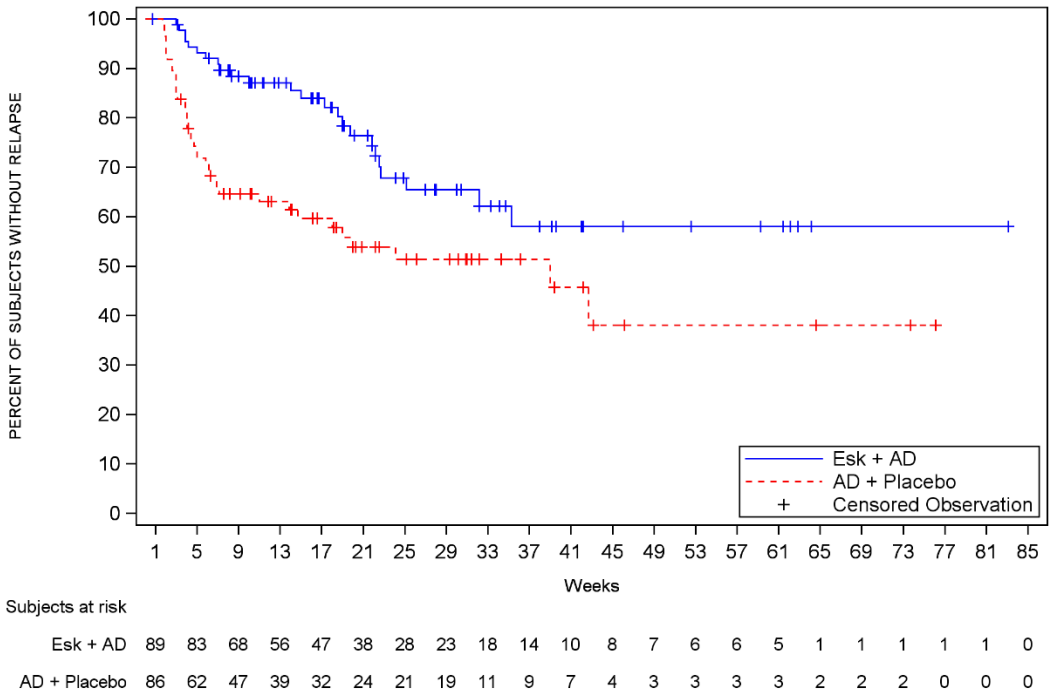
Table 22: Time to Relapse and Number (%) of Patients That Remained Relapse Free; Maintenance Phase (SUSTAIN-1: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo
Time to Relapse (days) (a)		
Number assessed	90	86
Number censored (%)	66 (73.3%)	47 (54.7%)
Number of relapses (%)	24 (26.7%)	39 (45.3%)
25% percentile (95% CI)	153.0 (105.0; 225.0)	33.0 (22.0; 48.0)
Median (95% CI)	NE	273.0 (97.0; NE)
75% percentile (95% CI)	NE	NE
Hazard Ratio (95% CI) (b)	0.49 (0.29; 0.84)	
Two-sided P-value (c)	0.003	

AD=antidepressant; CI=confidence interval; NE=not estimable

(a) Based on Kaplan-Meier product limit estimates.
(b) Hazard ratio and CI are weighted estimates based on Wassmer[114] and calculated using R.
(c) Two-sided P-value is based on the final test statistic, which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters.
Note: A total of 17 patients (8 in the esketamine + oral AD group, 9 in the oral AD + placebo group) discontinued the maintenance phase for reasons other than relapse or study termination (i.e., non-administrative censoring).

Figure 25: Cumulative Proportion (Kaplan-Meier Estimates) of Stable Remitter Patients Who Remained Relapse Free During the Maintenance Phase of SUSTAIN-1 (Full (Stable Remitters) Analysis Set)



AD=antidepressant; Esk=esketamine
Note: The data represent the full (stable remitters) analysis set, which included 175 stable remitters and 1 stable responder (who was incorrectly randomized as a stable remitter).

Among the patients who relapsed in the full (stable remitter) analysis set, none completed or attempted suicide or were hospitalized for suicide prevention. Among patients in this analysis set

who relapsed, all manifested a worsening of their depression, meeting the criteria for relapse either by:

- Having a MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days (18/24 and 38/39 relapsed patients in esketamine + oral AD and oral AD + placebo groups, respectively)
- Being hospitalized for worsening depression (3/24 patients in esketamine + oral AD group and 0/39 patients in oral AD + placebo group)
- Manifesting a clinically relevant event suggestive of relapse and confirmed by the adjudication committee as depression (3/24 and 1/39 patients in esketamine + oral AD and oral AD + placebo groups, respectively)

Evaluating the Effects of Early Relapses

A concern cited in the interpretation of randomized withdrawal studies is that an increased rate of depression observed after discontinuing the antidepressant and switching to placebo could be a pharmacological consequence of antidepressant withdrawal.[11] All patients in SUSTAIN-1 continued the oral antidepressant after randomization into the Maintenance Phase. A high early (in the first few weeks) rate of relapses in the arm randomized to discontinue esketamine conceivably may indicate a possible esketamine withdrawal effect.

The results shown in Figure 25 demonstrate that patients who were randomized to continue esketamine were less likely to relapse than those who were randomized to discontinue esketamine. These results could be due to either a persistent treatment benefit or a possible withdrawal effect, or both, as a high number of relapses was observed in the first few weeks after the start of the maintenance phase. This outcome could also be explained by having a mixture of patient populations based on individual patient disease characteristics. To further explore this issue, an analysis by dosing frequency was performed to further explore the high early rate of relapses observed in SUSTAIN-1 (Section 6.3 in Appendix 13).

Based on the Kaplan-Meier analysis by dosing frequency shown in App 13 - Figure 6, there is evidence that the early relapses seen in Figure 25 may in part be due to a mixture of populations based on individual patient disease characteristics. The results from the more vulnerable patients who were not able to sustain remission unless given weekly treatment suggest that the observed effects may include both a persistent benefit of esketamine and an effect that is likely due to this more vulnerable group relapsing very quickly, as has been shown in electroconvulsive therapy.[89]

Subgroup Analyses

Results of analyses of the primary endpoint in various subpopulations by gender, age group, region, number of previous treatment failures in current episode, functional impairment, race, class of oral AD medication, country, consented protocol (before or after implementation of a protocol amendment in which criteria for stable remission were amended), entry source (direct-entry or transferred-entry), and oral AD medication (performed using the full [stable remitters] analysis set) generally showed a longer time to relapse for the esketamine + oral AD treatment group compared with the oral AD + placebo group, as indicated by the forest plots presented in Appendix 7.

7.3.2.2. Secondary Efficacy Endpoint: Time to Relapse in Patients Achieving Stable Response on Esketamine + Oral AD

The secondary efficacy results for the time to relapse by stable responders (but who were not in remission) showed a statistically significantly longer time to relapse in patients randomized to continue esketamine compared to those randomized to discontinue esketamine (2-sided p<0.001; Table 23). Kaplan-Meier curves of the time to relapse in the full (stable responders) analysis set are presented for the 2 treatment groups in Figure 26. A total of 8 patients (5 in the esketamine + oral AD group, 3 in the oral AD + placebo group) discontinued the maintenance phase for reasons other than relapse or study termination (non-administrative censoring; also see Figure 13).

Overall, 16 (25.8%) stable responders randomized to the esketamine + oral AD group, compared with 34 (57.6%) stable responders randomized to the oral AD + placebo group, experienced a relapse event during the double-blind maintenance phase (number needed to treat=4; see App 12 - Table 6). The estimated hazard ratio of esketamine + oral AD relative to oral AD + placebo was 0.30 (95% CI: 0.16; 0.55). The median time to relapse (95% CI) for stable responders was 88 (46.0, 196.0) days for the oral AD + placebo group and 635 (264.0, 635.0) days for the esketamine + oral AD group.

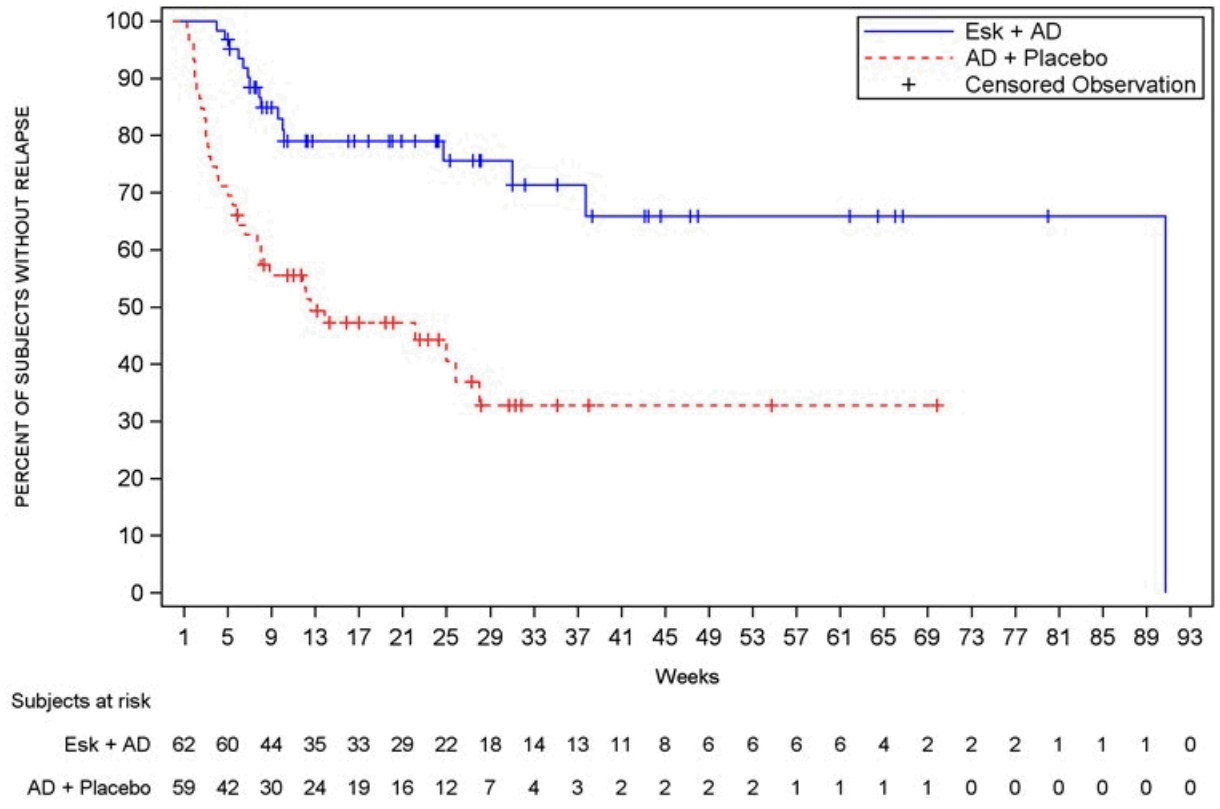
Table 23: Time to Relapse and Number (%) of Patients That Remained Relapse Free; Maintenance Phase (Study SUSTAIN-1: Full (Stable Responders) Analysis Set)

	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo
Time to Relapse (days) (a)		
Number assessed	62	59
Number censored (%)	46 (74.2%)	25 (42.4%)
Number of relapses (%)	16 (25.8%)	34 (57.6%)
25% percentile (95% CI)	217.0 (56.0; 635.0)	24.0 (17.0; 46.0)
Median (95% CI)	635.0 (264.0; 635.0)	88.0 (46.0; 196.0)
75% percentile (95% CI)	635.0 (NE)	NE
Hazard Ratio (95% CI)(b)	0.30 (0.16; 0.55)	
Two-sided P-value(c)	<0.001	

AD=antidepressant; CI=confidence interval; NE=not estimable

(a) Based on Kaplan-Meier product limit estimates.
(b) Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor.
(c) Log-rank test.
Note: A total of 8 patients (5 in the esketamine + oral AD group, 3 in the oral AD + placebo group) discontinued the maintenance phase for reasons other than relapse or study termination (non-administrative censoring).

Figure 26: Cumulative Proportion (Kaplan-Meier Estimates) of Stable Responder Patients Who Remained Relapse Free During the Maintenance Phase of SUSTAIN-1 (Full Stable Responder Analysis Set)



AD=antidepressant; Esk=esketamine

7.3.3. Long-term Efficacy: Supportive Results from Phase 3 Study SUSTAIN-2

Overview

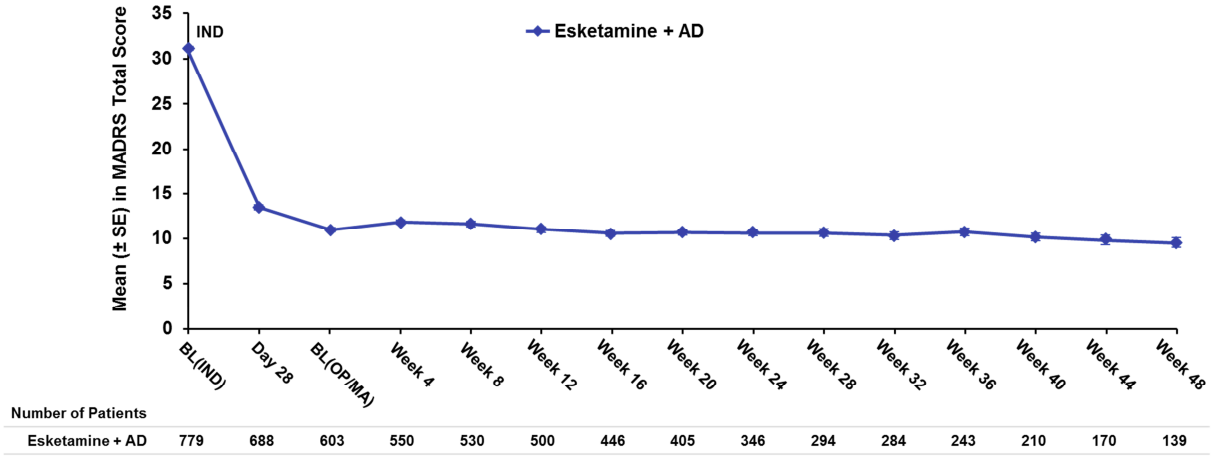
- In the open-label study SUSTAIN-2, improvements in measures of depression were consistent across multiple assessments of depressive symptoms over the 4-week induction phase and appeared to be sustained in patients who continued treatment with esketamine + oral AD for up to 1 year.
- Improvements with esketamine + oral AD observed in SUSTAIN-2 were in the range of the previous Phase 2 and Phase 3 short-term studies.
- Improvements in depressive symptoms observed with esketamine + oral AD were sustained when the dosing frequency was decreased from twice weekly during the 4-week induction phase to weekly or every other week in the 48-week optimization/maintenance phase.

Results

As shown in Figure 27, the mean change from baseline in the MADRS total score at end point of the 4-week induction phase of -16.4 remained largely unchanged throughout the 48-week

optimization/maintenance phase for those patients who entered that phase; the mean change from baseline to end point of the optimization/maintenance phase was 0.3.

Figure 27: Mean Change from Baseline in MADRS Total Score in SUSTAIN-2



AD=antidepressant; BL=baseline; IND=induction phase; MADRS=Montgomery-Asberg Depression Rating Scale; OP/MA=optimization/maintenance phase; SE=standard error

At the end of the induction phase (Day 28) and the end of the optimization/maintenance phase (Week 48), over 80% of patients were responders, and over 50% of patients were remitters (Table 24).

In the STAR*D study, of patients at the third or fourth treatment step who were in remission at entry to the follow-up phase, 50% relapsed (mean time to relapse was 2.5 months). Of patients who were not in remission at entry to the follow-up phase, 83% relapsed (mean time to relapse was 3.5 months).[88]

Table 24: Response and Remission Rates at Day 28 and Week 48 in SUSTAIN-2 (Full Analysis Set)

	Day 28 (N=688)	Week 48 (N=139)
Response, n (%)	581 (84.4%)	124 (89.2%)
Remission, n (%)	349 (50.7%)	95 (68.3%)

Response defined as ≥50% improvement from baseline in MADRS total score. Remission defined as MADRS total score ≤12. Remitters are also shown as responders.

8. CLINICAL SAFETY

The primary safety assessment is based on data from the 6 completed Phase 2 and 3 studies in patients with TRD (SYNAPSE; TRANSFORM-1, 2, and 3; SUSTAIN-1 and 2). Supportive Phase 2 and 3 safety data are provided for the ongoing Phase 3 open-label safety extension study in patients with TRD (SUSTAIN-3) through a clinical cutoff date of 04 March 2018 and the

completed Phase 2 study in the related population of patients with MDD at imminent risk for suicide (PERSEVERE).

Overall, an estimated 2,309 participants have been exposed to esketamine nasal spray across the completed Phase 1, 2, and 3 studies in the clinical development program, including 566 participants across the completed Phase 1 studies, 1,708 participants across the completed Phase 2 or 3 studies in TRD, and 35 participants in the completed Phase 2 study in patients with MDD at imminent risk for suicide.

8.1. Key Features of the Safety Analyses

In the Phase 2 and 3 studies in patients with TRD, safety was evaluated through adverse event monitoring, clinical laboratory tests including a urine drug screen, vital sign measurements, pulse oximetry, electrocardiograms (ECGs), nasal examination/nasal symptom questionnaire, physical examinations, and specific scales to systematically evaluate key potential adverse effects. Results from the following scales are presented in this document: Clinician Administered Dissociative States Scale (CADSS), Columbia-Suicide Severity Rating Scale (C-SSRS), Modified Observer's Assessment of Alertness/Sedation (MOAA/S), 20-Item Physician Withdrawal Checklist (PWC-20), CogState® computerized cognitive test battery, Hopkins Verbal Learning Test-Revised, and clinical assessment of discharge readiness.

In this document, the following safety topics are discussed: suicidal ideation and behavior, dissociation and perceptual changes, hypomania and mania, sedation and somnolence, effects on cognition, cardiovascular effects, effects on respiratory rate and oxygen saturation, readiness for discharge, effects on ability to drive or operate machinery, interstitial or ulcerative cystitis, hepatic safety, potential abuse and potential withdrawal.

Due to differences in study design, limited pooling of safety data was done for these studies. Data for select safety parameters were pooled for the Phase 3 short-term studies in adults 18-64 years of age, TRANSFORM-1 and 2.

Adverse Events

An adverse event is any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product.

Verbatim terms used by investigators to describe adverse events were coded to preferred terms using the Medical Dictionary for Regulatory Activities Terminology (MedDRA). Unless otherwise specified, all adverse events discussed in subsequent sections were treatment-emergent adverse events (TEAEs, defined as those events that were first reported or worsened in severity after starting study treatment).

In the clinical studies, TEAEs of special interest were evaluated separately in the following categories: TEAEs suggestive of abuse potential, increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, cystitis, and events potentially related to

suicidality. See Appendix 11 for a list of preferred terms used to search for TEAEs of special interest.

Patients were advised to wait at least 3 hours after nasal spray administration to take the concurrent oral AD as most of the adverse events associated with esketamine nasal spray were expected to resolve within 2 hours after dose administration. This minimized the potentially confounding effects of oral AD treatment on the safety evaluation of esketamine.

8.2. Extent of Exposure

Phase 1, 2, and 3 Studies

A summary of the number of patients who received at least 1 dose of esketamine nasal spray in the completed Phase 1, 2, and 3 clinical studies and the ongoing open-label extension study SUSTAIN-3 as of the cutoff date for the NDA (4 March 2018) is shown in Table 25.

Table 25: Exposure to Esketamine Nasal Spray in Phase 1, 2 and 3 Studies with Esketamine Nasal Spray

			Esketamine Nasal Spray		Placebo Nasal Spray	
Study Phase	Study Population	Number of Studies	Number of Unique Patients Exposed	Patient-years of Exposure	Number of Unique Patients Exposed	Patient-years of Exposure
Phase 1	Healthy participants, special populations, patients with MDD	18[a]	566	7	Not determined	Not determined
Phase 2	Patients with TRD	1	107	10	54	1
	Patients with MDD at imminent risk for suicide	1	35	2	31	2
Phase 3 Completed	Patients with TRD	5	1601	601[d]	432	107[e]
Phase 3 Ongoing[b]	Patients with TRD	1	153[c]	434	N/A	N/A

N/A=not applicable; MDD=major depressive disorder; TRD=treatment-resistant depression

[a] Of 19 Phase 1 studies, 1 is not included as esketamine nasal spray was not administered in 1 study (54135419TRD1016).

[b] SUSTAIN-3 as of the cutoff date of 4 March 2018

[c] Of 1092 patients enrolled in SUSTAIN-3, 153 patients were not previously exposed to esketamine in any of the completed Phase 3 studies.

[d] During the Phase 3 double-blind studies/study phases, exposure to esketamine nasal spray totaled 112 patient-years.

[e] During the Phase 3 double-blind studies/study phases, exposure to placebo nasal spray totaled 99 patient-years (note, this does not include patients who transferred to the longer-term studies SUSTAIN-1 and 2 from short-term studies TRANSFORM-1, 2 and 3 and continued to receive placebo nasal spray during the longer-term studies to maintain blinding).

In the completed Phase 3 clinical studies:

- 479 patients were treated with esketamine nasal spray for ≥180 days
- 178 were treated with esketamine nasal spray for ≥350 days

- 194 patients were ≥65 years of age; 25 patients were ≥75 years of age
- 232 patients received only oral AD + placebo and were not exposed to esketamine nasal spray

8.3. Adverse Events

Overview of Adverse Events

- The most commonly observed adverse drug reactions (ADRs, defined as adverse events reasonably associated with the use of esketamine) in TRD patients treated with esketamine + oral AD (with incidence ≥10% and greater than in oral AD + placebo group) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.
- Most (94.9%) TEAEs with esketamine in Phase 2 and 3 TRD studies were mild to moderate in severity.
- Most TEAEs in esketamine-treated patients occurred shortly after dosing, were transient, and resolved on the same day. In the esketamine + oral AD groups in the short-term studies (TRANSFORM-1, 2, and 3), over 86% of all TEAEs occurred on nasal spray dosing days and of those events, over 85% also resolved the same day.
- There were no new safety concerns identified with long-term repeated, intermittent weekly or every-other-week administration of esketamine doses (28, 56, or 84 mg) over a duration of up to 1 year in the uncontrolled, open-label safety study SUSTAIN-2.
- The TEAE profile for patients ≥65 years of age was generally consistent with that observed in patients <65 years of age. In the long-term safety study SUSTAIN-2, a slowing of reaction time in the absence of any other change in cognitive performance was observed in patients ≥65 years of age; however, the observation could not be attributed to study medication and the clinical relevance and consequences have not been established.
- In the fixed-dose study TRANSFORM-1, the overall rates of TEAEs and severe TEAEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, and most TEAEs across both dose groups were mild or moderate in severity, occurred on the day of dosing, and resolved the same day. TEAEs of dissociation occurred at a higher rate (6.4% higher) in the esketamine 84 mg group than the 56 mg group, and severe TEAEs of dissociation and nausea occurred at a higher rate (2.9% higher for both dissociation and nausea) in the esketamine 84 mg group.
- A total of 5 deaths occurred in the completed and ongoing Phase 2 and 3 clinical studies in patients with TRD as of the clinical cutoff date of 4 March 2018 (1861 unique patients treated with esketamine; 1045 patient-years of exposure):
  - Completed double-blind studies/study phases: One death (multiple injuries sustained in a road traffic accident) occurred among esketamine-treated patients during the double-blind phases of the completed Phase 2 and 3 studies (122 patient-years of exposure). No deaths occurred in the oral AD + placebo groups of these studies (100 patient-years of exposure).

  - Completed and ongoing open-label studies/study phases: There were 3 deaths (2 completed suicides and 1 case of acute cardiac and respiratory failure) among patients treated with esketamine + oral AD during the open-label studies/study phases (923 patient-years of exposure).
  - Follow-up phases: There was 1 death (completed suicide) during the follow-up phases of these studies when the patient was not receiving nasally-administered study medication.
  - All 5 deaths were assessed by the investigator and the Sponsor as not related to the esketamine treatment.

- Across the completed Phase 3 studies/study phases in patients with TRD, the incidence of serious adverse events ranged from 0.9% to 6.9% in the esketamine + oral AD treatment groups and from 0.5% to 3.1% in the oral AD + placebo groups.
- Across the completed Phase 3 studies/study phases, the incidence of TEAEs leading to discontinuation of study medication ranged from 1.1% to 9.5% in the esketamine + oral AD treatment groups and from 1.4% to 3.1% in the oral AD + placebo groups.

8.3.1. Common Treatment-emergent Adverse Events in Completed Studies

8.3.1.1. Pooled Short-term Phase 3 Studies in Adults with TRD (TRANSFORM-1 and TRANSFORM-2)

Data from TRANSFORM-1 and 2 provide information about the safety and tolerability of induction treatment with esketamine + oral AD compared to oral AD + placebo in patients 18 to 64 years of age.

All randomized patients who received at least 1 dose of nasal spray study medication (esketamine or placebo) or 1 dose of oral AD in the double-blind induction phase were included in the safety analysis sets for TRANSFORM-1 and 2. Data relating to adverse events in these 2 studies were pooled. A summary of TEAEs reported by ≥5% of patients in any treatment group in the pooled studies TRANSFORM-1/2 is provided in Table 26.

- Most patients experienced one or more TEAEs
- The most common TEAEs (reported by ≥10% of patients) were:
  - Total esketamine + oral AD group: nausea, dissociation, dizziness, vertigo, headache, dysgeusia, somnolence, paraesthesia, hypoaesthesia, hypoaesthesia oral
  - Oral AD + placebo group: headache and dysgeusia
- Each of the most common TEAEs was observed more frequently (with a difference of at least 3%) in the total esketamine + oral AD group versus the oral AD + placebo group

Table 26: Treatment-emergent Adverse Events in at Least 5% of Patients in Any Treatment Group; Double-blind Induction Phase (Pooled Studies TRANSFORM-1, TRANSFORM-2: Safety Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=116)	Flexible-dose Esketamine (N=115)	Total Esketamine (a) (N=346)	Oral AD + Intranasal Placebo (N=222)
Total no. subjects with TEAE	100 (87.0%)	103 (88.8%)	98 (85.2%)	301 (87.0%)	143 (64.4%)
Nervous system disorders	74 (64.3%)	74 (63.8%)	72 (62.6%)	220 (63.6%)	86 (38.7%)
Dizziness	32 (27.8%)	26 (22.4%)	24 (20.9%)	82 (23.7%)	15 (6.8%)
Headache	23 (20.0%)	24 (20.7%)	23 (20.0%)	70 (20.2%)	38 (17.1%)
Dysgeusia	17 (14.8%)	20 (17.2%)	28 (24.3%)	65 (18.8%)	30 (13.5%)
Somnolence	24 (20.9%)	21 (18.1%)	15 (13.0%)	60 (17.3%)	20 (9.0%)
Paraesthesia	19 (16.5%)	11 (9.5%)	13 (11.3%)	43 (12.4%)	4 (1.8%)
Hypoaesthesia	14 (12.2%)	16 (13.8%)	8 (7.0%)	38 (11.0%)	3 (1.4%)
Dizziness postural	7 (6.1%)	7 (6.0%)	8 (7.0%)	22 (6.4%)	1 (0.5%)
Sedation	6 (5.2%)	8 (6.9%)	5 (4.3%)	19 (5.5%)	2 (0.9%)
Lethargy	7 (6.1%)	5 (4.3%)	1 (0.9%)	13 (3.8%)	1 (0.5%)
Tremor	4 (3.5%)	6 (5.2%)	2 (1.7%)	12 (3.5%)	2 (0.9%)
Mental impairment	6 (5.2%)	3 (2.6%)	2 (1.7%)	11 (3.2%)	2 (0.9%)
Gastrointestinal disorders	57 (49.6%)	58 (50.0%)	52 (45.2%)	167 (48.3%)	52 (23.4%)
Nausea	31 (27.0%)	37 (31.9%)	30 (26.1%)	98 (28.3%)	19 (8.6%)
Hypoaesthesia oral	16 (13.9%)	12 (10.3%)	9 (7.8%)	37 (10.7%)	3 (1.4%)
Vomiting	7 (6.1%)	14 (12.1%)	11 (9.6%)	32 (9.2%)	4 (1.8%)
Diarrhoea	8 (7.0%)	5 (4.3%)	10 (8.7%)	23 (6.6%)	13 (5.9%)
Dry mouth	5 (4.3%)	5 (4.3%)	9 (7.8%)	19 (5.5%)	7 (3.2%)
Paraesthesia oral	9 (7.8%)	1 (0.9%)	9 (7.8%)	19 (5.5%)	3 (1.4%)
Psychiatric disorders	49 (42.6%)	56 (48.3%)	55 (47.8%)	160 (46.2%)	43 (19.4%)
Dissociation	30 (26.1%)	32 (27.6%)	30 (26.1%)	92 (26.6%)	8 (3.6%)
Anxiety	10 (8.7%)	9 (7.8%)	12 (10.4%)	31 (9.0%)	12 (5.4%)
Insomnia	10 (8.7%)	8 (6.9%)	11 (9.6%)	29 (8.4%)	16 (7.2%)
Euphoric mood	8 (7.0%)	2 (1.7%)	5 (4.3%)	15 (4.3%)	2 (0.9%)
Ear and labyrinth disorders	30 (26.1%)	27 (23.3%)	34 (29.6%)	91 (26.3%)	10 (4.5%)
Vertigo	24 (20.9%)	24 (20.7%)	30 (26.1%)	78 (22.5%)	5 (2.3%)
General disorders and administration site conditions	30 (26.1%)	20 (17.2%)	30 (26.1%)	80 (23.1%)	31 (14.0%)
Fatigue	12 (10.4%)	8 (6.9%)	5 (4.3%)	25 (7.2%)	11 (5.0%)
Feeling drunk	7 (6.1%)	3 (2.6%)	9 (7.8%)	19 (5.5%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	20 (17.4%)	20 (17.2%)	24 (20.9%)	64 (18.5%)	33 (14.9%)
Throat irritation	5 (4.3%)	9 (7.8%)	9 (7.8%)	23 (6.6%)	9 (4.1%)
Nasal discomfort	4 (3.5%)	5 (4.3%)	8 (7.0%)	17 (4.9%)	9 (4.1%)
Eye disorders	17 (14.8%)	14 (12.1%)	18 (15.7%)	49 (14.2%)	4 (1.8%)
Vision blurred	8 (7.0%)	9 (7.8%)	14 (12.2%)	31 (9.0%)	3 (1.4%)
Investigations	13 (11.3%)	18 (15.5%)	14 (12.2%)	45 (13.0%)	9 (4.1%)
Blood pressure increased	9 (7.8%)	11 (9.5%)	11 (9.6%)	31 (9.0%)	5 (2.3%)
Renal and urinary disorders	7 (6.1%)	5 (4.3%)	9 (7.8%)	21 (6.1%)	3 (1.4%)
Pollakiuria	6 (5.2%)	2 (1.7%)	3 (2.6%)	11 (3.2%)	1 (0.5%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.
(a) Total esketamine column includes both the fixed-dose and flexible-dose esketamine treatment groups.

8.3.1.2. Short-term Phase 3 Studies in Patients ≥65 Years with TRD (TRANSFORM-3)

Data from TRANSFORM-3 provide information about the safety and tolerability of induction treatment with esketamine + oral AD compared to oral AD + placebo in patients ≥65 years of age. All randomized patients who received at least 1 dose of nasal spray study medication (esketamine or placebo) or 1 dose of oral AD in the double-blind induction phase were included in the safety analysis sets for TRANSFORM-3 (72 esketamine + oral AD, 65 oral AD + placebo). A summary of TEAEs reported in ≥5% of patients in both treatment groups is shown in Table 27.

- More patients in the esketamine + oral AD group experienced one or more TEAE (70.8%) compared to oral AD + placebo group (60.0%).
- The most common TEAEs (reported by ≥10% of patients) observed more frequently (with a difference of at least 3%) in the esketamine + oral AD group versus the oral AD + placebo group were dizziness, nausea, headache, fatigue, blood pressure increased, dissociation, and vertigo.
- The most common TEAE (reported by ≥5% of patients) observed more frequently (>3%) in the oral AD + placebo group was anxiety.
- The adverse event profile of esketamine observed in patients ≥65 years of age was generally consistent with that observed in the short-term studies in patients 18-64 years of age in the short-term studies; however, the incidence of some TEAEs was different (>3%) between the age groups. The most common TEAEs reported at higher incidence in esketamine-treated patients ≥65 years than the total esketamine-treated population 18-64 years:
  - Blood pressure increased: 12.5% of patients ≥65 years and 9.0% of those 18-64 years
  - Fatigue: 12.5% of patients ≥65 years and 7.2% of those 18-64 years

Table 27: Treatment-emergent Adverse Events in at Least 5% of Patients in Either Treatment Group; Double-blind Induction Phase (TRANSFORM-3: Safety Analysis Set)

	Intranasal Esk + Oral AD (N=72)	Oral AD + Intranasal Placebo (N=65)
Total no. subjects with TEAE	51 (70.8%)	39 (60.0%)
Psychiatric disorders	26 (36.1%)	11 (16.9%)
Dissociation	9 (12.5%)	1 (1.5%)
Dysphoria	4 (5.6%)	0
Insomnia	4 (5.6%)	3 (4.6%)
Anxiety	2 (2.8%)	5 (7.7%)
Nervous system disorders	25 (34.7%)	16 (24.6%)
Dizziness	16 (22.2%)	5 (7.7%)
Headache	9 (12.5%)	2 (3.1%)
Dysgeusia	4 (5.6%)	3 (4.6%)
Hypoaesthesia	4 (5.6%)	1 (1.5%)
Paraesthesia	4 (5.6%)	2 (3.1%)
Gastrointestinal disorders	19 (26.4%)	8 (12.3%)
Nausea	13 (18.1%)	3 (4.6%)
Hypoaesthesia oral	5 (6.9%)	0
Vomiting	5 (6.9%)	1 (1.5%)
General disorders and administration site conditions	15 (20.8%)	8 (12.3%)
Fatigue	9 (12.5%)	5 (7.7%)
Investigations	14 (19.4%)	6 (9.2%)
Blood pressure increased	9 (12.5%)	3 (4.6%)
Ear and labyrinth disorders	10 (13.9%)	4 (6.2%)
Vertigo	8 (11.1%)	2 (3.1%)
Infections and infestations	8 (11.1%)	6 (9.2%)
Urinary tract infection	6 (8.3%)	1 (1.5%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

8.3.1.3. Phase 3 Maintenance of Effect Study with TRD (SUSTAIN-1)

Data from the maintenance phase of the double-blind maintenance of effect study SUSTAIN-1 provide information about the safety and tolerability of esketamine + oral AD compared to oral AD + placebo following extended treatment of at least 16 weeks in the context of a randomized withdrawal design. Data from the induction phase and optimization phase of SUSTAIN-1 provide information on the safety and tolerability of esketamine + oral AD for up to 5 months of treatment.

The safety (maintenance) analysis set included the 297 randomized patients who received at least 1 dose of nasal spray study medication or 1 dose of oral AD during the double-blind maintenance phase (152 esketamine + oral AD, 145 oral AD + placebo), including both stable remitters and stable responders. The safety (induction) analysis set included 437 patients who received at least 1 dose of esketamine or 1 dose of oral AD in the induction phase. The safety (optimization)

analysis set included 455 patients who received at least 1 dose of esketamine or 1 dose of oral AD in the optimization phase.

- Most patients treated with esketamine in the induction and optimization phases experienced TEAEs (induction phase: 76.9%; optimization phase: 73.6%).
- In the double-blind maintenance phase, the rates of TEAEs in the esketamine + oral AD group and oral AD + placebo group were 82.2% and 45.5%, respectively.
- In patients treated with esketamine, the most common TEAEs (≥10% patients) were:
  - Induction phase: vertigo, dizziness, nausea, dysgeusia, dissociation, somnolence, headache, paraesthesia, vision blurred, and sedation
  - Optimization phase: vertigo, dysgeusia, dissociation, somnolence, dizziness, headache, and nausea
  - Double-blind maintenance phase: dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoaesthesia oral
- In the oral AD + placebo group, no TEAEs were reported by ≥10% patients during the double-blind maintenance phase.
- Of the TEAEs reported in ≥5% of patients, all except viral upper respiratory tract infection were reported at higher rates in esketamine + oral AD group than in oral AD + placebo group (with a difference of 3% or more).

The TEAEs reported in ≥5% of patients in any treatment group during the induction, optimization and maintenance phases of SUSTAIN-1 are shown in Appendix 8.

8.3.1.4. Long-term Safety Study with TRD (SUSTAIN-2)

Data from the Phase 3 long-term open-label safety study SUSTAIN-2 provide information on the long-term safety and tolerability of esketamine + oral AD for up to 1 year in an open-label setting.

The all enrolled analysis set included 802 direct-entry and transferred-entry patients who received at least 1 dose of esketamine or 1 dose of oral AD; of these, 624 patients were 18-64 years and 178 were ≥65 years. The full (induction) analysis set included 779 patients who received at least 1 dose of esketamine or 1 dose of oral AD in the open-label induction phase; the full (optimization/maintenance) analysis set included 603 patients who received at least 1 dose of esketamine or 1 dose of oral AD in the optimization/maintenance phase.

- Most patients enrolled in the study reported TEAEs (90.1%).
  - During the induction and optimization/maintenance phases, the overall rates of TEAEs were similar (83.8% and 85.6%, respectively).
- The most common TEAEs (≥10% of patients) in each study phase were:
  - Induction phase: dizziness, dissociation, nausea, headache, somnolence, hypoaesthesia
  - Optimization/maintenance phase: dizziness, headache, dissociation, somnolence, nausea, viral upper respiratory tract infection

- There were no new safety concerns identified with long-term, repeated, intermittent weekly or every-other-week administration of esketamine doses (28, 56, or 84 mg) over a duration of up to 1 year in SUSTAIN-2 in patients 18-64 years and those ≥65 years. The types and relative incidence of common TEAEs with longer-term repeated dosing of esketamine + oral AD of up to 1 year of exposure in SUSTAIN-2 was consistent with that in the short-term Phase 3 studies.

The TEAEs reported in ≥5% of patients in any treatment group during the induction, and optimization/maintenance phases of SUSTAIN-2 are shown in Appendix 9.

8.3.1.5. Phase 2 Study in Adults with TRD (SYNAPSE)

Data from the adjunctive, Phase 2 dose-response study in patients with TRD (SYNAPSE) provide additional information about the safety and tolerability after short-term exposure to several fixed doses of esketamine in comparison to a placebo control.

The safety (double-blind) analysis set included 84 randomized patients who received at least 1 dose of esketamine and 54 randomized patients who received at least 1 dose of placebo during the double-blind phase. The safety (open-label) analysis set included 96 patients who received treatment with esketamine in the optional open-label phase, which followed the double-blind phase.

- 78.6% patients in the total esketamine group and 61.1% patients in the placebo group experienced at least 1 TEAE during the double-blind phase.
- The most common TEAEs (≥10% of patients) were dizziness, headache, dysgeusia, dissociation, nausea, hypoaesthesia, feeling abnormal, and somnolence.
- The most common TEAEs that occurred more frequently in the total esketamine group than the placebo group were dizziness, headache, dissociation, nausea, hypoaesthesia, and feeling abnormal.
- The most common TEAEs that occurred more frequently in the placebo group than in the esketamine group were dysgeusia and somnolence.
- During the open-label phase, 88.5% of patients experienced at least 1 TEAE. The most commonly reported TEAEs were generally similar to those reported by patients who received esketamine during the double-blind phase.

8.3.1.6. Phase 2 Study in Adults with MDD at Imminent Risk for Suicide (PERSEVERE)

Data from the adjunctive, Phase 2 study in patients with MDD at imminent risk for suicide (PERSEVERE) provide additional information about the safety and tolerability after short-term exposure to the 84 mg dose of esketamine compared with placebo (in addition to standard of care treatment) in a population with MDD, related to TRD.

The safety (double-blind) analysis set included all randomized patients who received at least 1 dose of study medication in the double-blind phase (35 esketamine 84 mg; 31 placebo).

- During the double-blind phase, overall rates of TEAEs were 94.3% for the esketamine 84 mg group and 80.6% for the placebo group.
- The most common (≥10% of patients) TEAEs in the esketamine 84 mg group were nausea, dizziness, dysgeusia, headache, dissociation, vomiting, anxiety, paraesthesia, sedation, euphoric mood, somnolence, and vertigo.
- The most common (≥10% of patients) TEAEs in the placebo group were headache, dysgeusia, dissociation, and dizziness.

8.3.2. Adverse Drug Reactions

Adverse drug reactions (ADRs) are adverse events reasonably associated with the use of esketamine based on a comprehensive assessment of available adverse event information. The assessment of ADRs with esketamine was based on data from the 6 completed Phase 2 and 3 studies in TRD (SYNAPSE; TRANSFORM-1, 2, and 3; SUSTAIN-1 and 2).

Table 28 summarizes the incidence of identified ADRs following treatment with esketamine + oral AD in a double-blind setting (data from the double-blind phase of SYNAPSE, double-blind induction phases of TRANSFORM-1, 2, and 3, and double-blind maintenance phase of SUSTAIN-1), in an open-label setting (data from the induction and optimization phases of SUSTAIN-1 [direct-entry patients], all phases of SUSTAIN-2, and open-label phase in SYNAPSE), and following treatment with esketamine + oral AD in any phase of these studies (the 'All Esketamine Population'). Data for the oral AD + placebo groups in a double-blind setting are also shown for reference.

A total of 31 individual preferred terms were identified as ADRs for esketamine. To provide a meaningful estimate of the proportion of patients experiencing ADRs, preferred terms belonging to the same medical concept were also grouped together, resulting in a total of 24 ADR terms (15 grouped ADR terms and 9 individual ADR terms). A summary of the ADR grouping is provided in Appendix 10.

- The most commonly observed ADRs in TRD patients treated with esketamine + oral AD (incidence ≥10% and greater than in oral AD + placebo group) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.

Table 28: Incidence of Treatment-Emergent Adverse Drug Reactions Identified in Completed Phase 2 and Phase 3 Studies (Open-Label and Double-Blind Phases)

	Double-Blind Population		Open-Label Population	
	Esketamine + Oral AD (N=587)	Oral AD + Placebo (N=486)	Esketamine + Oral AD (N=1335)	All Esketamine Population (N=1709)
Psychiatric disorders	253 (43.1%)	55 (11.3%)	590 (44.2%)	792 (46.3%)
Anxiety*	63 (10.7%)	29 (6.0%)	159 (11.9%)	224 (13.1%)
Dissociation*	221 (37.6%)	31 (6.4%)	512 (38.4%)	691 (40.4%)
Euphoric mood	20 (3.4%)	3 (0.6%)	51 (3.8%)	73 (4.3%)
Nervous system disorders	343 (58.4%)	147 (30.2%)	831 (62.2%)	1098 (64.2%)
Dizziness*	176 (30.0%)	33 (6.8%)	491 (36.8%)	630 (36.9%)
Dysarthria*	18 (3.1%)	1 (0.2%)	37 (2.8%)	56 (3.3%)
Dysgeusia*	113 (19.3%)	54 (11.1%)	207 (15.5%)	293 (17.1%)
Headache*	115 (19.6%)	60 (12.3%)	294 (22.0%)	411 (24.0%)
Hypoaesthesia*	103 (17.5%)	7 (1.4%)	204 (15.3%)	285 (16.7%)
Lethargy*	47 (8.0%)	21 (4.3%)	95 (7.1%)	148 (8.7%)
Mental impairment	14 (2.4%)	4 (0.8%)	27 (2.0%)	42 (2.5%)
Sedation*	124 (21.1%)	35 (7.2%)	321 (24.0%)	434 (25.4%)
Tremor*	13 (2.2%)	2 (0.4%)	28 (2.1%)	46 (2.7%)
Ear and labyrinth disorders	115 (19.6%)	16 (3.3%)	211 (15.8%)	303 (17.7%)
Vertigo*	115 (19.6%)	16 (3.3%)	211 (15.8%)	303 (17.7%)
Cardiac disorders	6 (1.0%)	2 (0.4%)	19 (1.4%)	27 (1.6%)
Tachycardia*	6 (1.0%)	2 (0.4%)	19 (1.4%)	27 (1.6%)
Respiratory, thoracic and mediastinal disorders	43 (7.3%)	21 (4.3%)	96 (7.2%)	133 (7.8%)
Nasal discomfort*	43 (7.3%)	21 (4.3%)	96 (7.2%)	133 (7.8%)
Gastrointestinal disorders	173 (29.5%)	38 (7.8%)	385 (28.8%)	550 (32.2%)
Dry mouth	23 (3.9%)	8 (1.6%)	42 (3.1%)	68 (4.0%)
Nausea	144 (24.5%)	28 (5.8%)	321 (24.0%)	458 (26.8%)
Salivary hypersecretion	5 (0.9%)	1 (0.2%)	5 (0.4%)	9 (0.5%)
Vomiting	49 (8.3%)	6 (1.2%)	123 (9.2%)	177 (10.4%)
Skin and subcutaneous tissue disorders	21 (3.6%)	6 (1.2%)	53 (4.0%)	78 (4.6%)
Hyperhidrosis	21 (3.6%)	6 (1.2%)	53 (4.0%)	78 (4.6%)
Renal and urinary disorders	13 (2.2%)	2 (0.4%)	26 (1.9%)	40 (2.3%)
Pollakiuria*	13 (2.2%)	2 (0.4%)	26 (1.9%)	40 (2.3%)
General disorders and administration site conditions	46 (7.8%)	4 (0.8%)	82 (6.1%)	121 (7.1%)
Feeling abnormal	25 (4.3%)	3 (0.6%)	53 (4.0%)	73 (4.3%)
Feeling drunk	23 (3.9%)	1 (0.2%)	31 (2.3%)	51 (3.0%)
Investigations	69 (11.8%)	19 (3.9%)	166 (12.4%)	222 (13.0%)
Blood pressure increased*	69 (11.8%)	19 (3.9%)	166 (12.4%)	222 (13.0%)

AD: antidepressant

*Represents grouped term; see Appendix 10 for further information.

Notes: The following studies are included in the Double-blind Population: SYNAPSE (Panels A and B double-blind phase), TRANSFORM-1 (double-blind phase), TRANSFORM-2 (double-blind phase), SUSTAIN-1 (maintenance phase), TRANSFORM-3 (double-blind phase). The following studies are included in the Open-label Population: SYNAPSE (Panels A and B open-label phase), SUSTAIN-1 (induction and optimization phase data from direct-entry patients), SUSTAIN-2. The 'All Esketamine Population' includes all patients in the esketamine arm in any phase in the Phase 2 dose-response study (SYNAPSE) and the Phase 3 studies (TRANSFORM-1, 2, and 3, and SUSTAIN-1 and 2). Incidence is based on the number of patients experiencing at least one adverse event, not the number of events. Adverse reactions are coded using MedDRA version 20.0.

8.3.3. Characterization of Treatment-emergent Adverse Events in Completed Studies

8.3.3.1. Severity of Treatment-emergent Adverse Events in Completed Phase 2 and 3 Studies

In all Phase 2 and 3 studies, most TEAEs (94.9%) were mild or moderate in severity. The most common severe TEAEs (reported at the incidence of at least 1%) in esketamine-treated patients included primarily events related to the underlying disease state under study (e.g., depression, anxiety) or common events occurring after dose administration (e.g., dissociation, dizziness, nausea). A summary of TEAEs of severe intensity in the completed Phase 2 and 3 clinical trials is provided in Appendix 14.

Common events occurring on dosing days and reported as severe were mostly transient and resolved without clinical sequelae. An overview of severe TEAEs in the Phase 3 TRD studies is provided in Table 29. Notably, the incidence of severe TEAEs the short-term study with patients ≥65 years TRANSFORM-3 was lower (4.2% of esketamine-treated patients) than that in the pooled short-term studies with patients 18-64 years TRANSFORM-1/2 (14.7% of esketamine-treated patients).

Table 29: Occurrence and Resolution of Severe Treatment-emergent Adverse Events on Intranasal Dosing Days in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Patients with a Severe TEAE[a]	Proportion of Severe TEAEs Occurring on Dosing Days[b]	Proportion of Severe TEAEs Which Occur on Dosing Days with Same Day Resolution
TRANSFORM-1 (Fixed-Dose)					
Induction Phase	Esk 56 mg:	115	16 (13.9%)	53/58 (91.4%)	46/53 (86.8%)
	Esk 84 mg:	116	20 (17.2%)	79/94 (84.0%)	74/79 (93.7%)
	Placebo:	113	8 (7.1%)	4/13 (30.8%)	3/4 (75%)
TRANSFORM-2 (Flexible-Dose)					
Induction Phase	Esk 56-84 mg:	115	15 (13.0%)	21/26 (80.8%)	16/21 (76.2%)
	Placebo:	109	3 (2.8%)	2/9 (22.2%)	2/2 (100%)
Pooled TRANSFORM-1/2					
Induction Phase	Total Esk[c]:	346	51 (14.7%)	153/178 (86.0%)	136/153 (88.9%)
	Total Placebo:	222	11 (5.0%)	6/22 (27.3%)	5/6 (83.3%)
TRANSFORM-3					
Induction Phase	Esk 28-84 mg:	72	3 (4.2%)	1/3 (33.3%)	1/1 (100%)
	Placebo:	65	1 (1.5%)	0/3 (0%)	0
SUSTAIN-1					
Induction Phase	Esk 56-84 mg:	437	44 (10.1%)	113/124 (91.1%)	103/113 (91.2%)
Optimization Phase	Esk 56-84 mg:	455	34 (7.5%)	79/106 (74.5%)	79/79 (100%)
Maintenance Phase	Esk 56-84 mg:	152	12 (7.9%)	78/80 (97.5%)	78/78 (100%)
	Placebo:	145	6 (4.1%)	0/8 (0%)	0/0
SUSTAIN-2					
Induction Phase	Esk 28-84 mg:	779	64 (8.2%)	83/122 (68%)	61/83 (73.5%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	62 (10.3%)	41/91 (45.1%)	32/41 (78.0%)
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	118 (14.7%)	124/213 (58.2%)	93/124 (75.0%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
[a] Note: Incidence in this column is based on the number of patients experiencing at least one adverse event, not the number of events.
[b] Note: Numerator is the number of severe TEAEs occurring post-dose on a dosing day. Denominator is the total number of occurrences of a severe TEAE. A patient may be counted more than once if they had multiple occurrences of a TEAE.
[c] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.

The most common severe TEAEs occurring after dosing among esketamine-treated patients that were not reported as resolved on the day of dosing across the Phase 3 studies were anxiety, insomnia, and nausea. Across phases in the Phase 3 studies, in the esketamine groups, the mean duration of:

- Severe TEAEs of anxiety ranged from 0.6 hours to ~20 days (there were 2 severe TEAEs of anxiety in the oral AD + placebo groups with durations of ~10 days and ~27 days)
- Severe TEAEs of insomnia ranged from ~6 days to ~57 days (there was 1 severe TEAE of insomnia in the oral AD + placebo groups with duration of ~38 days)
- Severe TEAEs of nausea ranged from ~1.7 days to ~10 days (there were no severe TEAEs of nausea in the oral AD + placebo groups)

Data from the Phase 2 adjunctive study in TRD were consistent with the Phase 3 studies, showing that few reported TEAEs were assessed as severe; vertigo (n=2) was the only severe event reported in >1 patient exposed to esketamine in double-blind population.

8.3.3.2. Occurrence and Resolution of Treatment-emergent Adverse Events on Nasal Spray Dosing Days in Phase 3 Studies

Most TEAEs, including those commonly occurring in esketamine-treated patients in the Phase 3 studies, were reported and resolved on the day of nasal spray dosing. Note, TEAEs occurring and resolving on the day of dosing were not analyzed for the Phase 2 dose-response study SYNAPSE.

The proportion of TEAEs occurring on nasal spray dosing days and of those the proportion that resolve on the same day in the Phase 3 studies are summarized in Table 30. The rate of occurrence of the TEAEs on the day of nasal spray dosing, as well as the proportion of those TEAEs that resolved the same day were higher in the esketamine + oral AD group, compared with the oral AD + placebo group in the short-term studies.

The proportion of TEAEs occurring on dosing days and resolving the same day was notably high for the most common TEAEs reported by esketamine-treated patients. In the pooled short-term studies TRANSFORM-1/2, >96% of TEAEs of dissociation, dysgeusia, dizziness, sedation, hypoaesthesia, vertigo, and blood pressure increased occurred on the day of dosing, and >93% of these TEAEs which occurred in esketamine-treated patients on the day of dosing resolved on the same day.

This same pattern of occurrence and resolution for TEAEs was observed across the Phase 3 studies for the subset of TEAEs assessed as severe in intensity.

Table 30: Occurrence and Resolution of Treatment-emergent Adverse Events on Intranasal Dosing Days in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Patients with any TEAE[a]	Proportion of TEAEs Occurring on Dosing Days[b]	Proportion of TEAEs Which Occur on Dosing Days with Same Day Resolution
TRANSFORM-1 (Fixed-Dose)					
Induction Phase	Esk 56 mg:	115	100 (87.0%)	1144/1284 (89.1%)	1047/1144 (91.5%)
	Esk 84 mg:	116	103 (88.8%)	1149/1285 (89.4%)	1076/1149 (93.6%)
	Placebo:	113	77 (68.1%)	312/438 (71.2%)	254/312 (81.4%)
TRANSFORM-2 (Flexible-Dose)					
Induction Phase	Esk 56-84 mg:	115	98 (85.2%)	1400/1518 (92.2%)	1312/1400 (93.7%)
	Placebo:	109	66 (60.6%)	212/324 (65.4%)	180/212 (84.9%)
Pooled TRANSFORM-1/2					
Induction Phase	Total Esk[c]:	346	301 (87.0%)	3693/4087 (90.4%)	3435/3693 (93.0%)
	Total Placebo:	222	143 (64.4%)	524/762 (68.8%)	434/524 (82.8%)
TRANSFORM-3					
Induction Phase	Esk 28-84 mg:	72	51 (70.8%)	300/346 (86.7%)	255/300 (85.0%)
	Placebo:	65	39 (60.0%)	96/149 (64.4%)	56/96 (58.3%)
SUSTAIN-1					
Induction Phase	Esk 56-84 mg:	437	336 (76.9%)	4199/4485 (93.6%)	4014/4199 (95.6%)
Optimization Phase	Esk 56-84 mg:	455	335 (73.6%)	3695/4250 (86.9%)	3631/3695 (98.3%)
Maintenance Phase	Esk 56-84 mg:	152	125 (82.2%)	2999/3262 (91.9%)	2957/2999 (98.6%)
	Placebo:	145	66 (45.5%)	257/402 (63.9%)	247/257 (96.1%)
SUSTAIN-2					
Induction Phase	Esk 28-84 mg:	779	653 (83.8%)	5123/5841 (87.7%)	4631/5123 (90.4%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	516 (85.6%)	6030/7780 (77.5%)	5597/6030 (92.8%)
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	723 (90.1%)	11153/13621 (81.9%)	10228/11153 (91.7%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
[a] Note: Incidence in this column is based on the number of patients experiencing at least one adverse event, not the number of events.
[b] Note: Numerator is the number of TEAEs occurring post-dose on a dosing day. Denominator is the total number of occurrences of a TEAE. A patient may be counted more than once if they had multiple occurrences of a TEAE.
[c] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.

Of the most commonly observed TEAEs associated with esketamine treatment and identified as ADRs, events of headache, anxiety, and nausea were not reported as resolved on the day of dosing in more than 15% of events in at least 1 of the Phase 3 study phases. Across all study phases, 54.9% to 95% of TEAEs of headache, 73.3% to 100% of TEAEs of nausea, and 47.4% to 100% of TEAEs of anxiety reported on the day of dosing in the esketamine + oral AD groups resolved on the same day. Across phases in the Phase 3 studies, the mean duration of:

- TEAEs of headache ranged from ~20 hours to ~14.8 days in the esketamine groups and from ~3.2 days to ~16.7 days in oral AD + placebo groups
- TEAEs of nausea ranged from 6.3 hours to ~7 days in the esketamine groups and from ~1.3 days to ~4.6 days in the oral AD + placebo groups
- TEAEs of anxiety ranged from 12 hours to~28.8 days in the esketamine groups and from ~4.9 days to ~38.5 days in the oral AD + placebo groups

8.3.3.3. Longer-term Dosing in SUSTAIN-2

The pattern of TEAEs reported with longer-term repeated dosing of esketamine + oral AD (of up to 1 year of exposure) in SUSTAIN-2 was consistent with the experience for the short-term Phase 3 studies TRANSFORM-1/ 2 with respect to the types and relative incidence of common TEAEs, the overall frequency of severe TEAEs, and the overall frequency of postdose TEAEs that resolved the day of dosing.

8.3.3.4. TEAEs That Did Not Start on Dosing Days

In the long-term safety study SUSTAIN-2, 18.1% of the TEAEs reported during the study did not start on dosing days; Table 31 shows the proportion of TEAEs that did not start on dosing days by system organ class and preferred term for TEAEs with over 20 events reported. TEAEs of headache, viral upper respiratory tract infection, insomnia and nausea were the most frequently reported events on days when patients did not receive nasal spray study medication.

A generally similar profile was observed in the short-term Phase 3 studies:

- In pooled studies TRANSFORM-1/2 with patients 18-64 years, 9.6% of the TEAEs reported in the esketamine + oral AD group and 31.2% of TEAEs reported in the oral AD + placebo group during the study did not start on dosing days. The most frequently reported TEAEs not starting on dosing days were headache, nausea and diarrhea in the esketamine + oral AD group and headache, diarrhea and insomnia in the oral AD + placebo group.
- In TRANSFORM-3 with patients ≥65 years, 13.3% of the TEAEs reported in the esketamine + oral AD group and 35.6% of TEAEs reported in the oral AD + placebo group during the study did not start on dosing days. The most frequently reported TEAEs not starting on dosing days were nausea, fatigue and urinary tract infection in the esketamine + oral AD group and insomnia, nausea, and anxiety in the oral AD + placebo group.

Table 31: Proportion of Treatment-emergent Adverse Events Not Starting on Dosing Days; Induction and Optimization/Maintenance Phases, >20 Events Reported (SUSTAIN-2: All Enrolled Analysis Set)

	Intranasal Esk + Oral AD (N=802)
Total no. of TEAEs	2468/13621 (18.1%)
Nervous system disorders	
Headache	270/479 (56.4%)
Dizziness	38/1662 (2.3%)
Somnolence	34/708 (4.8%)
Infections and infestations	
Viral upper respiratory tract infection	101/117 (86.3%)
Urinary tract infection	60/90 (66.7%)
Upper respiratory tract infection	46/51 (90.2%)
Influenza	44/45 (97.8%)
Gastroenteritis	22/24 (91.7%)
Gastrointestinal disorders	
Nausea	71/422 (16.8%)
Diarrhoea	58/79 (73.4%)
Vomiting	28/144 (19.4%)
Abdominal pain upper	23/30 (76.7%)
Constipation	21/29 (72.4%)
Psychiatric disorders	
Insomnia	73/105 (69.5%)
Anxiety	55/128 (43%)
Suicidal ideation	20/30 (66.7%)
Musculoskeletal and connective tissue disorders	
Back pain	45/60 (75%)
Myalgia	21/28 (75%)
Musculoskeletal pain	20/23 (87%)
Respiratory, thoracic and mediastinal disorders	
Epistaxis	34/41 (82.9%)
General disorders and administration site conditions	
Fatigue	45/95 (47.4%)

AD= antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Notes: Numerator is the number of adverse events not occurring on a dosing day. Denominator is the total number of occurrences of a TEAE. A subject may be counted more than once if they had multiple occurrences of a TEAE. TEAEs with imputed start dates are excluded. Adverse events are coded using MedDRA version 20.0.

8.3.3.5. Assessment of Dose Effects in Fixed-dose Study TRANSFORM-1

In the Phase 3 short-term fixed-dose study TRANSFORM-1, the overall rates of TEAEs and serious TEAEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, and most TEAEs across both dose groups were mild or moderate in severity, occurred postdose on the day of dosing, and resolved the same day.

To compare the incidence of TEAEs between the esketamine dose groups in the fixed-dose study, it is important to look at events that were reported on or after the second dose of nasal spray study medication as, per protocol, all patients were to receive 56 mg on Day 1. Patients assigned to the esketamine 84 mg + oral AD group were then titrated to the 84 mg dose beginning at Day 4 (dose 2).

As shown in Table 32, common TEAEs (≥10% of patients) in the esketamine 84 mg + oral AD group which had onset on or after the second dose of nasal spray study medication (i.e., patients who received at least one 84-mg dose) were dissociation, nausea, dizziness, somnolence and vertigo, headache, dysgeusia, hypoaesthesia, and paraesthesia. The corresponding incidences of these TEAEs were overall consistent with those reported in the esketamine 56 mg + oral AD group (onset on or after second dose).

There was evidence of a dose response with respect to the incidence of dissociation, a higher rate of dissociation (6.4%) was observed in the esketamine 84 mg treatment group than in the esketamine 56 mg group.

Table 32: Treatment-Emergent Adverse Events in at Least 10% of Patients in Any Esketamine Dose Group by Timing of Onset in Relation to the Second Intranasal Medication Dosing Session (TRANSFORM-1: Safety Analysis Set)

	Intranasal Esk 56 mg + Oral AD		Intranasal Esk 84 mg + Oral AD	
	Onset before second dose (56 mg) (N=115)	Onset on or after second dose (56 mg) (N=115)	Onset before second dose (56 mg) (N=116)	Onset on or after second dose (84 mg) (N=105)
Nervous system disorders	57 (49.6%)	65 (56.5%)	49 (42.2%)	63 (60.0%)
Dizziness	22 (19.1%)	24 (20.9%)	18 (15.5%)	20 (19.0%)
Somnolence	11 (9.6%)	18 (15.7%)	11 (9.5%)	17 (16.2%)
Headache	14 (12.2%)	16 (13.9%)	12 (10.3%)	16 (15.2%)
Dysgeusia	12 (10.4%)	15 (13.0%)	8 (6.9%)	15 (14.3%)
Hypoaesthesia	5 (4.3%)	12 (10.4%)	10 (8.6%)	13 (12.4%)
Paraesthesia	7 (6.1%)	15 (13.0%)	2 (1.7%)	11 (10.5%)
Psychiatric disorders	35 (30.4%)	36 (31.3%)	40 (34.5%)	41 (39.0%)
Dissociation	18 (15.7%)	20 (17.4%)	22 (19.0%)	25 (23.8%)
Gastrointestinal disorders	33 (28.7%)	49 (42.6%)	41 (35.3%)	38 (36.2%)
Nausea	17 (14.8%)	23 (20.0%)	27 (23.3%)	22 (21.0%)
Hypoaesthesia oral	10 (8.7%)	14 (12.2%)	7 (6.0%)	10 (9.5%)
Ear and labyrinth disorders	14 (12.2%)	27 (23.5%)	19 (16.4%)	20 (19.0%)
Vertigo	13 (11.3%)	21 (18.3%)	17 (14.7%)	17 (16.2%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event

Note: Patients randomized to esketamine 84 mg + oral AD were to receive esketamine 56 mg in the first dose and 84 mg for all subsequent doses, therefore this subgroup had received only a 56 mg dose at the time the TEAE occurred.
Note: For each treatment group, a patient with 2 occurrences of the same adverse event with an onset before and an onset on or after the second dose is included in both columns. Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.

Common severe TEAEs reported in TRANSFORM-1 are summarized in Table 33. Although the overall rates of severe TEAEs in TRANSFORM-1 were higher in the esketamine 84 mg + oral AD group (17.2%) than in the esketamine 56 mg + oral AD group (13.9%), a large proportion of the reported severe TEAEs in the esketamine 84 mg + oral AD group occurred after patients received the starting dose of 56 mg and before the patients received the first 84-mg dose of esketamine. Rates of severe TEAEs of dissociation and nausea were higher in the esketamine 84 mg group (2.9% higher for each of these TEAEs); otherwise, there was no conclusive evidence of a dose effect in the incidence of TEAEs assessed as severe with an onset on or after the second dose of nasal study medication.

Furthermore, while treatment discontinuation due to adverse events was more frequent in the esketamine 84 mg + oral AD group than in the esketamine 56 mg + oral AD group (6.0% vs 0.9%), 5 of the 7 patients who discontinued esketamine due to an adverse event in the 84-mg dose group were withdrawn after the first dose (i.e., a 56-mg dose as specified by the study protocol).

Table 33: Treatment-emergent Severe Adverse Events in at Least 1% of Patients in Any Treatment Group by Timing of Onset in Relation to the Second Intranasal Medication Dosing Session; Double-blind Induction Phase (TRANSFORM-1: Safety Analysis Set)

	Intranasal Esk 56 mg + Oral AD		Intranasal Esk 84 mg + Oral AD		Oral AD + Intranasal Placebo
	Total (N=115)	Onset on or after second dose (N=115)	Total (N=116)	Onset on or after second dose (N=105)	Total (N=113)
Total no. patients with TEAE	16 (13.9%)		20 (17.2%)		8 (7.1%)
Nervous system disorders	9 (7.8%)	4 (3.5%)	11 (9.5%)	9 (8.6%)	3 (2.7%)
Dizziness	3 (2.6%)	1 (0.9%)	3 (2.6%)	2 (1.9%)	1 (0.9%)
Somnolence	0	0	2 (1.7%)	2 (1.9%)	0
Dysarthria	0	0	2 (1.7%)	2 (1.9%)	0
Mental impairment	0	0	2 (1.7%)	2 (1.9%)	0
Dysgeusia	3 (2.6%)	2 (1.7%)	1 (0.9%)	1 (1.0%)	0
Headache	2 (1.7%)	1 (0.9%)	1 (0.9%)	0	2 (1.8%)
Psychiatric disorders	5 (4.3%)	5 (4.3%)	9 (7.8%)	5 (4.8%)	3 (2.7%)
Dissociation	2 (1.7%)	1 (0.9%)	7 (6.0%)	4 (3.8%)	0
Depression	2 (1.7%)	2 (1.7%)	0	0	0
Panic attack	1 (0.9%)	0	0	0	2 (1.8%)
Gastrointestinal disorders	0	0	7 (6.0%)	5 (4.8%)	0
Nausea	0	0	4 (3.4%)	3 (2.9%)	0
Vomiting	0	0	3 (2.6%)	1 (1.0%)	0
Ear and labyrinth disorders	2 (1.7%)	2 (1.7%)	6 (5.2%)	5 (4.8%)	0
Vertigo	2 (1.7%)	2 (1.7%)	4 (3.4%)	3 (2.9%)	0
Hypoacusis	0	0	2 (1.7%)	2 (1.9%)	0
General disorders and administration site conditions	2 (1.7%)	2 (1.7%)	6 (5.2%)	5 (4.8%)	2 (1.8%)
Fatigue	1 (0.9%)	1 (0.9%)	3 (2.6%)	2 (1.9%)	0
Eye disorders	1 (0.9%)	1 (0.9%)	3 (2.6%)	2 (1.9%)	0
Vision blurred	0	0	2 (1.7%)	1 (1.0%)	0
Respiratory, thoracic and mediastinal disorders	2 (1.7%)	1 (0.9%)	2 (1.7%)	1 (1.0%)	0
Throat irritation	1 (0.9%)	1 (0.9%)	2 (1.7%)	1 (1.0%)	0

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Notes: Patients randomized to esketamine 84 mg + oral AD were to receive 56 mg of intranasal esketamine in the first dose and 84 mg for all subsequent doses. For each treatment group, a patient with 2 occurrences of the same adverse event with an onset before and an onset on or after the second dose is included in both columns. Incidence is based on the number of patients experiencing at least one adverse event, not the number of events. Adverse events are coded using MedDRA version 20.0.

8.3.3.6. Adverse Events by Subgroup

Although sex, race, and age-associated differences in adverse event rates were observed in some Phase 3 studies or study phases, the results did not suggest that administration of esketamine at the doses used in the Phase 3 studies was associated with a clinically meaningful increased risk in any of the subgroups evaluated. Furthermore, there were no consistent, meaningful differences

in the TEAE rates across Phase 3 studies/study phases as a function of geographic region or class of AD study medication (SSRI, SNRI).

8.3.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

8.3.4.1. Deaths

Based on a recent study, the risk of death for patients with depressive disorders who had been hospitalized for depression was 4 to 5 times higher than for those who had not been diagnosed with depressive disorders.[42] In another study of patients with TRD in the Medicare system, the risk of suicide attempt was 7-fold higher in patients with TRD than the risk in patients with major depression.[38] This study further showed that the all-cause mortality rate for patients with TRD was 46.2 deaths per 1000 patient-years.[38]

A total of 5 deaths occurred in the completed and ongoing Phase 2 and 3 clinical studies in patients with TRD as of the clinical cutoff date of 4 March 2018, which encompassed 1045 patient-years of exposure and 1861 unique patients treated with esketamine; see Section 8.2 for additional information about exposure):

- Completed double-blind studies/study phases: One death (multiple injuries sustained in a road traffic accident) occurred among esketamine-treated patients during the double-blind phases of the completed Phase 2 and 3 studies (122 patient-years of exposure). No deaths occurred in the oral AD + placebo groups of these studies (100 patient-years of exposure).
- Completed and ongoing open-label studies/study phases: There were 3 deaths (2 completed suicides and 1 case of acute cardiac and respiratory failure) among patients treated with esketamine + oral AD during the open-label studies/study phases (923 patient-years of exposure).
- Follow-up phases: There was 1 death (completed suicide) during the follow-up phases of these studies when the patient was not receiving nasally-administered study medication.

All 5 deaths were assessed by the investigator and the Sponsor as not related to the esketamine treatment.

Three of the deaths listed above were due to completed suicide:

- One occurred during the follow-up phase of the Phase 2 dose-response study SYNAPSE, 20 days after last dose of esketamine. The patient had achieved remission on esketamine treatment and there was no evidence of suicidal ideation or behavior based on C-SSRS scores. The patient showed reemergence of depressive symptoms based on MADRS total score 6 days prior to the suicide and was reported to have experienced significant psychosocial stressors in the days prior to the suicide. The day before the suicide, the following medications were newly prescribed because of irritability, anxiety, and insomnia: aripiprazole 6 mg as needed, perphenazine maleate 12 mg three times daily, quetiapine 100 mg daily, and ethyl loflazepate 1 mg daily.

- One occurred during the optimization/maintenance phase of SUSTAIN-2, 12 days after the last dose of esketamine. The patient had achieved remission on esketamine treatment and there was no evidence of suicidal ideation or behavior based on C-SSRS scores. The patient was reported to have experienced significant psychosocial stressors in the days prior to the suicide.
- One occurred during SUSTAIN-3, 4 days after the last dose of esketamine. The patient had started to experience an improvement in symptoms of depression based on MADRS total scores, but was not in remission.

An additional discussion of suicidality events in the esketamine program in TRD is included in Section 8.4.

The other two deaths in the completed Phase 2 and 3 studies were as follows:

- One occurred during the double-blind phase of TRANSFORM-2 due to multiple injuries sustained during a road traffic accident that occurred approximately 28 hours after receiving the last dose of esketamine (note, the mean terminal half-life of esketamine ranges from 7 to 12 hours).
- One occurred due to acute cardiac and respiratory failure during the optimization/maintenance phase of SUSTAIN-2, 5 days after the last dose of esketamine. The patient had a history of hypertension, obesity, and vein surgery. Pulse oximetry, respiratory rate, and blood pressure values remained normal during the study, and the patient did not report any adverse events other than transient nausea and headache during the first week of the study.

There were no deaths among the 579 patients treated with esketamine in the completed Phase 1 studies, in the completed Phase 2 study in patients with MDD at imminent risk for suicide, or in other ongoing blinded studies with esketamine nasal spray through the clinical cutoff date.

8.3.4.2. Serious Adverse Events

Phase 3 Studies

The incidence of serious TEAEs reported in the esketamine + oral AD and oral AD + placebo groups in the controlled Phase 3 studies in patients with TRD are shown in Table 34. The most frequent serious TEAEs in esketamine-treated patients across the completed Phase 3 studies in TRD were in the MedDRA system organ class, Psychiatric Disorders, and were associated with the underlying disease state (depression, suicidal ideation, suicide attempt and anxiety). A summary of serious TEAEs in the completed Phase 2 and 3 clinical trials is provided in Appendix 15.

Serious TEAEs assessed by the investigator as at least possibly related (i.e., possibly, probably or very likely related) to study treatment that were reported in the esketamine + oral AD groups included:

- 1 patient each with a serious TEAE of depression, headache, blood pressure increased, and anxiety disorder across the Phase 3 short-term studies

- 1 patient each with a serious TEAE of disorientation, suicidal ideation, sedation, lacunar stroke, and hypothermia, and 1 patient with 2 serious TEAEs of autonomic nervous system imbalance and simple partial seizures in the maintenance of effect study SUSTAIN-1 (all reported during the induction phase)
- 1 patient each with a serious TEAE of delirium, suicidal ideation, and suicidal attempt during the induction phase, and 1 patient with 2 serious TEAEs of anxiety and delusion during the optimization/maintenance phase of the long-term safety study SUSTAIN-2.

Table 34: Overall Incidence of Serious Adverse Events in Completed Phase 3 TRD studies

Study Phase	Treatment (+ Oral AD)	N	Serious Adverse Events	Serious Adverse Events Considered as at Least Possibly Related
TRANSFORM-1 (Fixed-Dose)				
Induction Phase	Esk 56 mg:	115	2 (1.7%)	2 (1.7%)
	Esk 84 mg:	116	0	0
	Placebo:	113	0	0
TRANSFORM-2 (Flexible-Dose)				
Induction Phase	Esk 56-84 mg:	115	1 (0.9%)	0
	Placebo:	109	1 (0.9%)	0
Pooled TRANSFORM-1/2				
Induction Phase	Total Esketamine[a]:	346	3 (0.9%)	2 (0.6%)
	Total Placebo:	222	1 (0.5%)	0
TRANSFORM-3				
Induction Phase	Esk 28-84 mg:	72	3 (4.2%)	2 (2.8%)
	Placebo:	65	2 (3.1%)	1 (1.5%)
SUSTAIN-1				
Induction Phase	Esk 56-84 mg:	437	13 (3.0%)	6 (1.4%)
Optimization Phase	Esk 56-84 mg:	455	11 (2.4%)	0
Maintenance Phase	Esk 56-84 mg:	152	4 (2.6%)	0
	Placebo:	145	1 (0.7%)	0
SUSTAIN-2				
Induction Phase	Esk 28-84 mg:	779	17 (2.2%)	1 (0.1%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	38 (6.3%)	3 (0.5%)
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	55 (6.9%)	4 (0.5%)

AD=antidepressant; Esk=esketamine; TRD=treatment-resistant depression
Note: Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
Note: Serious adverse events with onset during the follow-up phase are not included.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.

Phase 2 Dose-response Study (SYNAPSE)

One patient who received placebo experienced a serious TEAE (esophagitis) during the double-blind phase. Another patient who received esketamine had a serious TEAE (ectopic pregnancy) during the open-label phase followed by another related serious adverse event of general physical health deterioration during the follow-up phase. The investigator assessed all three serious adverse events as not related to study medication.

Phase 2 Study in Patients with MDD at Imminent Risk for Suicide (PERSEVERE)

Four patients in the esketamine 84 mg group experienced serious TEAEs during the double-blind phase. Two patients experienced an exacerbation of suicidal ideation, one experienced increased

agitation, and one experienced exacerbation of depressive symptoms. Except for exacerbation of depressive symptoms, which was considered possibly related to study medication by the investigator, none of the other serious TEAEs were considered related to study medication.

8.3.4.3. Adverse Events Leading to Discontinuation of Study Medication

TEAEs leading to discontinuation of esketamine nasal spray were reported in 5% to 6% of patients in the Phase 3 short-term studies in patients 18-64 years and those ≥65 years; these rates were higher than for the oral AD + placebo groups (pooled TRANSFORM-1/TRANSFORM-2: 4.6% [vs 1.4% for oral AD + placebo]; TRANSFORM-3: 5.6% [vs 3.1% for oral AD + placebo]). After longer-term exposure to esketamine in SUSTAIN-1, discontinuation rates for nasal study medication during the double-blind maintenance phase were similar for the esketamine + oral AD (2.6%) and oral AD + placebo (2.1%) groups. In SUSTAIN-1, the rate of discontinuations due to TEAEs was higher in the induction phase, compared with the subsequent optimization and maintenance phases (5.0% vs. 1.1% and 2.6%, respectively).

The relatively low rates of discontinuation due to TEAEs in the oral AD + placebo groups of the Phase 3 studies may reflect the fact that patients in these studies represent a population who are tolerant of oral AD medications, as indicated by their history of prior AD use for the current depression episode as well as the >1 year average duration of use of the last AD prior to randomization.

The overall discontinuation rate due to TEAEs observed in the Phase 3 uncontrolled, open-label safety study (SUSTAIN-2) with long-term esketamine treatment (exposure of up to 1 year) was 9.5%.

Across the Phase 3 studies, TEAEs leading to esketamine discontinuation in more than 2 patients (>0.1%) were (in order of frequency): anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack, and sedation.

The rates of discontinuations of esketamine treatment due to TEAEs were generally highest shortly after treatment initiation. In the Phase 3 short-term studies in patients 18-64 years (TRANSFORM-1 and 2), nearly all discontinuations due to TEAEs in esketamine-treated patients occurred within the first 2 weeks of the double-blind phase. In the Phase 3 maintenance of effect (SUSTAIN-1) and open-label long-term safety (SUSTAIN-2) studies, discontinuations due to TEAEs in esketamine-treated patients occurred at higher rates in the induction phase compared to the optimization and/or maintenance phases (SUSTAIN-1: 5.0% vs 1.1% [optimization] and 2.6% [maintenance]; SUSTAIN-2: 6.8% vs 3.8% [optimization/maintenance combined]).

In the Phase 2 dose-response study SYNAPSE, 4 patients discontinued esketamine due to TEAEs of syncope, headache, dissociative disorder and ectopic pregnancy (each 1 patient). In the Phase 2 study in patients with MDD at imminent risk for suicide PERSEVERE, 4 patients discontinued esketamine due to TEAEs of dysgeusia, aggression, agitation, ventricular

extrasystoles (1 patient each), and 1 patient discontinued due to TEAEs of dizziness, nausea, and dyspnea.

Adverse Events Leading to Dose Reduction or Interruption

As observed for TEAEs leading to discontinuation, TEAEs in the MedDRA system organ classes of Psychiatric Disorders and Nervous System Disorders (e.g., dissociation, dizziness) were the most common reasons for esketamine dose reduction/interruption of nasal spray study medication in Phase 2 and 3 studies in TRD.

8.4. Suicidal Ideation and Behavior

In patients with TRD, it is important to determine the effect of treatment on the risk of experiencing a suicide-related event. An evaluation was conducted to identify the occurrence of potentially suicide-related events. This assessment involved a review of the data based on the C-SSRS, a measure of suicidal ideation and behavior, as well as incidence, type, and severity of suicidality-related adverse events and clinical evaluation of individual cases.[109] The C-SSRS was categorized into scores ranging from 0 (no event that can be assessed on the basis of C-SSRS) to 10 (completed suicide). The maximum score assigned for each patient was also summarized into one of three categories: no suicidal ideation or behavior (0), suicidal ideation (1-5), and suicidal behavior (6-10).

Patients were excluded from the Phase 2 or 3 studies in TRD if they had suicidal ideation with some intent to act within the 6 months prior to enrollment or history of suicidal behavior within the past 1 year. Across the completed Phase 3 studies in TRD, 25% to 37% of enrolled patients had a lifetime history of suicidal ideation, and between 14% to 19% of patients had a lifetime history of suicidal behavior, as assessed using the C-SSRS.

Evaluation of C-SSRS scores and TEAEs of suicidal ideation and behavior in the Phase 2 and 3 clinical studies in patients with TRD as presented below did not suggest that esketamine is associated with increased risk of suicidal ideation and behavior. The proposed labeling for esketamine nasal spray includes FDA's class antidepressant boxed warning for young adults (18-24 years of age). Also note, esketamine should be administered in conjunction with an oral AD.

Changes in C-SSRS Scores

Most patients stayed within the same suicidality category based on C-SSRS score throughout the duration of the Phase 3 studies. For the subgroup of patients with no suicidal ideation or behavior at baseline, the percentage who reported suicidal ideation (based on C-SSRS) at any time postbaseline in the controlled Phase 3 studies/study phases was similar for the esketamine + oral AD and oral AD + placebo groups (Table 35).

Table 35: Patients Who Had a Worsening in Suicidality with Postbaseline Suicidal Ideation Based on the C-SSRS in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	Patients with No Suicidal Ideation or Behavior (no Event) at Baseline N	*n (%) with Suicidal Ideation at any time postbaseline*
TRANSFORM-1 (Fixed-dose)			
Induction Phase	Esk 56 mg:	87	12 (13.8%)
	Esk 84 mg:	78	8 (10.3%)
	Placebo:	77	13 (16.9%)
TRANSFORM-2 (Flexible-dose)			
Induction Phase	Esk 56-84 mg:	89	6 (6.7%)
	Placebo:	85	7 (8.2%)
Pooled TRANSFORM-1/2			
Induction Phase	Total Esk[a]:	254	26 (10.2%)
	Total Placebo:	162	20 (12.3%)
TRANSFORM-3			
Induction Phase	Esk 28-84 mg:	58	8 (13.8%)
	Placebo:	54	9 (16.7%)
SUSTAIN-1			
Induction Phase	Esk 56-84 mg:	362	41 (11.3%)
Optimization Phase	Esk 56-84 mg:	387	22 (5.7%)
Maintenance Phase	Esk 56-84 mg:	126	3 (2.4%)
	Placebo:	133	6 (4.5%)
SUSTAIN-2			
Induction Phase	Esk 28-84 mg:	637	71 (11.1%)
Optimization/Maintenance Phase	Esk 28-84 mg:	509	59 (11.6%)

AD=antidepressant; C-SSRS=Columbia-Suicide Severity Rating Scale; Esk=esketamine; TRD=treatment-resistant depression
Note: For each study, each patient is counted only once in the above table, based on the most severe postbaseline C-SSRS category: No event=0; Suicidal ideation =1, 2, 3, 4, 5; Suicidal behavior =6, 7, 8, 9, 10.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.
Baseline is 7 days prior to enrollment/randomization.

Among patients treated with esketamine + oral AD in the Phase 3 studies, 10 patients (8 from the uncontrolled, open-label long-term study SUSTAIN-2) reported suicidal behavior postbaseline based on the C-SSRS (score of 6-10) (Table 36). All of these patients had a lifetime history of suicidal ideation or suicidal behavior, and 5 of these patients had suicidal ideation at baseline.

Table 36: Patients Who Had a Worsening in Suicidality With Postbaseline Suicidal Behavior Based on the C-SSRS in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	Patients with No Suicidal Ideation or Behavior (no Event) at Baseline N	Patients with No Suicidal Ideation or Behavior (no Event) at Baseline *n (%) with Suicidal Behavior at any time postbaseline*	Patients with Suicidal Ideation at Baseline N	Patients with Suicidal Ideation at Baseline *n (%) with Suicidal Behavior at any time postbaseline*
TRANSFORM-1 (Fixed-dose)					
Induction Phase	Esk 56 mg:	87	0	28	1 (3.6%)
	Esk 84 mg:	78	0	35	0
	Placebo:	77	0	36	0
TRANSFORM-2 (Flexible-dose)					
Induction Phase	Esk 56-84 mg:	89	0	23	0
	Placebo:	85	0	24	0
Pooled TRANSFORM-1/2					
Induction Phase	Total Esk[a]:	254	0	86	1 (1.2%)
	Total Placebo:	162	0	60	0
TRANSFORM-3					
Induction Phase	Esk 28-84 mg:	58	0	12	0
	Placebo:	54	0	11	0
SUSTAIN-1					
Induction Phase	Esk 56-84 mg:	362	1 (0.3%)	62	0
Optimization Phase	Esk 56-84 mg:	387	0	64	0
Maintenance Phase	Esk 56-84 mg:	126	0	25	0
	Placebo:	133	0	12	0
SUSTAIN-2					
Induction Phase	Esk 28-84 mg:	637	2 (0.3%)	124	2 (1.6%)
Optimization/Maintenance Phase	Esk 28-84 mg:	509	2 (0.4%)	93	2 (2.2%)

AD=antidepressant; C-SSRS=Columbia-Suicide Severity Rating Scale; Esk=esketamine; TRD=treatment-resistant depression
Note: For each study, each patient is counted only once in the above table, based on the most severe postbaseline C-SSRS category: No event=0; Suicidal ideation =1, 2, 3, 4, 5; Suicidal behavior =6, 7, 8, 9, 10.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.
Baseline is 7 days prior to enrollment/randomization.

No patient in the Phase 2 dose-response study SYNAPSE reported treatment-emergent postbaseline suicidal ideation or behavior (based on C-SSRS) in the double-blind phase; in the open-label phase, 2 patients reported treatment-emergent postbaseline suicidal ideation, and 1 patient, who had a history of suicidal behavior, reported treatment-emergent postbaseline suicidal behavior.

Treatment-emergent Adverse Events of Suicidal Ideation or Behavior

There were 3 cases of completed suicide among the 1861 patients treated with esketamine + oral AD (1045 patient-years of exposure) in the Phase 2 and 3 studies in patients with TRD (see Section 8.3.4.1). No suicides occurred among the 486 patients treated with oral AD + placebo (108 patient-years of exposure).

Several preferred terms were used to search for TEAEs related to suicidality; see Appendix 11 for a list of preferred terms. Overall, across the Phase 2 and 3 studies in TRD, the incidence of suicidality-related TEAEs ranged from 0% to 5.5%; most of the reported cases were those of suicidal ideation. In the controlled Phase 3 studies, the incidence of these events was similar for

the esketamine + oral AD and oral AD + placebo groups (Table 37). In the uncontrolled, open-label long-term safety study, 5.5% of patients reported a suicidality-related TEAE across the entire study (Table 37). Severe suicidality-related TEAEs were reported at a low incidence (<1% for individual preferred terms) in each of the Phase 2 and 3 studies. A total of 15 patients across the completed Phase 3 studies reported a severe suicidality-related TEAE (7 patients with TEAEs of suicidal ideation; 7 patients with TEAEs of suicide attempt, and 1 patient with a TEAE of completed suicide). Clinical review of suicidality-related TEAEs indicated that most of these events were likely associated with the underlying disease condition. Most of these events resulted in no change to dosing of the nasal spray study medication and resolved without intervention/hospitalization.

Across the 346 patients treated with esketamine + oral AD in the Phase 3 short-term studies TRANSFORM-1/2, the overall incidence of specific TEAEs of suicidal ideation and intentional self-injury (i.e., suicidal behavior) was 1.2% in the esketamine + oral AD group (3 patients reporting suicidal ideation; 1 patient reporting intentional self-injury) and 0.9% in the oral AD + placebo group (1 patient reporting suicidal ideation; 1 patient reporting intentional self-injury).

The incidence of suicidality-related TEAEs among patients 18-24 years of age during the Phase 3 studies is presented in Table 37. None of the patients 18-24 years of age reported suicidality-related TEAEs in pooled short-term studies TRANSFORM-1/2. In SUSTAIN-1, 1 patient 18-24 years of age treated with esketamine + oral AD during the induction phase reported a TEAE of intentional self-injury, and 1 patient treated with oral AD + placebo during the maintenance phase reported a TEAE of suicidal ideation. During SUSTAIN-2, 1 patient 18-24 years of age treated with esketamine + oral AD reported TEAEs of suicidal ideation and intentional self-injury and 1 patient reported a TEAE of suicidal ideation.

Table 37: Overall Incidence of Treatment-emergent Adverse Events in the Category of Suicidality in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Any TEAE related to Suicidality	Patients 18-24 Years N	Patients 18-24 Years Any TEAE related to Suicidality
TRANSFORM-1 (Fixed-Dose)					
Induction Phase	Esk 56 mg:	115	2 (1.7%)		
	Esk 84 mg:	116	2 (1.7%)		
	Placebo:	113	1 (0.9%)		
TRANSFORM-2 (Flexible-Dose)					
Induction Phase	Esk 56-84 mg:	115	0 (0%)		
	Placebo:	109	1 (0.9%)		
Pooled TRANSFORM-1/2					
Induction Phase	Total Esk[a]:	346	4 (1.2%)	14	0
	Total Placebo:	222	2 (0.9%)	11	0
TRANSFORM-3					
Induction Phase	Esk 28-84 mg:	72	1 (1.4%)	N/A	N/A
	Placebo:	65	0 (0%)	N/A	N/A
SUSTAIN-1					
Induction Phase	Esk 56-84 mg:	437	6 (1.4%)	19	1 (5.3%)
Optimization Phase	Esk 56-84 mg:	455	3 (0.7%)	20	0
Maintenance Phase	Esk 56-84 mg:	152	3 (2.0%)	6	0
	Placebo:	145	1 (0.7%)	5	1 (20.0%)
SUSTAIN-2					
Induction Phase	Esk 28-84 mg:	779	20 (2.6%)		
Optimization/Maintenance Phase	Esk 28-84 mg:	603	24 (4.0%)		
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	44 (5.5%)	21	2 (9.5%)

AD=antidepressant; Esk=esketamine; N/A=not applicable; TEAE=treatment-emergent adverse event: TRD=treatment-resistant depression
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, Suicide attempt.* Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.

8.5. Dissociation and Perceptual Changes

Administration of subanesthetic doses of ketamine are associated with transient, dose-related dissociation/perceptual changes.[4,17,63] The extent of potential treatment-emergent dissociative symptoms associated with esketamine administration was evaluated in the Phase 2 and 3 clinical program using the CADSS rating scale to capture the extent of the treatment-emergent dissociative/perceptual changes (including distortion of time and space, illusions, derealization, and depersonalization), as well as through assessment of the incidence, type, and severity of relevant TEAEs and clinical evaluation of individual cases. The total CADSS score ranges from 0 to 92, with a higher score representing a more severe condition. Scores between 0 and 4 are considered to be in the normal range.

Changes in CADSS Total Score

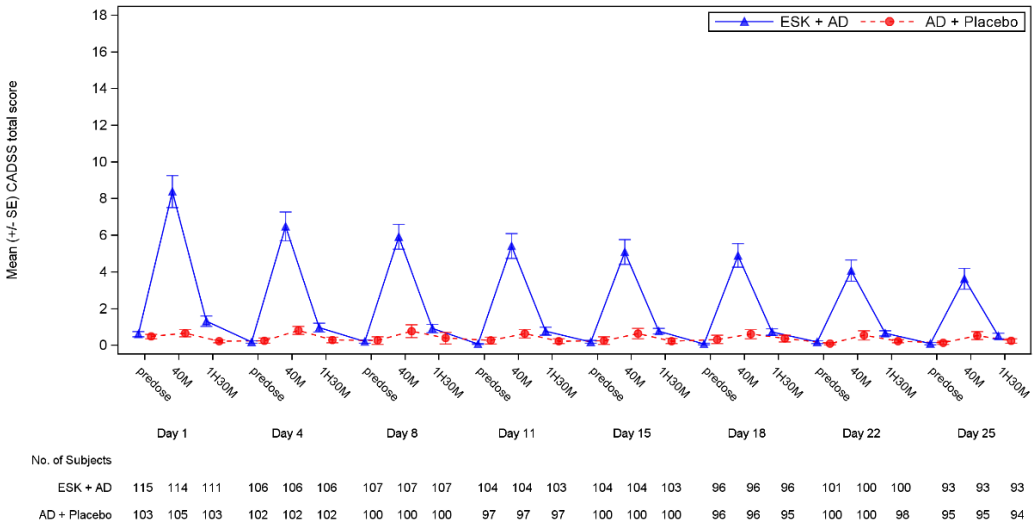
Across the Phase 2 and 3 studies, the following similar pattern of change was observed in the mean CADSS score in esketamine dosing sessions: dissociative/perceptual changes had an onset shortly after the start of dosing, peaked by 40 minutes after dose administration, and typically returned to predose levels at the 1.5-hour postdose assessment. The maximum mean values did not exceed 10.

In the short-term controlled Phase 3 studies, the percentage of patients with an increase in the CADSS total score from predose at any time during the induction phase in the esketamine + oral AD groups ranged from 89.5% to 93.1%. A substantial nocebo response (adverse effect following an 'inert' treatment) was observed in CADSS total scores for the oral AD + placebo groups in the short-term Phase 3 studies, 28% to 40% of patients in these groups experienced an increase in CADSS total score after administration of placebo nasal spray with a bittering agent to facilitate blinding.

Over the course of each Phase 3 study, the peak mean CADSS total score at the 40-minute postdose timepoint in the esketamine + oral AD groups generally decreased with consecutive doses. This attenuation was apparent both in the short-term studies as well as with prolonged exposure in the long-term studies.

Data for patients in the short-term flexible-dose study TRANSFORM-2 are displayed in Figure 28. The mean CADSS total score at the 40-minute postdose assessment decreased from Day 1 to Day 25. A CADSS total score of 0 to 4 is considered to be in the normal range.

Figure 28: Arithmetic Mean (+/- SE) Clinician Administered Dissociative States Scale (CADSS) Total Score Over Time; Double-blind Induction Phase (TRANSFORM-2: Safety Analysis Set)



AD=antidepressant; Esk=esketamine; SE=standard error

TEAEs Related to Dissociative Symptoms/Perceptual Changes

Across all Phase 2 and 3 studies in TRD, the most common psychological effects of esketamine have been dissociative symptoms/perceptual changes. Dissociation, feeling abnormal, and feeling drunk are identified as adverse drug reactions for esketamine (see Section 8.3.2). The latter 2 events were mostly reported at incidences under 5% in the Phase 2 and 3 studies, and the incidence of severe events was ≤0.9% across Phase 3 study phases. The individual TEAE of dissociation, by comparison, was one of the most common TEAEs in esketamine-treated patients across the Phase 2 and 3 studies.

- In the short-term Phase 2 and 3 studies, dissociation was reported in the esketamine + oral AD groups at the rates of 26.6% in the pooled TRANSFORM-1/2 studies (vs 3.6% for oral AD + placebo), and there was no apparent increase in the overall incidence of this event with longer-term treatment (23.0% in the double-blind maintenance phase of SUSTAIN-1 [vs 0% for oral AD + placebo] and 27.6% across the long-term open-label safety study SUSTAIN-2).
- In TRANSFORM-3, dissociation was reported in 12.5% of patients ≥65 years treated with esketamine + oral AD (vs 1.5% for oral AD + placebo). Note, the percentage of patients ≥65 years in TRANSFORM-3 reporting dissociation was lower than that for patients 18-64 years in the pooled short-term Phase 3 studies TRANSFORM-1/2.
- Across all Phase 3 studies, reported TEAEs of dissociation were primarily mild or moderate in intensity, with severe events reported for <6% of patients in each Phase 3 study: 9 patients in TRANSFORM-1 (2 treated with esketamine 56 mg + oral AD and 7 treated with esketamine 84 mg + oral AD); 4 patients in TRANSFORM-2; no patients in TRANSFORM-3; 5 patients in the induction phase of SUSTAIN-1, 5 in the optimization phase, and 1 in the maintenance phase; and 15 patients in SUSTAIN-2. Dissociation was not reported as serious for any patient in completed Phase 2 and 3 studies. Across the Phase 3 studies, 7 patients discontinued esketamine due to a TEAE of dissociation.

Dose relationship: As discussed in Section 8.3.3, transient dissociative/perceptual changes (based on the overall and severe TEAE incidence rates) in the Phase 3 fixed-dose study TRANSFORM-1 were more pronounced in patients receiving the esketamine 84 mg dose than in those receiving the esketamine 56 mg doses.

Time course of dissociative/perceptual change TEAEs: Nearly all TEAEs reflecting dissociative symptoms/perceptual changes were reported on the day of esketamine administration and resolved the same day; across Phase 3 studies/study phases >98% of TEAEs of dissociation reported on the day of administration resolved on the same day), consistent with the observation for the CADSS scores. A total of 17 TEAEs of dissociation reported in 13 patients across the Phase 3 studies were not reported as resolved on the day of dose administration. However, objective measurement of symptoms of dissociation using the CADSS on the day of dosing showed that the TEAE of dissociation had resolved by 1.5 hours after dose administration for all of these patients, and all were discharged on the day of dosing in accordance with the protocol.

Over 90% of patients were ready for discharge without any adverse clinical outcome or complications based on the clinician's assessment by the 1.5-hour postdose timepoint in each Phase 3 study (see further details in Section 8.11).

8.6. Hypomania and Mania

The emergence of symptoms of hypomania or mania has been reported with the use of oral ADs in patients with MDD,[6,7] and emergence of such symptoms may be related to undiagnosed bipolar disorder. The overall risk of emergence of manic symptoms was estimated as 3.4% per year of treatment.[6] Patients with bipolar disorder or related disorders were excluded from enrollment in the esketamine TRD clinical program, and the use of lithium, anticonvulsants (valproate, carbamazepine), and antipsychotics was prohibited during these studies.

Overall, there was insufficient evidence to associate administration of esketamine with the onset of acute mania or hypomania. Across the Phase 2 and 3 studies in TRD, the TEAE of mania was reported in only 2 esketamine-treated patients (one report after the first dose of esketamine and oral AD [duloxetine] and a second report during the posttreatment follow-up phase), while hypomania was not reported in any patient. Both events of mania resolved without sequelae.

8.7. Sedation and Somnolence

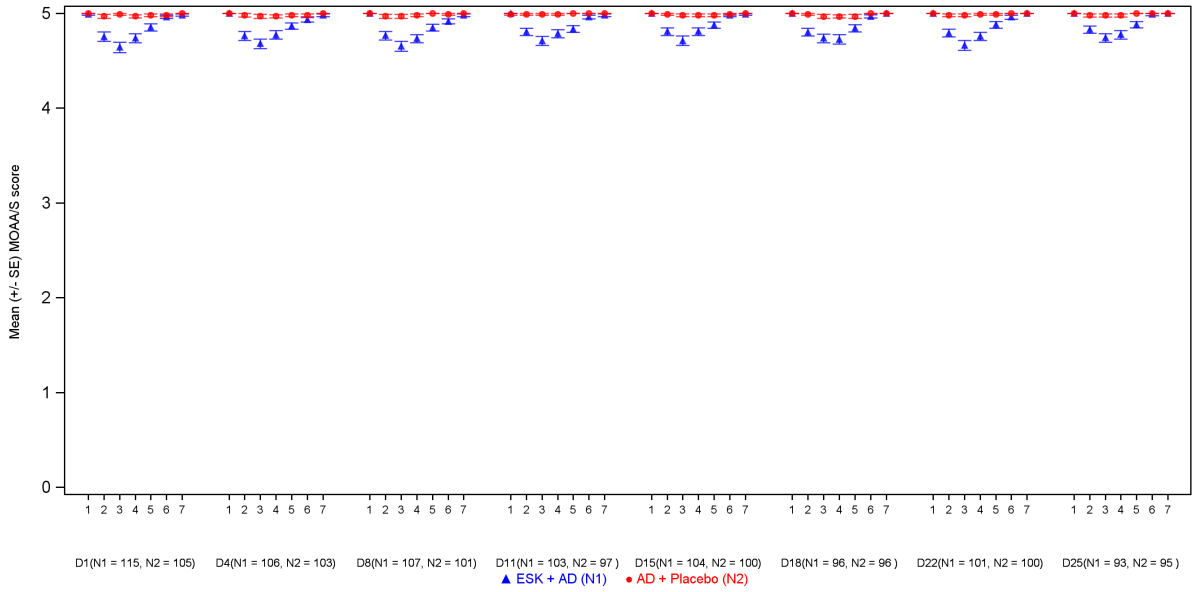
Sedation is identified as an adverse drug reaction for esketamine (see Section 8.3.2 for the analysis of adverse drug reactions and Appendix 10 for preferred terms used to identify events of sedation). In the Phase 2 and 3 studies in patients with TRD, adverse effects of sedation were assessed using the MOAA/S rating scale (measured each day of nasal spray dosing at 15-minute intervals from predose until 1.5 hours postdose or longer if necessary until the patient had a score of 5 [awake]) and based on review of the incidence, type, and severity of sedation-related adverse events. A MOAA/S score of 0 would be expected for anesthetic doses of ketamine or esketamine.[95]

Changes in MOAA/S Score

Based on the pattern of responses on the MOAA/S scale in the Phase 2 and 3 studies, sedative effects of esketamine were generally mild (corresponding to MOAA/S score of 4 [lethargic response to name spoken in normal tone]), had an onset shortly after nasal spray dose administration, typically peaked at 30 to 45 minutes postdose, and resolved by 1 to 1.5 hours postdose (Figure 29). Among esketamine treatment groups, 10% or fewer patients across the Phase 3 studies/study phases had a MOAA/S score of 3 or less (corresponding to moderate or greater sedation). Across the Phase 3 studies in patients with TRD, 11 of 1,601 patients treated with esketamine + oral AD (and 1 of 432 patients who received oral AD + placebo), had a MOAA/S score of 0 (corresponding to general anesthesia; no reaction to painful stimulus [trapezius squeeze]) or 1 (corresponding to deep sedation/analgesia; response to trapezius squeeze, including purposeful and reflexive withdrawal). These instances of MOAA/S scores of 0 or 1 generally did not repeat with subsequent dosing; 1 patient reported scores of 0 or 1 on multiple dosing days. Three patients had a MOAA/S score of 0 or 1 at or after the 1-hour postdose time point. One of these cases was reported as a serious adverse event (deep sedation); this patient had a MOAA/S score of 0 starting at 1 hour after dose administration which resolved

spontaneously within an hour. Across the Phase 3 studies, decreases in MOAA/S score (including decreases to 1 or 0) were not associated with symptoms of respiratory distress. No intervention was required in cases of decreased MOAA/S score.

Figure 29: Arithmetic Mean (+/- SE) Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score Over Time; Double-blind Induction Phase (TRANSFORM-2: Safety Analysis Set)



AD=antidepressant; Esk=esketamine; SE=standard error
Time(Days): 1 = Predose, 2 = 15M, 3 = 30M, 4 = 45M, 5 = 1H, 6 = 1H15M, 7 = 1H30M
On each nasal spray dosing day, the MOAA/S was to be performed every 15 minutes from predose to 1.5 hours postdose.

TEAEs of Sedation and Somnolence

The most commonly reported individual preferred terms (≥5%) related to sedation symptoms in the Phase 2 and 3 TRD studies were somnolence and sedation, and these events were reported at higher rates after treatment with esketamine + oral AD than with oral AD + placebo in controlled Phase 3 studies/study phases (Table 38).

The reported TEAE data for sedation and somnolence were consistent with MOAA/S findings. Across the Phase 2 and 3 TRD studies, TEAEs of somnolence or sedation were primarily mild or moderate in intensity and nonserious. In the Phase 3 studies, there were 12 patients with a severe event of somnolence, and 8 patients with a severe event of sedation. One patient experienced a serious TEAE of sedation. Four patients discontinued esketamine due to TEAEs of somnolence and/or sedation (somnolence: 1 patient; sedation: 2 patients; both somnolence and sedation: 1 patient). Most (>95%) reported TEAEs of somnolence or sedation occurred on the day of dosing in the short-term and long-term Phase 3 studies/study phases and of these, ≥96% resolved spontaneously the same day. For those TEAEs not reported as resolved on the same day (31 TEAEs of somnolence and 12 TEAEs of sedation), all patients had final recorded MOAA/S scores of 4 (lethargic response to name spoken in normal tone) or 5 (awake) on the day of dosing when the TEAE occurred.

Table 38: Incidence of Treatment-emergent Adverse Events of Sedation and Somnolence in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Sedation	Somnolence
TRANSFORM-1 (fixed-dose)				
Induction Phase	Esk 56 mg:	115	6 (5.2%)	24 (20.9%)
	Esk 84 mg:	116	8 (6.9%)	21 (18.1%)
	Placebo:	113	1 (0.9%)	13 (11.5%)
TRANSFORM-2 (flexible-dose)				
Induction Phase	Esk 56-84 mg:	115	5 (4.3%)	15 (13.0%)
	Placebo:	109	1 (0.9%)	7 (6.4%)
Pooled TRANSFORM-1/2				
Induction Phase	Total Esk[a]:	346	19 (5.5%)	60 (17.3%)
	Total Placebo:	222	2 (0.9%)	20 (9.0%)
TRANSFORM-3				
Induction Phase	Esk 28-84 mg:	72	0	1 (1.4%)
	Placebo:	65	0	3 (4.6%)
SUSTAIN-1				
Induction Phase	Esk 56-84 mg:	437	44 (10.1%)	65 (14.9%)
Optimization Phase	Esk 56-84 mg:	455	19 (4.2%)	63 (13.8%)
Maintenance Phase	Esk 56-84 mg:	152	10 (6.6%)	32 (21.1%)
	Placebo:	145	1 (0.7%)	3 (2.1%)
SUSTAIN-2				
Induction Phase	Esk 28-84 mg:	779	51 (6.5%)	94 (12.1%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	29 (4.8%)	85 (14.1%)

AD=antidepressant; Esk=esketamine; TRD=treatment-resistant depression

8.8. Effects on Cognition

Study ESKETINTRD1005

A Phase 1 double-blind, placebo-controlled, cross-over study (ESKETINTRD1005) was conducted in healthy adults to assess the impact of esketamine on cognitive function and the duration of any cognitive effects. The CogState® computerized test battery was used to assess cognitive functioning; this test battery provides an assessment of multiple cognitive domains, including attention/processing speed, visual learning and memory, working memory, and executive function. Results from Study ESKETINTRD1005 showed that treatment with a single esketamine 84 mg dose produced a transient decline in cognitive function in all domains at 40 minutes after dosing, which resolved by 2 hours after dosing in healthy participants.

Phase 3 Studies

In the Phase 3 studies in TRD, the potential effect of esketamine on cognition was evaluated using standardized tests: (1) the CogState® battery described above and (2) the Hopkins Verbal Learning Test, a brief measure of verbal learning and memory. Both the CogState® battery and Hopkins Verbal Learning Test include domains that have shown sensitivity to ketamine/esketamine effects in studies with healthy volunteers or patients with MDD or TRD at doses used for depression treatment. The frequency and severity of reported TEAEs of impaired cognition were also examined.

In the Phase 3 short-term studies, performance on each of the cognitive tests generally demonstrated either an improvement from baseline or appeared stable relative to baseline both at the end of the double-blind induction phase and at the 2-week follow-up assessment. Specifically, in TRANSFORM-1 and 2 (with patients 18-64 years of age) cognitive performance was stable or slightly improved on all assessments through 4 weeks. In TRANSFORM-3 (with patients ≥65 years of age) the same was true for higher cognitive function (e.g., verbal memory, executive function), but there was slight slowing of simple reaction time at Day 28 versus baseline for both the esketamine + oral AD group and the oral AD + placebo group. Crucially, the slowing was greater in the oral AD + placebo group than in the esketamine + oral AD group. These results suggest that treatment with esketamine + oral AD for up to 4 weeks did not impair the aspects of cognition studied in patients 18-64 years of age with TRD and was not associated with systematic short-term impairment in cognition in patients ≥65 years of age. Similarly, results for the double-blind maintenance phase of the maintenance of effect study SUSTAIN-1 suggested cognitive performance remained stable with repeated, longer-term intermittent esketamine dose administration.

In the open-label safety study SUSTAIN-2, results on tests of attention/reaction time and higher level cognitive domains either remained stable or showed slight improvement from baseline for all patients and among subgroups of patients aged <65 years and those aged ≥65 years. However, reaction times, measured using the simple and choice reaction time tests, were slowed at Week 20 of the optimization/maintenance phase in the subgroup of patients ≥65 years.

As the number of patients ≥65 years decreased at later timepoints in this study due, in part, to the study termination after the target exposure to esketamine was met (see Section 6.4), post hoc analyses were conducted for patients ≥65 years who completed the study. In completers ≥65 years old, the mean slowing in reaction time at the Week 52 endpoint was of a magnitude representing an effect size of 0.52 for simple reaction test and 0.47 for choice reaction test (Cohen's d). There was considerable inconsistency in reaction time among patients ≥65 years with large increases as well as large decreases over time within participants. No patient ≥65 years demonstrated impaired reaction time performance (z-score < -1.5) at the Week 52 endpoint that persisted at the Week 4 follow-up assessment. For comparison, slowed reaction time was seen at 45 minutes following a single 0.5-mg or 1-mg dose of alprazolam on CogState® tests among healthy adult patients (Cohen's d values of >0.80 for simple and choice reaction tests with 1-mg dose).[101] In the absence of a comparator group in SUSTAIN-2 or published longitudinal studies of reaction time in older MDD/TRD patients, firm conclusions cannot be made as to whether

observed changes in reaction time observed in SUSTAIN-2 is characteristic of the older MDD/TRD population.[85]

Importantly, results of the completer analyses with patients ≥65 years showed that the performance on tests of high cognitive functions was not affected, which was consistent with results of analyses involving the all enrolled analysis set (and by-age subgroup analyses). Specifically, the performance of completers ≥65 years old either remained stable or showed slight improvement throughout SUSTAIN-2 on measures of visuospatial memory/function, and verbal episodic memory performance. Thus, the slowed reaction time in patients ≥65 years observed at the latter timepoints in SUSTAIN-2 appears to represent an isolated observation related to processing speed, rather than a broad attentional impairment. This observation was not clearly attributable to study medication, and the clinical relevance and consequences have not been established. It may be related to the underlying disease, antidepressant use including esketamine, impact of the experimental methodology, or a combination of these factors.

No TEAEs related to cognitive impairment (i.e., preferred terms of cognitive disorder or cognitive motor disorder) were reported in the Phase 3 studies in TRD.

8.9. Cardiovascular Effects

The hemodynamic changes (elevated blood pressure and pulse rate) associated with ketamine are well recognized. In the Phase 3 studies, dosing with esketamine was deferred in patients having a supine systolic/diastolic blood pressure of >140/90 mm Hg (>150/90 mm Hg for patients ≥65 years) until blood pressure values normalized.

Assessment of the cardiovascular safety of esketamine was evaluated in the Phase 2 and 3 studies in TRD based assessment of:

- Postdose changes in blood pressure, pulse rate, and pulse oximetry measures
- Cardiovascular TEAEs
- Treatment-emergent ECG abnormalities and changes from baseline in recorded ECG parameters
- Phase 1 thorough QT study specifically designed to evaluate of the effect of esketamine on the cardiac repolarization

8.9.1. Vital Sign Measurements

The impact of esketamine on blood pressure and heart rate was evaluated in the Phase 2 and 3 studies through vital sign measurements performed pre- and post-dosing with the nasal spray study medication.

Effects on Blood Pressure

Transient increases in systolic and diastolic blood pressure were observed following esketamine administration in all Phase 2 and 3 studies in patients with TRD, with maximum mean changes typically observed within 40 minutes of dosing and mean blood pressure values subsequently

returning to, or close to, predose values within 1.5-2 hours after administration. As a result of the observed transient changes in blood pressure seen with esketamine, the proposed product labeling recommends that blood pressure be monitored prior to esketamine dosing and includes other information to limit the risk to patients; further details are provided in Section 10.2.2.

In the short-term Phase 3 studies:

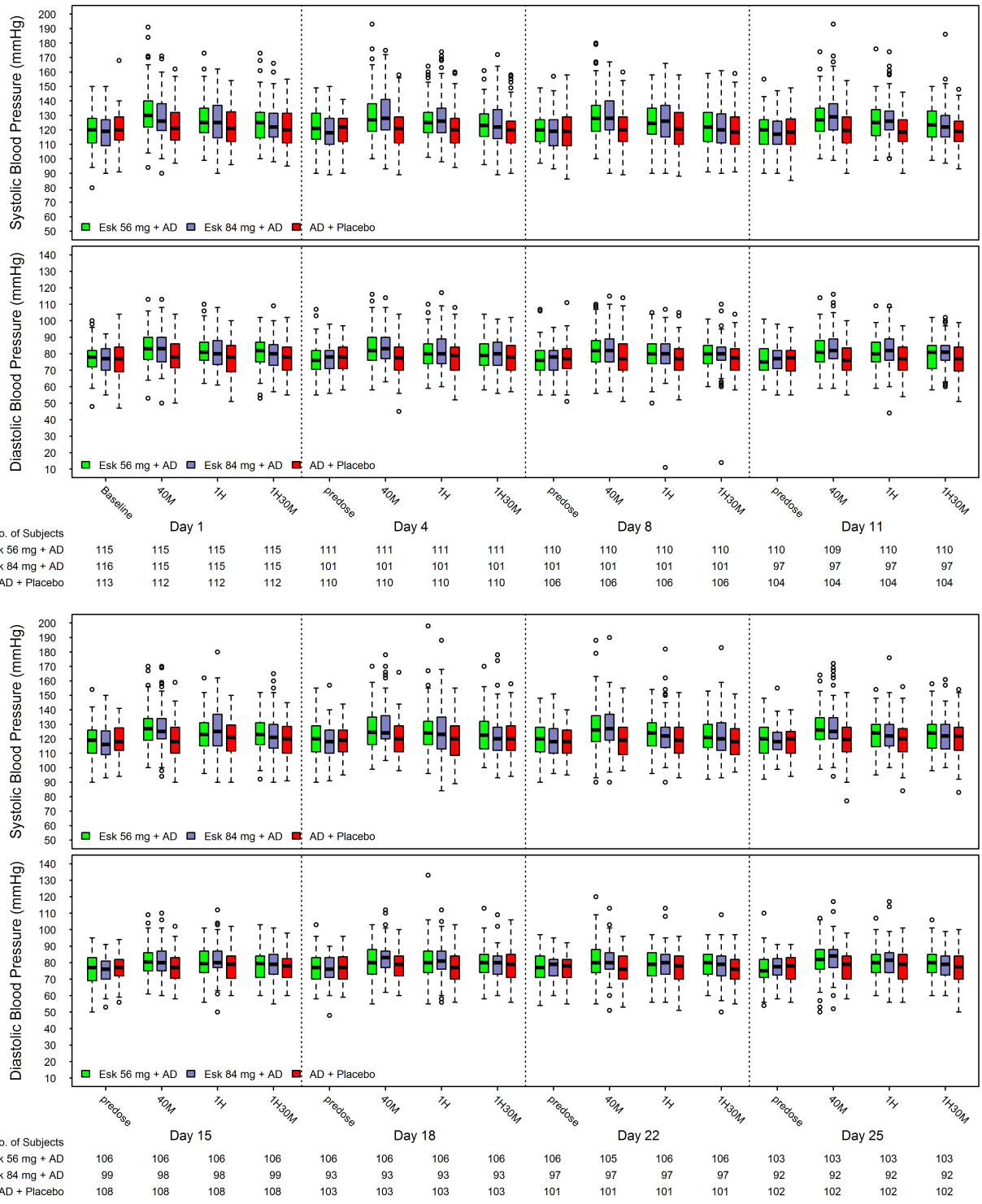
- The largest mean maximum systolic and diastolic blood pressure increases across all nasal spray dosing days compared to predose values in the pooled short-term studies TRANSFORM-1/2 studies are shown in Table 39. The mean maximum increases in the systolic and diastolic blood pressure were larger for the esketamine + oral AD group than for the oral AD + placebo group.
- In the short-term fixed-dose study TRANSFORM-1, differences between the maximum mean changes in blood pressure between the 56 mg and 84 mg doses of esketamine doses did not demonstrate a dose-response relationship (Table 39 and Figure 30).
- A similar pattern for transient increases in blood pressure were observed in patients ≥65 years in the short-term flexible-dose study TRANSFORM-3 (Table 39 and Figure 31).
- For context, the acute effects of caffeine (200-250 mg, equivalent to 2 to 3 cups of coffee) increases systolic blood pressure by 3-14 mm Hg and diastolic blood pressure by 4-13 mm Hg in normotensive individuals.[80] In hypertensive individuals, this exposure to caffeine produces an increase in systolic and diastolic blood pressure of 8 and 6 mm Hg, respectively, that lasts for about 3 hours.[67]
- In the short-term studies TRANSFORM-1/2, the increase in blood pressure in the esketamine + oral AD groups appeared to be unrelated to pretreatment blood pressure values.

Table 39: Largest Mean (SD) of the Maximum Systolic and Diastolic Blood Pressure Increases Across Intranasal Dosing Days Compared to Predose Values in the Short-term Phase 3 Studies

Study Phase	Treatment (+ Oral AD)	*Systolic Blood Pressure (mm Hg) Mean Increase (SD)*	*Diastolic Blood Pressure (mm Hg) Mean Increase (SD)*
TRANSFORM-1 (Fixed-dose)			
Induction Phase	Esk 56 mg:	14.3 (13.26)	8.9 (8.15)
	Esk 84 mg:	15.0 (14.00)	9.4 (8.51)
	Placebo:	7.2 (11.41)	5.3 (7.54)
Pooled TRANSFORM-1/2			
Induction Phase	Total Esk:	13.3 (12.49)	8.7 (7.40)
	Total Placebo:	6.1(9.99)	4.9 (6.66)
TRANSFORM-3 (Flexible-dose)			
Induction Phase	Esk 28-84 mg:	16.0 (15.59)	9.5 (8.17)
	Placebo:	11.1 (9.73)	6.8 (5.90)

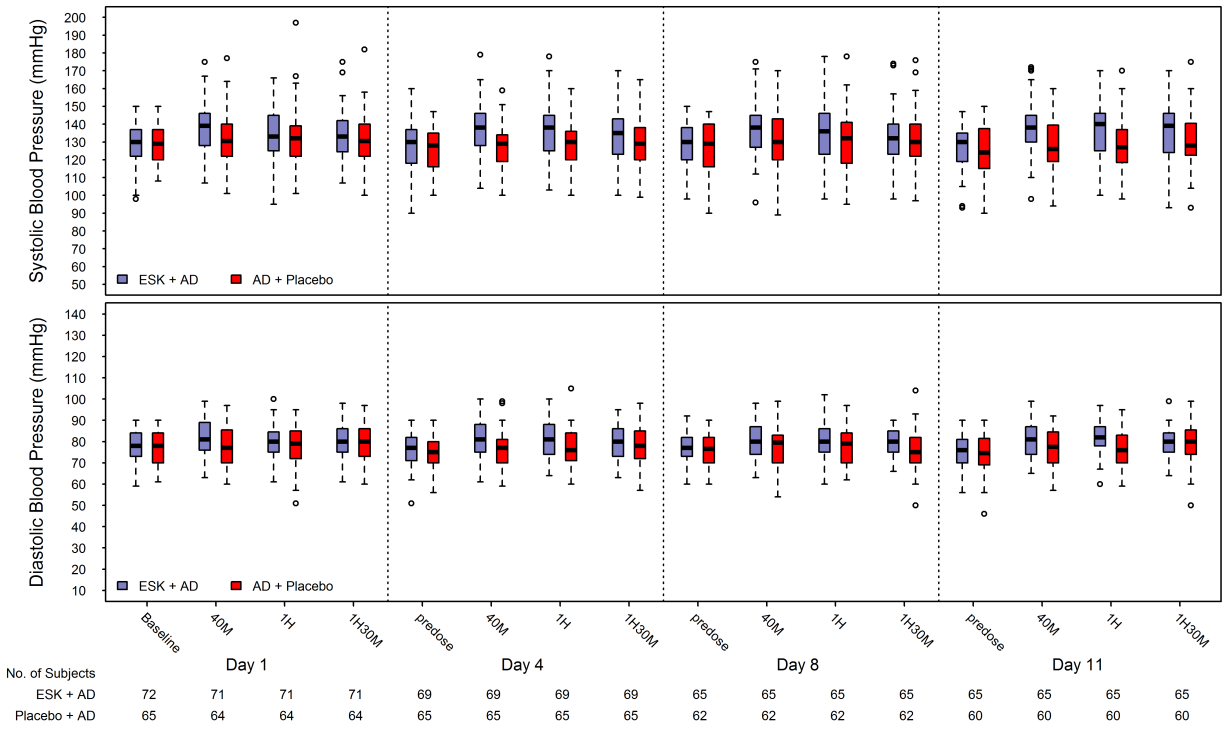
AD=antidepressant; Esk=esketamine; SD=standard deviation

Figure 30: Box Plot of Blood Pressure Over Time in the Short-term Fixed-dose Study in Patients 18 to 64 Years; Double-blind Induction Phase (TRANSFORM-1: Safety Analysis Set)

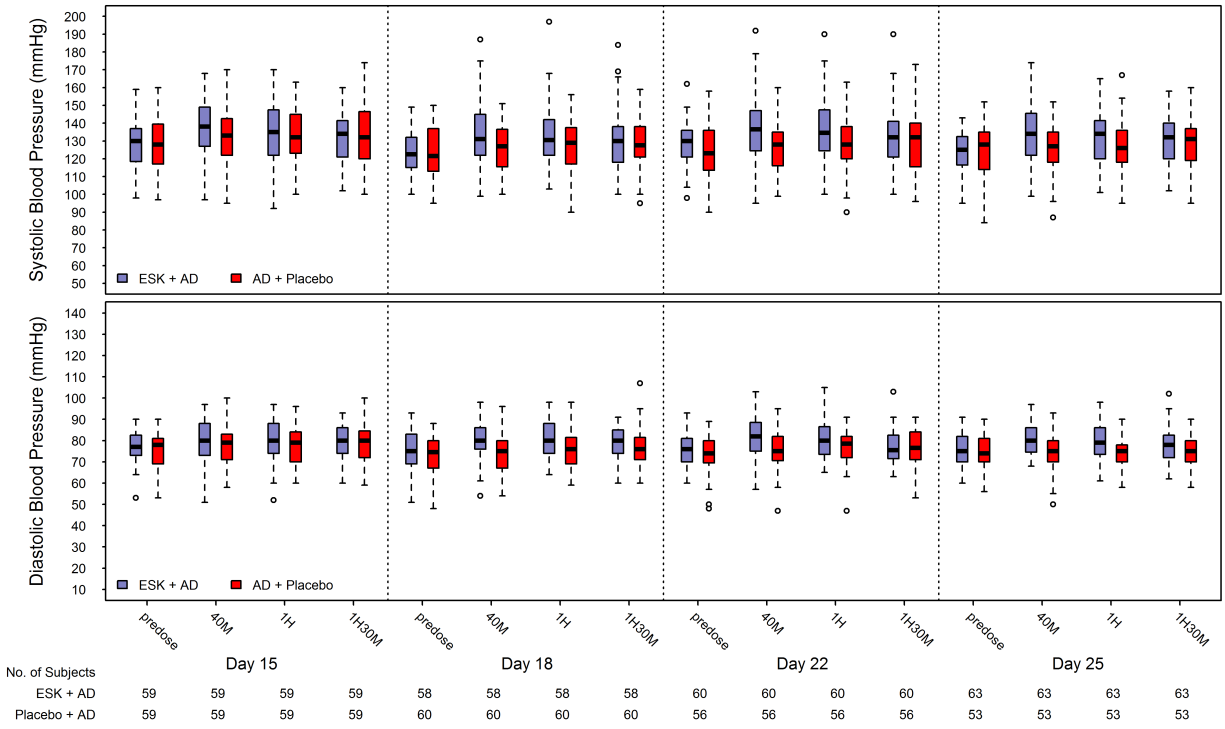


AD=antidepressant; Esk=esketamine

Figure 31: Box Plot of Blood Pressure Over Time in the Short-term Flexible-dose Study in Patients ≥65 Years; Double-blind Induction Phase (TRANSFORM-3: Safety Analysis Set)



No. of Subjects																
ESK + AD	72	71	71	71	69	69	69	69	65	65	65	65	65	65	65	65
Placebo + AD	65	64	64	64	65	65	65	65	62	62	62	62	60	60	60	60



No. of Subjects																
ESK + AD	59	59	59	59	58	58	58	58	60	60	60	60	63	63	63	63
Placebo + AD	59	59	59	59	60	60	60	60	56	56	56	56	53	53	53	53

AD=antidepressant; ESK=esketamine

In the long-term safety study SUSTAIN-2:

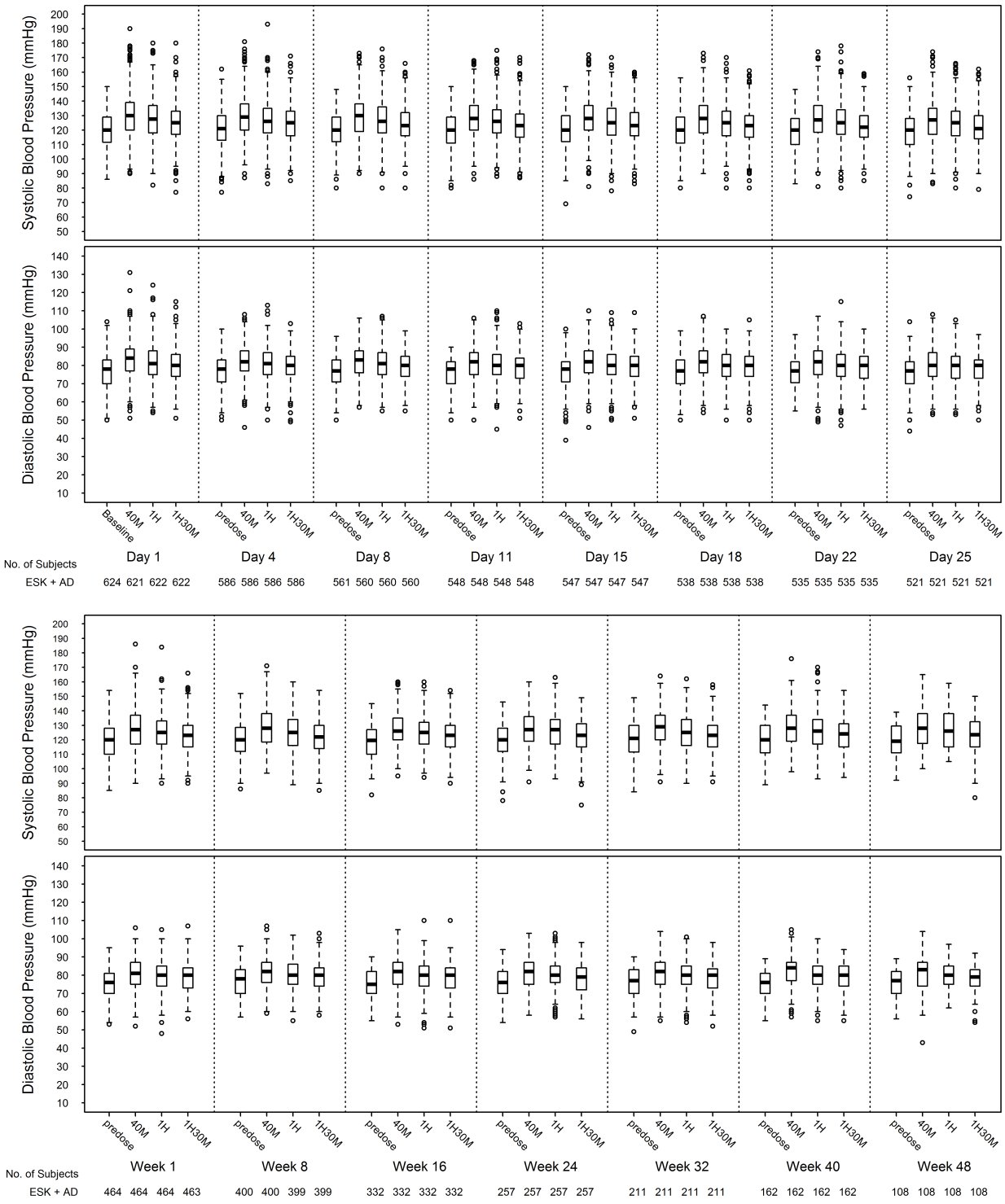
- The maximum mean changes in systolic and diastolic blood pressure compared to predose values in SUSTAIN-2 were generally similar at 40 minutes after dose administration on Day 1 of the induction phase and at Weeks 4 and 48 of the optimization/maintenance phase (Table 40).
- Box plots showing the blood pressure changes over time in SUSTAIN-2 are presented for patients 18 to 64 years in Figure 32 and for patients ≥65 years in Figure 33.
- There were no cumulative effects of the changes in blood pressure and the pattern of transient blood pressure increases (i.e., maximum changes were typically observed within 40 minutes of dosing and mean values subsequently returned to, or close to, predose values within 1.5-2 hours after administration) remained consistent over time for patients 18-64 years and those ≥65 years.

Table 40: Maximum Change (SD) in Systolic and Diastolic Blood Pressure Compared to Predose Values Over Time in the Long-term Safety Study

Study Day/Week (Phase) at 40 min after dose	**Treatment (+ Oral AD)**	**N**	***Systolic Blood Pressure (mm Hg) Mean Change (SD)***	***Diastolic Blood Pressure (mm Hg) Mean Change (SD)***
SUSTAIN-2				
Day 1 (induction)	Esk 28-84 mg:	771	9.6 (11.99)	5.6 (8.32)
Week 4 (optimization/maintenance)	Esk 28-84 mg:	651	7.6 (11.04)	4.7 (7.75)
Week 48 (optimization/maintenance)	Esk 28-84 mg:	127	8.4 (10.28)	4.5 (7.02)

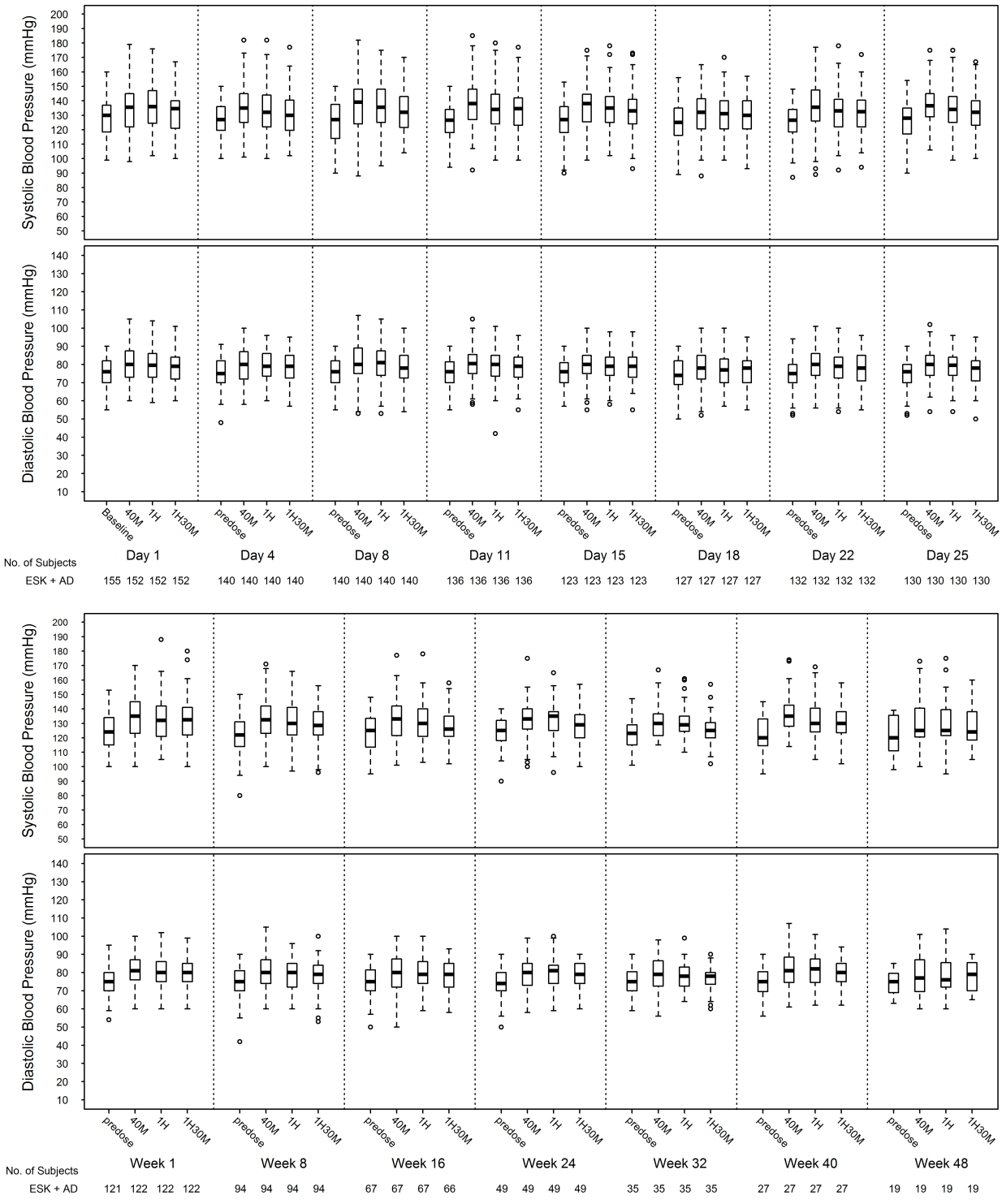
AD=antidepressant; Esk=esketamine; SD=standard deviation

Figure 32: Box Plot of Blood Pressure Over Time in the Long-term Safety Study in Patients 18 to 64 Years; Optimization/Maintenance Phase (SUSTAIN-2: Safety Analysis Set)



AD=antidepressant; ESK=esketamine

Figure 33: Box Plot of Blood Pressure Over Time in the Long-term Safety Study in Patients ≥65 Years; Optimization/Maintenance Phase (SUSTAIN-2: Safety Analysis Set)



AD=antidepressant; ESK=esketamine;

Treatment-emergent Acute Hypertension Across Phase 3 Studies/Study Phases

As shown in Table 41, treatment-emergent acute hypertension (elevations of systolic blood pressure to ≥180 mm Hg or diastolic blood pressure to ≥110 mm Hg) were reported at rates of 2-5% among the esketamine treatment groups for the pooled studies TRANSFORM-1/2 and all study phases of SUSTAIN-1 and 2. The exception was for TRANSFORM-3 in patients ≥65 years in which the rate was 11.1% for those treated with esketamine + oral AD and 6.2% for those treated with oral AD + placebo. These elevations primarily occurred within 1.5 hours after dosing, and the rates for patients meeting these acute hypertension criteria were higher among patients with a history of hypertension than in those without such a history.

Table 41: Incidence of Treatment-emergent Abnormal Blood Pressure Values Relative to Baseline at Any Time in Completed Phase 3 TRD Studies

Study Phase	Treatment (+Oral AD)	N	Systolic Blood Pressure (mm Hg) Decrease ≥20 and value ≤90	Systolic Blood Pressure (mm Hg) Increase ≥20 and value ≥180	Diastolic Blood Pressure (mm Hg) Decrease ≥15 and value ≤50	Diastolic Blood Pressure (mm Hg) Increase ≥15 and value ≥105	Acute Hypertension[b]
TRANSFORM-1 (Fixed-Dose)							
Induction Phase	Esk 56 mg:	115	3 (2.6%)	6 (5.2%)	2 (1.7%)	8 (7.0%)	8 (7.0%)
	Esk 84 mg:	116	3 (2.6%)	2 (1.7%)	6 (5.2%)	10 (8.6%)	5 (4.3%)
	Placebo:	113	3 (2.7%)	0	0	4 (3.5%)	2 (1.8%)
TRANSFORM-2 (Flexible-Dose)							
Induction Phase	Esk 56-84 mg:	115	1 (0.9%)	1 (0.9%)	0	10 (8.7%)	4 (3.5%)
	Placebo:	109	3 (2.8%)	0	3 (2.8%)	0	0
Pooled TRANSFORM-1/2							
Induction Phase	Total Esk[a]:	346	7 (2.0%)	9 (2.6%)	8 (2.3%)	28 (8.1%)	17 (4.9%)
	Total Placebo:	222	6 (2.7%)	0	3 (1.4%)	4 (1.8%)	2 (0.9%)
TRANSFORM-3							
Induction Phase	Esk 28-84 mg:	72	1 (1.4%)	2 (2.8%)	0	1 (1.4%)	8 (11.1%)
	Placebo:	65	6 (9.2%)	1 (1.5%)	4 (6.2%)	1 (1.5%)	4 (6.2%)
SUSTAIN-1							
Induction Phase	Esk 56-84 mg:	437	20 (4.6%)	4 (0.9%)	6 (1.4%)	43 (9.8%)	15 (3.4%)
Optimization Phase	Esk 56-84 mg:	455	14 (3.1%)	4 (0.9%)	6 (1.3%)	29 (6.4%)	12 (2.6%)
Maintenance Phase	Esk 56-84 mg:	152	5 (3.3%)	1 (0.7%)	3 (2.0%)	12 (7.9%)	3 (2.0%)
	Placebo:	145	7 (4.8%)	0	1 (0.7%)	2 (1.4%)	0
SUSTAIN-2							
Induction Phase	Esk 28-84 mg:	779	25 (3.2%)	10 (1.3%)	13 (1.7%)	39 (5.0%)	18 (2.3%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	37 (6.1%)	10 (1.7%)	24 (4.0%)	35 (5.8%)	18 (3.0%)
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	55 (6.9%)	18 (2.2%)	33 (4.1%)	66 (8.2%)	33 (4.1%)

AD=antidepressant; Esk=esketamine; TRD=treatment-resistant depression
Notes: Percentages calculated with the number of patients per parameter as denominator. If baseline value is missing, treatment-emergent abnormal vital signs will be evaluated based on the visit value only.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.
[b] Patients with treatment-emergent acute hypertension have either systolic blood pressure >=180 mm Hg (and baseline <180 mm Hg or missing) or diastolic blood pressure >=110 mm Hg (and baseline <110 mm Hg or missing).

Effects on Pulse Rate

Observed mean increases in pulse rate following esketamine administration were not clinically meaningful in any of the Phase 3 studies. In the controlled Phase 3 studies/study phases, the proportion of patients with a treatment-emergent abnormal increase in pulse rate (≥15 bpm relative to baseline to a value ≥100 bpm) was low (<9%) and similar for the esketamine + oral AD and oral AD + placebo groups.

8.9.2. Adverse Events Related to Cardiovascular Safety

Adverse events related to cardiovascular safety included an examination of TEAE grouped terms related to increased blood pressure and increased heart rate (preferred terms included for each type of event are listed in Appendix 11). TEAEs related to increased heart rate occurred at low incidence rates (<3%) across the Phase 3 studies/study phases (Table 42). By comparison, TEAEs related to increased blood pressure were reported at higher frequencies following treatment with esketamine + oral AD compared to oral AD + placebo in the controlled Phase 3 studies/study phases. Across the study phases in the open-label long-term safety study SUSTAIN-2, TEAEs related to increased blood pressure were reported for 13.0% of patients receiving esketamine + oral AD.

In the double-blind phases of Phase 2 dose-response study SYNAPSE, the reporting rate for TEAEs related to increased blood pressure was 13.1% across all esketamine groups and 7.4% for the placebo group; no TEAEs related to increased heart rate were reported in the double-blind phases of this study.

Table 42: Overall Incidence of Treatment-emergent Adverse Events in the Categories of Increased Blood Pressure and Increased Heart Rate in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Increased Blood Pressure	Increased Heart Rate
TRANSFORM-1 (Fixed-Dose)				
Induction Phase	Esk 56 mg:	115	10 (8.7%)	2 (1.7%)
	Esk 84 mg:	116	14 (12.1%)	3 (2.6%)
	Placebo:	113	5 (4.4%)	1 (0.9%)
TRANSFORM-2 (Flexible-Dose)				
Induction Phase	Esk 56-84 mg:	115	12 (10.4%)	0
	Placebo:	109	1 (0.9%)	0
Pooled TRANSFORM-1/2				
Induction Phase	Total Esk[a]:	346	36 (10.4%)	5 (1.4%)
	Total Placebo:	222	6 (2.7%)	1 (0.5%)
TRANSFORM-3				
Induction Phase	Esk 28-84 mg:	72	10 (13.9%)	0
	Placebo:	65	4 (6.2%)	0
SUSTAIN-1				
Induction Phase	Esk 56-84 mg:	437	40 (9.2%)	2 (0.5%)
Optimization Phase	Esk 56-84 mg:	455	30 (6.6%)	3 (0.7%)
Maintenance Phase	Esk 56-84 mg:	152	13 (8.6%)	0
	Placebo:	145	5 (3.4%)	0
SUSTAIN-2				
Induction Phase	Esk 28-84 mg:	779	71 (9.1%)	6 (0.8%)
Optimization/Maintenance Phase	Esk 28-84 mg:	603	64 (10.6%)	9 (1.5%)
Induction and Optimization/Maintenance Phases	Esk 28-84 mg:	802	104 (13.0%)	14 (1.7%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
Note: TEAEs in the category of Increased Blood Pressure included *blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, hypertension and hypertensive crisis.* TEAEs in the category of Increased Heart Rate included: *heart rate increased, tachycardia.* Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
[a] Total esketamine row includes both the fixed-dose and flexible-dose esketamine groups.

Among esketamine-treated patients in the Phase 3 studies, there were 3 patients with a severe TEAE of blood pressure increased and 1 patient with severe TEAEs of hypertensive crisis and sinus tachycardia. One patient experienced a serious adverse event of blood pressure increased and 1 patient experienced serious adverse events of hypertensive crisis and sinus tachycardia. Discontinuation of esketamine treatment due to TEAEs of increased blood pressure or tachycardia occurred in <2% of patients across studies/study phases.

At least 90% of the reported TEAEs of increased blood pressure occurred on the day of dosing in the Phase 3 studies/study phases and of these, >93% resolved spontaneously the same day. There were 20 esketamine-treated patients who experienced TEAEs of increased blood pressure on the day of dosing that were not reported as resolved on the same day. Further clinical review indicated that for 19 patients objective blood pressure measurements were at or near predose levels by 1.5 hours after dose administration or the patient was considered clinically stable and discharged on the same day with no additional measures (including blood pressure monitoring) required. Esketamine was discontinued in 1 patient due to a TEAE of increased blood pressure that did not resolve the day of dosing; blood pressure values on subsequent days following discontinuation had normalized.

Across all completed and ongoing studies of esketamine, 1 cardiovascular-related death was reported (death due to acute cardiac and respiratory failure in a patient with a history of obesity, hypertension, and vein surgery; see description in Section 8.3.4.1). Serious cerebrovascular TEAEs were reported in 2 of the 1,601 esketamine-treated patients across the Phase 3 studies (lacunar stroke on the day of the first esketamine dose with plausible mechanism of microatheroma; cerebrovascular accident occurring in the posttreatment follow-up phase 25 days after the last esketamine dose in a patient with vasculitis).

8.9.3. Electrocardiographic Changes

Twelve-lead ECGs were obtained from treated patients in the Phase 1 thorough QTc study and all completed Phase 2 and 3 studies and were read and interpreted by a central facility. Special attention was paid to the QT interval corrected by Fridericia's equation (QTcF interval), as this formula was considered more clinically relevant and accurate given the known association of esketamine with heart rate elevations. QTc limits were in accordance with ICH E14 guidelines.[47,48]

Phase 1 Thorough QTc Study

Esketamine does not adversely impact cardiac repolarization or the prolong the QTcF interval. The effect of esketamine (84 mg nasal spray and 0.8 mg/kg esketamine infused IV over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy patients (mean, 39 years; range: 18-54) (ESKETINTRD1013). The upper bound of the 90% CI for the largest placebo-adjusted, baseline-corrected QTcF interval was below the 10-msec threshold specified in the ICH E14 guideline[47,48] at all the time points. Maximum esketamine concentrations in plasma produced by the IV infusion were approximately 3-times higher than the maximum concentrations produced by the nasal 84 mg dose.

Phase 2 and 3 Studies

In all completed Phase 2 and 3 studies in TRD, there was a single patient treated with esketamine + oral AD (in SUSTAIN-2) with a QTcF value >500 msec. This patient had a normal Day 1 predose QTcF interval value (391 msec); study treatment was discontinued due to this finding per protocol requirements and the QTcF value returned to predose values.

Increases in the QTcF interval of >60 msec were infrequent (0% to 0.5%) among esketamine-treated patients 18-64 years old in the completed Phase 2 and 3 studies and did not occur at higher rates than for oral AD + placebo groups in the pooled studies TRANSFORM-1/2 or for the double-blind maintenance phase of SUSTAIN-1.

In TRANSFORM-3, 3 patients ≥65 years old (4.2%) in the esketamine + oral AD group (versus none in the oral AD + placebo group) had an increase in QTcF of >60 msec. The increased QTcF value in all 3 patients was asymptomatic.

Across the completed Phase 2 and 3 studies in TRD, there were no clinically relevant mean changes in ECG parameters (heart rate, PR duration, QRS duration, QTcF intervals, QT intervals

corrected by Bazett's equation, QT duration, and RR duration) from average predose values over time in any group.

8.10. Effects on Respiratory Rate and Oxygen Saturation

Treatment with esketamine nasal spray had no clinically meaningful effects on respiratory rate or oxygen saturation as measured by pulse oximetry. There were no cases of respiratory depression or TEAEs that required cardiopulmonary resuscitation or other medical intervention reported in any esketamine-treated patient in the Phase 2 or 3 studies in TRD.

8.11. Readiness for Discharge

Based upon the potential for esketamine to produce treatment-emergent, transient sedation, dizziness, dissociation symptoms or cognitive changes in some patients, it is recommended that at each esketamine treatment session, patients remain under observation under the supervision of a healthcare professional until ready for discharge (based on clinical judgment and individualized for each patient).

In the Phase 3 studies, a patient's readiness to be discharged from the study site on each nasal spray dosing day was assessed at 1 and 1.5 hours postdose (with assessments repeated every 15 minutes as necessary) based on the clinician's assessment of the patient's clinical status (e.g., sedation, blood pressure, and other adverse events). The proportion of patients ready for discharge without any adverse clinical outcome or complications was >90% by the 1.5-hour postdose timepoint in each Phase 3 study. Across the Phase 3 studies, there were 12 cases (in 7 patients) in which patients were considered ready for discharge at 4 hours after dose administration or later.

8.12. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

The Sponsor has conducted dedicated clinical studies to help inform product labeling with respect to a patient's ability to drive vehicles or operate machinery after use of esketamine nasal spray. Results from these studies guided recommendations in the esketamine product labeling that patients not engage in potentially hazardous activities such as driving and operating machinery after esketamine dosing until the next day following a restful sleep (Section 10.2.2).

The effects of esketamine (84 mg) on driving performance the day after dosing was assessed in patients with MDD (Study 54135419TRD1019). The primary parameter for assessment of performance in the on-the-road driving studies was the standard deviation of the lateral position (SDLP; i.e., "weaving" of the car), which has shown to be a sensitive measure to demonstrate dose dependent differences from placebo for alcohol and psychoactive drugs.[82,111] The SDLP after esketamine administration did not differ from placebo based on results from 25 patients who received esketamine and placebo. In contrast, ingestion of ethanol significantly impaired driving performance when compared to placebo in Study 54135419TRD1019.

Also relevant to an assessment of potential effects of esketamine on a patient's ability to drive or operate machinery are data from the Phase 1 study ESKETINTRD1005, which evaluated cognition and sleepiness in healthy volunteers after a single dose of esketamine 84 mg (see Section 8.8). Results from this study showed that esketamine was associated with an early, transient decline in cognitive function compared with placebo; cognitive function in esketamine-treated patients was restored to levels comparable to placebo-treated patients by 2 hours postdose. Esketamine also resulted in a more sustained, though transient, increase in sleepiness compared to placebo as assessed using the Karolinska Sleepiness Scale, with significant effects resolving by 4 hours postdose.

TEAEs of the preferred term of motor vehicle accident or road traffic accident were reported for 5 patients who had received esketamine treatment (including 1 during the posttreatment follow-up phase) across the completed Phase 2 and 3 studies in patients with TRD and MDD at imminent risk for suicide. The 5 events occurred 28 hours, 4 days, 5 days, 9 days, and 40 days after patients received a dose of esketamine. None of these events were considered related to esketamine treatment by the investigator.

8.13. Interstitial or Ulcerative Cystitis

There were no cases of interstitial cystitis (including ulcerative cystitis) in any of the clinical trials with esketamine.

Severe and permanent ulcerative cystitis is an identified complication of ketamine administration, particularly among daily recreational users of the drug.[73] Data from in vitro studies suggest that ketamine-induced toxicity to urothelial cells is associated with prolonged elevation of cytosolic calcium concentration triggered by ketamine urinary concentration >1 mmol/L.[5] To achieve this urinary concentration, a young adult with an average voiding rate of 6 × 300 mL per day would need to take more than 1 g of ketamine per session, and these high ketamine doses would need to be taken nearly daily so that the bladder did not have time to repair between sessions. The highest recommended esketamine dose for use in the treatment of TRD is 84 mg, administered twice weekly or at lower frequencies, ensuring a large margin of safety for this serious side effect.

8.14. Hepatic Safety

There was no evidence of treatment-emergent hepatotoxicity associated with esketamine nasal spray. Across the completed Phase 2 and 3 studies in TRD, increases in alanine aminotransferase and/or aspartate aminotransferase of greater than 3 times the upper limit of normal occurred at low rates among the esketamine + oral AD treatment groups (i.e., <2% in all studies/study phases). Consideration should be given to that fact that, in all Phase 3 studies, esketamine was systematically given with a new oral AD (duloxetine, escitalopram, sertraline, or venlafaxine extended release), and that transaminase increases as well as more severe hepatotoxicity reactions have been reported for some of these drugs.[25,112]

The observed increases in alanine aminotransferase / aspartate aminotransferase in the Phase 3 studies in TRD were primarily asymptomatic, transient, and resolved spontaneously without worsening while treatment with esketamine + oral AD continued. No persistent increases in liver transaminases were observed. A qualitative assessment of the individual cases showed that the majority of the patients with markedly elevated transaminases had an alternative etiology (e.g., co-medications with known hepatotoxic effect such as statins and acetaminophen; underlying disease such as viral hepatitis B, fatty liver, cholelithiasis; or history of excessive alcohol consumption).

Across all completed Phase 1, 2, and 3 studies with esketamine, no patient met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law. Further, no cases of treatment-emergent elevated total serum bilirubin levels to >2 times the upper limit of normal were identified in esketamine-treated patients.

Results of the Phase 1 single-dose pharmacokinetic study ESKETINTRD1011 indicated that the safety profile in patients with mild or moderate hepatic impairment was similar to patients with normal hepatic function. There were no deaths, serious TEAEs, persistent TEAEs, or discontinuations due to TEAEs reported in this study.

9. ABUSE POTENTIAL OF ESKETAMINE NASAL SPRAY

Abuse potential of a drug is characterized by actual abuse, misuse, or diversion of a drug, similarity in pharmacologic effects of the drug to other controlled substances, and whether the drug presents or is likely to present a hazard to the public health, affecting individuals and the community.

Ketamine is abused recreationally for its euphoric and perception-altering effects, typically by snorting (insufflation), or by oral, intranasal, intravenous or intramuscular administration.[29,93] The large majority of recreational ketamine users have a history of polydrug use. Patterns of recreational ketamine abuse vary among individuals. In one study, a group of frequent ketamine abusers (defined as using the drug more than 4 times per week) reported use of high doses (average of 2.8 g) at a high frequency (average of 20 days/month), while a group of infrequent abusers (defined as using the drug less than 4 times per week but at least once a month) reported using lower doses (average of 1.3 g) at a lower frequency (average of 3 days/month).[71]

Evidence from the literature suggests that the majority of esketamine and ketamine behavioral effects, including perceptual and dissociative symptoms and euphoria, are primarily driven by NMDA receptor blockade. Esketamine and ketamine show qualitatively similar pharmacological binding profiles, suggesting the 2 drugs are similar in terms of abuse potential. This was confirmed in the Phase 1 human abuse potential study (54135419TRD1015) conducted in otherwise healthy, nondependent, recreational polydrug users of perception-altering drugs (including ketamine) (n=41) in which measures of drug liking produced by 84 mg and 112 mg doses of esketamine nasal spray were similar to those produced by IV infusion of ketamine 0.5 mg/kg. Both compounds demonstrated significantly greater scores than placebo on subjective ratings of "drug liking" and on other measures of subjective drug effects.

In view of its abuse potential, ketamine as well as its salts, isomers and salts of isomers are controlled under Schedule III of the Controlled Substances Act in the US. As esketamine is an enantiomer of ketamine, it is also a Schedule III compound. All evidence taken together indicates that esketamine is appropriately characterized as a Schedule III substance in the US, indicating a potential for abuse that is less than substances in Schedules I or II, and indicating that abuse may lead to moderate or low physical dependence or high psychological dependence.

If approved, a comprehensive risk mitigation program will be in place to address the abuse potential of esketamine.

- In the US, esketamine nasal spray will be distributed directly to hospitals and certified clinical settings (such as physician's offices and clinics) and administered under the supervision of health care professionals.
- Esketamine nasal spray will not be available at community/retail pharmacies or shipped directly to patients; this is expected to mitigate the risk of diversion of the esketamine product.
  - No evidence of abuse, misuse or overdose was observed in the esketamine development program with a TRD population (note, patients with moderate to severe substance use disorder were excluded from the studies), and possible diversion was minimal; in the completed Phase 3 clinical studies, the incidence of unaccounted for clinical supply kits was <0.1%.
- Additional risk mitigation plans include a proposed Risk Evaluation and Mitigation Strategy (REMS) that will include requirements for certification of outpatient healthcare settings and pharmacies that dispense esketamine, a controlled distribution program, and dissemination of REMS communication materials (see Section 10.1.1). In addition, the proposed REMS will mitigate the risk of administration without appropriate monitoring by a healthcare professional through education.
- Unlike ketamine, which is supplied in multiple-dose vials, the nasal spray device for esketamine is manufactured as a disposable, single-use, single-dose product that is difficult to disassemble and produces a minimal residual amount of drug after it is used (Section 10.1.2). This design is intended to mitigate the risks of abuse and misuse of esketamine.

9.1. Recreational Abuse of Ketamine

Nationally the rate of illicit ketamine use is low compared with other hallucinogens and more widely abused substances. This relatively low rate has persisted even though ketamine was approved nearly 50 years ago and the number of clinics providing off-label IV ketamine to treat patients with major depression has steadily increased.

According to the national estimates provided by the National Survey on Drug Use and Health, 1.4% of adults (18 years and older) reported lifetime illicit use of ketamine in 2017 (1.4% in 2016).[104] Ketamine use was lower in this population compared with the estimates of lifetime illicit use (2017) for other hallucinogens including lysergic acid diethylamide (10.4%), psilocybin (mushrooms; 9.6%), ecstasy (3,4-methylenedioxymethamphetamine; 7.7%),

mescaline (3.1%), phencyclidine (angel dust, PCP; 2.4%) and peyote (2.3%).[104] In comparison, national estimates of misuse in 2017 of more widely abused products such as pain relievers were 11.8% for hydrocodone products, 13.5% for oxycodone products, and 10.0% for codeine 18 years and older.[104]

Diversion and trafficking (including via the internet) is considered the primary source of illicit ketamine.[107] The commercial distribution of ketamine is limited to hospital and clinic settings, which limits the extent of diversion. However, diversion and theft of ketamine from veterinary clinics have been reported.[32] Misuse of anesthetic drugs of abuse by anesthesiologists and other medical/health care professionals have been reported, including ketamine abuse and psychological dependence.[15,44]

For the past 2 years, the Sponsor has been monitoring reports on ketamine use from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) system, which uses a multifaceted mosaic approach to collect information across multiple data sources. During the past 2 years, the RADARS® reports indicate that the number of ketamine-containing posts in the US was low and remained stable despite an increase in the number of clinics providing IV ketamine to treat patients with depression.

9.2. Abuse Potential Assessment in the Esketamine Nasal Spray Clinical Development Program

9.2.1. Human Abuse Potential Study 54135419TRD1015

The primary objective of the human abuse potential study 54135419TRD1015 was to evaluate the abuse potential of esketamine in adult, nondependent, recreational polydrug users of perception-altering drugs (e.g., lysergic acid diethylamide, cannabinoids, ketamine, ecstasy [3,4-methylenedioxy-methamphetamine], phencyclidine, psilocybin, and ring-substituted amphetamines). This was a single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized crossover study. Participants were to have had at least 10 total lifetime occasions of use of perception-altering drugs and were to like the drugs' effects. Additionally, eligible participants reported having used racemic ketamine at least once in their lifetime and having used a perception-altering drug within 3 months prior to the screening phase, both without perceived moderate or severe adverse effects.

A qualification session was included as part of eligibility assessment to screen out participants who did not demonstrate discrimination between the positive control drug (0.5 mg/kg IV racemic ketamine [40-minute infusion]) and placebo based on predefined criteria, including a ≥15-point difference relative to placebo in maximum response on Drug Liking at the Moment. Of the 55 participants who were evaluated in the qualification session, 41 participants completed the qualification session, and 14 participants were withdrawn.

The remaining 41 participants continued in a randomized, single dose, double-blind, double-dummy, placebo-controlled treatment phase, in which 4 treatments were administered in a cross-over manner (i.e., 1 treatment in each period) to measure drug likability. Participants were

randomly assigned to 1 of 4 treatment sequence groups and received the concurrent IV treatments (40-minute infusions) and intranasal treatments as follows:

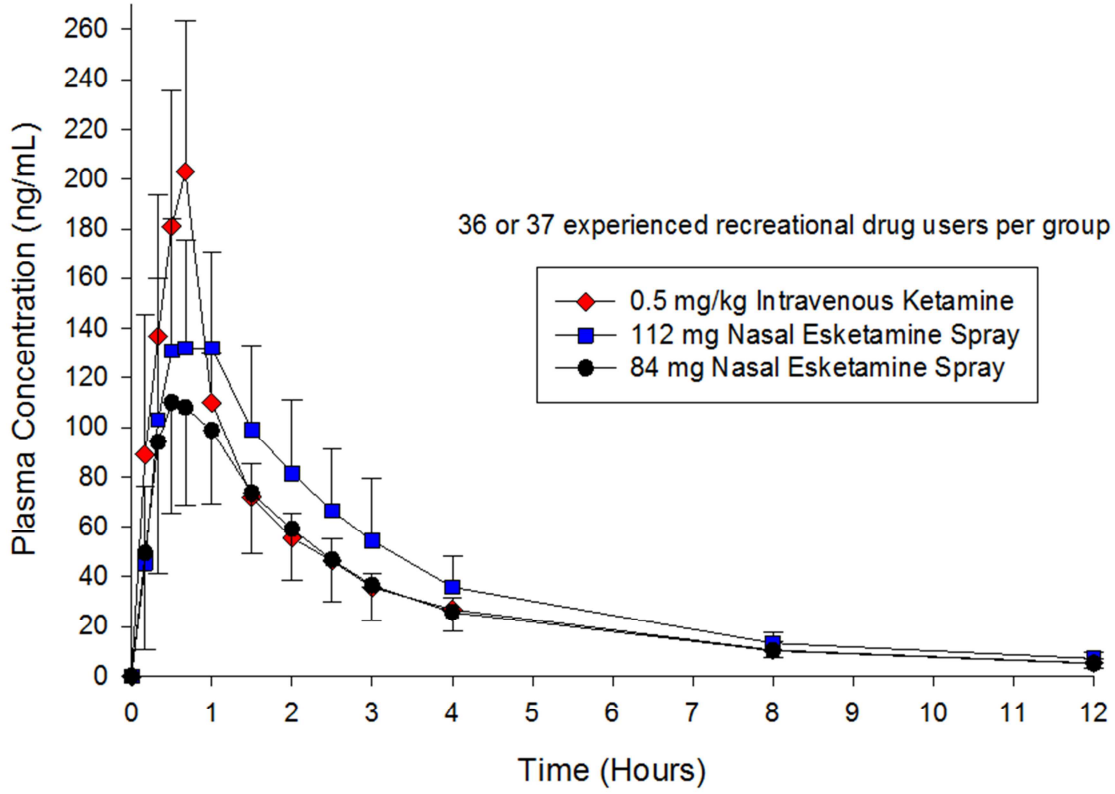
- IV placebo and placebo nasal spray
- 0.5 mg/kg IV racemic ketamine and placebo nasal spray
- IV placebo and 84 mg of esketamine nasal spray
- IV placebo and 112 mg of esketamine nasal spray

A total of 34 participants completed the treatment phase and 7 participants were withdrawn.

Pharmacokinetics

The mean pharmacokinetic profile after administration of IV racemic ketamine and esketamine nasal spray are presented in Figure 34.

Figure 34: Mean (± SD) Plasma Concentration-Time Curves of Ketamine After IV Administration of Racemic Ketamine at 0.5 mg/kg and Esketamine After Intranasal Administration of 84 mg and 112 mg (Study 54135419TRD1015)



SD=standard deviation

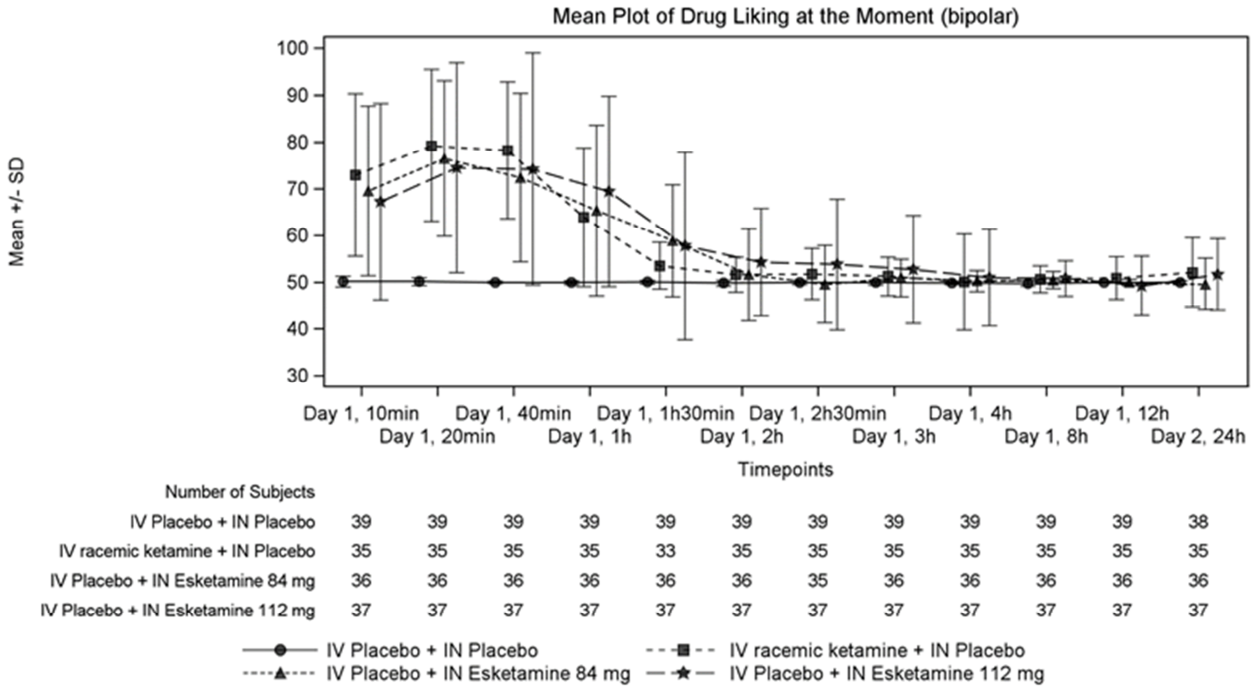
Drug Liking at the Moment

The primary measure of maximum score for Drug Liking at the Moment was assessed by a 100-point bipolar VAS. Greater responses for IV ketamine (in the direction of liking >50) relative to placebo (scores at midpoint 50) were readily apparent for assessments conducted during the initial 1-hour postdose interval. The mean maximum score was 84.24 for IV ketamine. Mean

differences in least-squares (LS) means between IV ketamine and placebo were statistically significant (p<0.0001) from 10 minutes to 1-hour after dosing, confirming assay sensitivity.

The mean Drug Liking at the Moment scores for esketamine were higher than placebo, particularly within 1 hour after administration (Figure 35). The mean maximum scores for the 84-mg and 112-mg doses of esketamine were 83.52 and 84.64, respectively, and were statistically significantly greater than that for placebo (50.53; p<0.0001). The mean maximum Drug Liking at the Moment scores produced by the 84-mg and 112-mg esketamine doses were not statistically significantly different from the scores produced by IV ketamine (p=0.7515 and p=0.8584, respectively).

Figure 35: Mean Plot of Drug Liking at the Moment (bipolar) Over Time; Treatment Phase; Pharmacodynamic Analysis Set (Study 54135419TRD1015)



IN=intranasal; IV=intravenous; SD=standard deviation

Overall Drug Liking

The measure for Overall Drug Liking was assessed using a 100-point bipolar VAS at 2 time points: on Day 1, 8 hours after dosing, and on Day 2, 24 hours after dosing. At each time point, the mean (SD) scores for IV ketamine and 84 mg and 112 mg esketamine were similar and numerically higher than the placebo at 8 hours and 24 hours after dosing (Table 43).

Table 43: Overall Drug Liking Visual Analogue Scores (Study 54135419TRD1015)

	Mean (SD)			
Time Point	0.5 mg/kg IV Ketamine	84 mg Intranasal Esketamine	112 mg Intranasal Esketamine	Placebo
N	35	36	37	39
Day 1, 8 hours	73.3 (17.48)	71.9 (16.57)	72.3 (21.42)	50.7 (7.00)
Day 2, 24 hours	73.2 (17.43)	68.0 (21.61)	72.9 (21.68)	51.2 (7.71)

IV = intravenous; SD=standard deviation

Take Drug Again

The measure for Take Drug Again was assessed using a 100-point bipolar VAS. The mean (SD) scores for IV ketamine and 84 mg and 112 mg esketamine were numerically higher than placebo at 8 hours and 24 hours after dosing (Table 44). In addition, the mean scores at each time point were numerically similar for each dose of esketamine and ketamine.

Table 44: Take Drug Again Visual Analogue Scores (Study 54135419TRD1015)

	Mean (SD)			
Time Point	0.5 mg/kg IV Ketamine	84 mg Intranasal Esketamine	112 mg Intranasal Esketamine	Placebo
N	35	36	37	39
Day 1, 8 hours	74.6 (19.56)	73.4 (18.32)	74.1 (25.72)	48.9 (13.20)
Day 2, 24 hours	74.1 (18.00)	70.4 (20.96)	75.4 (20.42)	49.3 (12.46)

IV = intravenous; SD=standard deviation

Summary

Single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug IV ketamine (0.5 mg/kg infused over 40 minutes) produced numerically greater scores that were statistically significant, relative to placebo on subjective ratings of "drug liking" and other subjective drug effects. Drug liking produced by both doses of esketamine nasal spray were similar to those produced by IV ketamine.

9.2.2. Abuse Potential Assessment in Phase 2 and 3 Studies

Treatment-emergent Adverse Events Suggestive of Abuse Potential

Data from all clinical studies (Phase 1, 2, and 3) with esketamine nasal spray were examined for the occurrence of adverse events related to the central nervous system suggestive that the drug might be sought out by patients for abuse purposes in accordance with FDA's guidance on assessment of a drug's abuse potential.[108] These potential abuse-related terms are associated with esketamine's pharmacology and were identified by the Sponsor prior to the start of the Phase 3 program in collaboration with FDA and the Controlled Substance staff based on the known properties of esketamine and ketamine (see Appendix 11).

Across all clinical studies, there were no reported TEAEs (individual preferred terms) of overdose or drug abuse. Furthermore, there were no reports from the investigational sites of any

patients engaging in drug-seeking behavior or requesting an increase in the frequency of treatment sessions (as a potential early indicator of drug-seeking behavior).

Approximately one-half of patients treated with esketamine in the Phase 2 and 3 studies reported at least 1 TEAE suggestive of abuse potential after dosing; events of dizziness, somnolence, and dissociation were the most common. As reviewed in Section 8.3.2, these symptoms are predominantly reported shortly after dosing on the day of esketamine administration, are transient and self-limiting, and mild or moderate in intensity. Dissociation, dizziness, sedation, euphoric mood, feeling abnormal, and feeling drunk are identified as adverse drug reactions for esketamine nasal spray (see Section 8.3.2).

Symptoms of Potential Withdrawal

Levels of esketamine in the circulation do not accumulate with twice-weekly or lower dosing frequency (Section 4.1). Thus, if dosed as proposed in the USPI, no clear withdrawal syndrome is expected after discontinuation of esketamine.

While there is no specific withdrawal syndrome described for ketamine in the literature among frequent ketamine users, in one study, 12 of 30 daily ketamine users reported withdrawal symptoms characterized by craving, anxiety, shaking, sweating and palpitations when they stopped using ketamine.[73] There is no published scale that measures ketamine specific withdrawal symptoms given its poor characterization. The PWC-20 was developed as a reliable and sensitive instrument to assess benzodiazepine-like discontinuation symptoms.[86] This scale includes some of the symptoms that have been reported with ketamine withdrawal by case reports. In the absence of a more specific scale, all Phase 3 studies included the PWC-20 to systematically assess the risk of dependence with short- and long-term use of esketamine nasal spray.

Across studies, the changes in withdrawal symptoms assessed by the PWC-20 after cessation of esketamine + oral AD treatment were consistent with observed changes in symptoms of depression and anxiety. Reported symptoms were primarily mild to moderate in severity. New worsening of depression symptoms was observed mostly in patients who discontinued treatment due to lack of therapeutic response. Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome in the longer-term studies, i.e., at 1 or 2 weeks after cessation of esketamine treatment in SUSTAIN-1 or at 1, 2, or 4 weeks after cessation of esketamine treatment in SUSTAIN-2.

10. RISK MITIGATION STRATEGIES

10.1. Risk Mitigation Strategies for Misuse and Abuse of Esketamine Nasal Spray

Following careful consideration of the potential for misuse and abuse of esketamine, the Sponsor proposes a comprehensive set of measures to mitigate these risks, which include activities to be covered under the proposed REMS, in addition to other measures, as described below.

10.1.1. Measures Covered Under the REMS

Certification of Outpatient Healthcare Settings and Pharmacies That Dispense Esketamine Nasal Spray

Outpatient healthcare settings and eligible pharmacies must be certified in the REMS to be able to receive and/or dispense esketamine. Certification will be achieved via completion of the Healthcare Setting and Pharmacy Enrollment Form by the authorized representative for an outpatient healthcare setting or pharmacy, who agrees to coordinate the requirements of the esketamine REMS.

To mitigate risks of abuse and misuse, the authorized representative must complete the certification process on behalf of the outpatient healthcare setting/pharmacy and must agree to establish processes and procedures to ensure that all relevant staff are educated about the potential risks of abuse and misuse and that esketamine must be self-administered by the patient under the supervision of a healthcare professional with appropriate postdose monitoring. The authorized representative must also agree to establish processes and procedures to ensure that esketamine is only dispensed to a healthcare professional and not dispensed or given to a patient to take home, and not distributed, transferred, loaned, sold, or dispensed to a non-REMS-certified outpatient healthcare setting or outpatient pharmacy.

Controlled Distribution Program

Esketamine will only be available through a controlled distribution program to hospitals and REMS-certified outpatient healthcare settings and pharmacies.

Full Line Wholesalers and Specialty Distributors

The Sponsor plans to restrict esketamine nasal spray distribution to a limited number of selected Full Line Wholesalers and Specialty Distributors that are properly licensed and Drug Enforcement Administration (DEA)-registered within their respective states of practice. All Full Line Wholesalers and Specialty Distributors must:

- have internal policies and processes to handle all aspects of federal and state requirements for handling of controlled substances, including a "suspicious order monitoring" program
- establish processes and procedures, including training of staff involved to ensure that esketamine nasal spray is distributed only to hospitals/institutions, and REMS-certified outpatient pharmacies

Outpatient Healthcare Settings: Mental Health Clinics and Physician Offices

Mental health clinics/physician offices must designate an authorized representative to complete the REMS certification process for that healthcare setting as described above. Only after completion of the REMS certification can the healthcare setting be allowed to order and receive product from distributors and/or pharmacies, dispense product, and provide supervised patient treatment of esketamine nasal spray. The Sponsor will provide the list of REMS-certified sites of care to the Sponsor's wholesaler/distributor partners.

Outpatient Pharmacies

Outpatient pharmacies that wish to receive product from wholesalers/distributors and dispense esketamine will be required to complete the REMS certification process with a designated authorized representative, as described above for healthcare settings.

For healthcare settings without a co-located/onsite pharmacy, the Sponsor has received permission from the DEA to allow specialty pharmacies, selected by the Sponsor and certified in the REMS, to deliver patient-specific esketamine nasal spray directly to prescribing practitioners who do not have co-located pharmacies. DEA would consider it permissible under the Controlled Substances Act and DEA regulations for the pharmacy to deliver the controlled substance to the practitioner, at a registered location, provided DEA conditions are met. For the purposes of the REMS, all outpatient healthcare settings must be certified in the REMS to receive esketamine.

Retail pharmacies will not be permitted to receive product from wholesalers/distributors and dispense esketamine.

REMS Communication Materials

To inform healthcare professionals about the REMS program and the risks and safe use of esketamine, the Sponsor must disseminate REMS communication materials to outpatient healthcare settings and outpatient pharmacies likely to prescribe or dispense esketamine (including a target audience comprised of psychiatrists, mental health professionals, and pharmacies likely to handle esketamine) to support implementation of the esketamine REMS.

The key messages included in the REMS communication materials support the REMS objectives of ensuring that outpatient healthcare settings and outpatient pharmacies are certified, esketamine is distributed/dispensed only to hospitals and certified outpatient pharmacies and outpatient healthcare settings, and esketamine is not dispensed to a patient to take home for self-administration.

Within 60 calendar days of the date esketamine is first commercially distributed, the Sponsor will send a Dear Healthcare Professional letter with the esketamine REMS Fact Sheet, United States Prescribing Information (USPI), and Medication Guide to the target audience identified above. In addition, the Dear Healthcare Professional letter and the other REMS materials described above will be distributed to a group of relevant professional societies within 60 calendar days of the REMS approval date. The Sponsor will also disseminate the Dear Healthcare Professional Letter and the esketamine REMS Fact Sheet at professional meetings for 1 year from the date esketamine is first commercially distributed.

The esketamine REMS Website and Call Center will also have the REMS communication materials (Dear Healthcare Professional letter and esketamine REMS Fact Sheet) and other REMS materials, USPI, and Medication Guide available, which can be downloaded or forwarded upon request.

10.1.2. Measures Outside of the REMS

In addition to the above proposed REMS components, the Sponsor's risk minimization plan includes the following measures proposed to be conducted outside of the REMS.

Proposed Product Labeling

The USPI and Instructions for Use will specify that esketamine should be administered under the supervision of a healthcare professional. The product labeling will advise prescribers that during and after administration of esketamine at each treatment session, a healthcare professional should observe the patient until the patient is ready to leave based on clinical judgment. In addition, guidance will be included to instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery until the next day.

The product labeling will warn prescribers that individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of esketamine, recommend caution in prescribing treatment to individuals with a history of substance use disorder, advise monitoring of all patients for signs of abuse or dependence, and recommend periodic re-evaluation of all patients for therapeutic benefit.

Esketamine is not intended for everyday use; the recommended dosing frequency is twice weekly for the first 4 weeks, followed by once weekly for 4 weeks, then individualized to weekly or every 2 weeks. The labeling will provide a recommendation that the dosing frequency during the maintenance phase should be individualized to the lowest frequency to maintain remission or response. Periodic re-evaluation of the need for continued treatment is recommended.

Unique Device Features

The nasal spray device has been designed with the following features to mitigate the risks of misuse and abuse of esketamine:

- Esketamine is supplied as a single-use, disposable nasal spray device containing 28 mg per device. The medication will be supplied in a limited pack size containing 1, 2, or 3 devices to deliver the prescribed dose of 28, 56, or 84 mg, respectively.
- The device does not require priming and delivers only 2 sprays with minimal residual medication remaining (the average residual volume after use is approximately 30 µL or ~4 mg base).
- The indicator feature displays the number of sprays expelled from the device and allows for differentiation between used and unused devices.
- The drug product is contained in a glass vial sealed with a rubber stopper. The stoppered glass vial is seated into a container holder, which is then assembled with the actuator subassembly. The device is difficult to disassemble due to interlocking design features of the actuator subassembly. Substantial force required to pull the device apart (at least 60 Newtons or ~13 lbs), which is a deterrent to disassembly.

Patient Medication Guide

The Sponsor has developed a Medication Guide for patients which will be included in each carton of medication along with the USPI. This is part of an education and training program that will include videos, print materials and a website. The Medication Guide will inform patients that esketamine is to be administered under the supervision of a healthcare professional.

Healthcare Professional Information

The Sponsor has developed a comprehensive education and training program for informing healthcare professionals about the appropriate use of esketamine according to the USPI, including education regarding the known safety profile of esketamine and the requirement for postdose monitoring. This will include an educational program with clinical educators, instructional materials, videos and web-based education.

Controlled Substance Status

Esketamine is a Schedule III controlled substance under the Controlled Substance Act, which imposes regulatory requirements on the manufacturing, distribution, prescribing, dispensing, and administration of controlled substances to prevent abuse and diversion. All evidence taken together indicates that esketamine is appropriately characterized as a Schedule III substance in the US; see further discussion in Section 9.

Monitoring of Ketamine and Esketamine Use

The Sponsor will develop a pharmacovigilance program that will conduct cumulative reviews and analyses of abuse potential adverse events. In addition, reports on ketamine and esketamine use from the RADARS® system or similar services will be used to identify any increases in ketamine and esketamine misuse, abuse, and diversion reporting rates and trends over time.

10.2. Risk Mitigation Strategies for Administration of Esketamine Nasal Spray Without Appropriate Monitoring

During the clinical studies, certain adverse reactions were commonly observed after administration of esketamine nasal spray (for example, elevations in blood pressure, dissociative effects, and sedation; see Section 8.3.2). As a result, the labeling recommends that patients should be monitored by a healthcare professional at each treatment session to assess when the patient is considered clinically stable and ready to leave the office or healthcare setting.

The Sponsor proposes the measures outlined below to mitigate the risks from administration of esketamine without appropriate monitoring.

10.2.1. Measures Covered Under the REMS

Certification of Outpatient Healthcare Settings and Pharmacies That Dispense Esketamine Nasal Spray

As described in Section 10.1.1, outpatient healthcare settings and pharmacies must be certified in the REMS to be able to receive and/or dispense esketamine. To mitigate the risk of administration without appropriate monitoring per the USPI, the authorized representative at the

certified outpatient healthcare setting must ensure that all relevant staff are educated about REMS requirements and the safe use of esketamine, including the need for supervising patients during self-administration and monitoring patients for treatment-emergent transient dissociative and blood pressure changes associated with esketamine administration. The Sponsor will develop an annual audit plan for certified healthcare settings to ensure all REMS processes and procedures are in place and functioning.

Controlled Distribution Program

As described in Section 10.1.1, only after completion of the REMS certification can the healthcare setting be allowed to order and receive product from distributors and/or pharmacies, dispense product, and provide supervised patient treatment of esketamine nasal spray.

REMS Communication Materials

To inform healthcare professionals about the REMS program and the risks and safe use of esketamine, the Sponsor must disseminate REMS communication materials (including a REMS Dear Healthcare Professional Letter, REMS Fact Sheet and REMS Website) to outpatient healthcare settings and outpatient pharmacies likely to prescribe or dispense esketamine to support implementation of the esketamine REMS (see details in Section 10.1.1). The REMS communication materials will support the REMS objective of ensuring that healthcare settings are educated about the requirement for patient monitoring for treatment-emergent transient dissociative and blood pressure changes after esketamine administration.

10.2.2. Measures Outside the REMS

Proposed Product Labeling

Effects on Blood Pressure

As a result of the observed transient elevations in blood pressure seen with esketamine (Section 8.9.1), the proposed product labeling recommends that blood pressure is monitored prior to esketamine dosing. For patients whose blood pressure values are judged to be elevated prior to dosing (as a general guide: >140/90 mm Hg for those <65 years; >150/90 mm Hg for those ≥65 years), lifestyle and/or pharmacologic therapies to reduce blood pressure are appropriate prior to initiating esketamine therapy. Blood pressure should also be monitored after each esketamine dose until it returns to acceptable levels. If blood pressure remains too high, assistance should promptly be sought from practitioners experienced in blood pressure management, and patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

The proposed product labeling also indicates that use of esketamine in the following patient groups is contraindicated as an acute increase in blood pressure can pose a serious risk:

- patients with known aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
- patients with known history of intracerebral hemorrhage

Additionally, esketamine should be used with caution in patients with:

- known uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability
- a history of conditions associated with increased intracranial pressure (e.g., brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts)
- hyperthyroidism that has not been sufficiently treated (due to the increased risk of hypertension and tachycardia in this patient group)

Furthermore, the proposed labeling cautions that patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing esketamine and that treatment with esketamine be initiated only if the benefit outweighs the risk. Examples of conditions which should be carefully considered before initiating esketamine therapy include:

- unstable or poorly controlled hypertension
- a history (within 6 weeks) of a cardiovascular event (including myocardial infarction); it is recommended that those with a history of myocardial infarction be clinically stable and free of cardiac symptoms prior to beginning esketamine therapy)
- a history (within 6 months) of ischemic stroke or transient ischemic attack
- hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation
- New York Heart Association Class III-IV heart failure of any etiology

Dissociative and Perceptual Changes

In the proposed product labeling, patients will be informed that dissociative/perceptual changes (including perception of distortion of time and space and illusions), derealization and depersonalization are common psychological effects of esketamine. Patients will be further advised that

- These adverse reactions were reported as transient and self-limited and occurred on the day of dosing.
- Dissociation was reported as severe in intensity at the incidence of less than 4% across studies.
- Dissociation symptoms typically resolved by 1.5 hours after dosing and the severity tended to reduce over time with repeated treatments.
- Dissociative and perception disturbances may decrease after a few treatment sessions.

Sedation and Somnolence

The proposed product label will include a brief description of the adverse reactions of sedation and somnolence reported in clinical studies with esketamine:

- Events of sedation and somnolence were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day.

- The sedative effects typically resolved by 1.5 hours after dosing.
- Rates of somnolence were relatively stable over time during long-term treatment.
- In the cases of sedation, no symptoms of respiratory distress were observed, and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges.

Potential for Cognitive and Motor Impairment

As esketamine nasal spray has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during clinical studies, the proposed product labeling cautions that these effects may impair attention, judgment, thinking, reaction speed and motor skills. Furthermore, the labeling recommends that patients should be monitored by a healthcare professional at each treatment session to assess when the patient is considered clinically stable and ready to leave the office or healthcare setting. The need for monitoring is individualized for each patient; no minimum monitoring period is specified in the proposed product label.

Effect on Driving

A Phase 1 clinical study in patients with MDD assessed the effects of esketamine on the ability to drive (see Section 8.12). Based on the results of this study, the proposed product labeling instructs patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep.

Patient Medication Guide

A Medication Guide for patients will be included with the medication and the USPI to inform and educate patients about:

- The risk of common adverse reactions such as dissociative and perception disturbances and blood pressure elevations after administration of esketamine nasal spray.
- The need for observation by a healthcare professional during and after esketamine administration until the healthcare professional considers the patient to be stable.
- The need to monitor the patient's blood pressure before esketamine dosing and at various times after dosing; patients also will be warned that if their blood pressure values increase significantly after esketamine dosing and remain elevated for more than a few hours, the doctor may send the patient to another doctor for evaluation.
- Not engaging in activities which require complete alertness, such as driving a motor vehicle or operating heavy machinery, after administration of esketamine until the next day following a restful sleep.

Healthcare Professional Information

Healthcare professionals will be informed about the appropriate use of esketamine according to the USPI, including further information about:

- The need for observation of patients during and after esketamine administration until the patient is clinically stable
- Blood pressure values that may trigger additional measures
- The influence of esketamine on the patient's ability to drive due to effects on attention and motor skills as described above in Section 8.12

The healthcare professional information will include an educational program with nurse educators, instructional materials, videos and web-based education.

11. BENEFIT-RISK EVALUATION

11.1. Medical Need and Available Treatments

- Approximately one-third of patients with major depression are not adequately treated with currently available medications, despite the availability of many AD agents.[88,116]
  - Treatment-resistant depression is a principal contributor to the morbidity and mortality associated with depression.[49] Compared to patients with MDD who respond to AD treatment, patients with TRD show pronounced decreases in daily functioning and health-related quality of life, 7-fold higher rates for suicide attempts, and 2-fold higher rate of relapse.[28,38,88]
  - Even for those patients with TRD who do eventually respond after multiple treatments, relapse rates are quite high (up to 80% within 12 months).[37,88,89]
  - Additionally, TRD is associated with higher direct and indirect costs due to increased use of healthcare resources and lost work productivity compared to those with MDD who respond to AD treatment.[3]
- There is a significant unmet medical need for a novel TRD treatment.
  - In the US, only a single FDA-approved pharmacotherapy for TRD is available (olanzapine/fluoxetine combination, Symbyax), and its use is limited by tolerability, especially due to potential side effects of olanzapine.[24]
  - For patients who have a partial response to their current treatment, augmentation with a second agent (e.g., aripiprazole, quetiapine, or brexpiprazole) may be an option; however, the tolerability of these agents also has limitations.[49]
  - The currently available non-pharmacological treatment options for TRD referred to in guidelines on the treatment of depression (electroconvulsive therapy, deep brain stimulation, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and vagus nerve stimulation) have considerable limitations in terms of efficacy and acceptability to patients.[2,21,75,76,77] While electroconvulsive therapy is reported to be effective in TRD,[21] it is associated with significant adverse events including memory loss, seizures, cardiovascular complications and the general complications associated with anesthesia. Recent controlled trials with deep brain stimulation have failed to show efficacy.[31] The availability of transcranial direct current stimulation and repetitive transcranial magnetic stimulation is limited, and evidence to support benefit in patients who are unresponsive to more than 3 or 4 AD treatments is currently lacking.[21] vagus nerve stimulation also has limited evidence of efficacy.[2,77]

11.2. Summary of Benefits for Esketamine Nasal Spray

11.2.1. Beneficial Features of Esketamine Nasal Spray

- Esketamine nasal spray has the potential to address the critical unmet medical need for patients with depression due to its novel mechanism of action. Esketamine is a NMDA receptor blocker hypothesized to modulate glutamate in the brain to restore synaptic function in key brain regions involved in mood. Unlike currently available antidepressants, which primarily target the monoamine system, esketamine targets the glutamate system to directly address the pathophysiology of depression.
- Relative to IV administration, the intranasal route of administration not only offers a non-invasive and more convenient dosing option for patients and physicians but is associated with a reduced likelihood of dosing errors since it is administered as a multiple of a fixed dosage unit (28 mg for esketamine) instead mg per kg dosage, which must be calculated.
- Doses of esketamine nasal spray will be administered intermittently, and the dosing frequency will be individualized to the lowest frequency needed to maintain remission or response of depressive symptoms.
- Esketamine is supplied as a single-use, disposable nasal spray device containing a fixed dose in each device. The device does not require priming.

11.2.2. Demonstrated Benefits of Esketamine Nasal Spray

- The Sponsor conducted 1 controlled, adjunctive Phase 2 dose-response study as well as 4 controlled and 1 uncontrolled Phase 3 studies to investigate the antidepressant effects of treatment with esketamine + an oral AD. Over 1,700 adults were exposed to esketamine in these studies, including 194 patients aged ≥65 years.
- Results from this program show that esketamine works within hours to days to relieve symptoms of depression, achieving high rates of response and remission within the first 4 weeks of starting esketamine plus a newly-initiated oral AD treatment.
  - The onset of improvement in depression symptoms with esketamine was observed as early as 24 hours after the first dose in Phase 2 and 3 studies, and increased in subsequent weeks, with the full antidepressant benefit achieved by Day 28 in Phase 3 studies in adults.
  - The magnitude of the treatment effect after 4 weeks of induction therapy with esketamine + oral AD (LS mean treatment difference vs oral AD + placebo ranging from -3.2 to -4.1) was consistent across the controlled Phase 3 studies with esketamine at the recommended dose range. These treatment differences were similar to those reported in controlled clinical studies of several antidepressants currently approved for patients with an inadequate response to previous AD therapy.
  - While remission is the ultimate goal for the treatment of depression, response is a clinically meaningful result for patients as well. Therefore, both remission and response rates represent important statistics to clinicians to decide whether a treatment effect is meaningful. The differences between the treatment groups in response rate and remission rate showed there is a clinically meaningful benefit for esketamine + oral AD as a greater proportion of patients experienced benefit with esketamine treatment than without. Although the response and remission rates at Day 28 in patients 18-64 years of

age in the oral AD + placebo comparator arm of TRANSFORM-1 and 2 were higher than expected for a population having confirmed nonresponse to multiple oral ADs, the magnitude of the treatment group differences in response rates at Day 28 between the esketamine + oral AD and oral AD + placebo groups are in the range of those considered clinically meaningful for other ADs.[14,66,70]

  - Consistent with observed improvements in clinician-rated symptoms of depression, numerically greater improvements were also observed with esketamine + oral AD therapy compared to oral AD + placebo across complementary patient-reported outcome endpoints in the short-term Phase 3 studies. These patient-reported outcomes measured different aspects of TRD including functional impairment and disability (based on SDS) and severity of depression symptoms as measured by PHQ-9. However, none of the results from patient-reported outcomes could be formally tested for statistical significance.

- An important goal of the TRD clinical program was to determine the lowest frequency of esketamine administration needed to achieve and sustain remission.
  - Results of the maintenance of effect study SUSTAIN-1, using a randomized withdrawal design, demonstrated that, among patients who had achieved stable remission or stable response after 16 weeks of treatment with esketamine + oral AD, randomized continuation of treatment with esketamine provided a statistically significantly longer time to relapse relative to discontinuation of esketamine. The hazard ratio for time to relapse for continuation versus discontinuation of esketamine was 0.49 in stable remitters and 0.30 in stable responders.
- The clinical studies further demonstrated that esketamine nasal spray can reduce depressive symptoms with intermittent dose administration, which is an important benefit for the TRD population. Esketamine doses were given twice per week during the first 4 weeks of induction treatment, and after induction, efficacy was maintained when doses were given once per week or once every 2 weeks.
- Another benefit of esketamine treatment is the low potential for drug-drug interactions, which is particularly important in older population with TRD, many of whom suffer from comorbid conditions requiring drug therapy.

11.3. Summary of Risks with Esketamine Nasal Spray

Overview of Adverse Events

- The most commonly observed adverse drug reactions (defined as adverse events reasonably associated with the use of esketamine) in TRD patients treated with esketamine + oral AD (with incidence ≥10% and greater than in oral AD + placebo group) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.
- Most (94.9%) TEAEs with esketamine in the Phase 2 and 3 TRD studies were mild to moderate in severity.

- Most TEAEs in esketamine-treated patients occurred shortly after dosing, were transient, and resolved on the same day. In the esketamine + oral AD groups in the short-term studies (TRANSFORM-1, 2, and 3), over 86% of all TEAEs occurred on nasal spray dosing days and of those events, over 85% also resolved the same day.
- There were no new safety concerns identified with long-term repeated, intermittent weekly or every-other-week dose administration of esketamine (28, 56, or 84 mg) over a duration of up to 1 year in the uncontrolled, open-label safety study SUSTAIN-2.
- The TEAE profile for patients ≥65 years of age was generally consistent with that observed in patients <65 years of age. In the long-term safety study SUSTAIN-2, a slowing of reaction time in the absence of any other change in cognitive performance was observed in patients ≥65 years of age; however, the observation could not be attributed to study medication and the clinical relevance and consequences have not been established.
- In the fixed-dose study TRANSFORM-1, the overall rates of TEAEs and severe TEAEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, and most TEAEs across both dose groups were mild or moderate in severity, occurred on the day of dosing, and resolved the same day. TEAEs of dissociation occurred at a higher rate in the esketamine 84 mg group than the 56 mg group, and severe TEAEs of dissociation and nausea occurred at a higher rate in the esketamine 84 mg group.
- A total of 5 deaths occurred in the completed and ongoing Phase 2 and 3 clinical studies in patients with TRD as of the clinical cutoff date of 4 March 2018 (1861 unique patients treated with esketamine; 1045 patient-years of exposure):
  - Completed double-blind studies/study phases: One death (multiple injuries sustained in a road traffic accident) occurred among esketamine-treated patients during the double-blind phases of the completed Phase 2 and 3 studies (122 patient-years of exposure). No deaths occurred in the oral AD + placebo groups of these studies (100 patient-years of exposure).
  - Completed and ongoing open-label studies/study phases: There were 3 deaths (2 completed suicides and 1 case of acute cardiac and respiratory failure) among patients treated with esketamine + oral AD during the open-label studies/study phases (923 patient-years of exposure).
  - Follow-up phases: There was 1 death (completed suicide) during the follow-up phases of these studies when the patient was not receiving nasally-administered study medication.
  - All 5 deaths were assessed by the investigator and the Sponsor as not related to the esketamine treatment.
- Across the completed Phase 3 studies/study phases in patients with TRD, the incidence of serious adverse events ranged from 0.9% to 6.9% in the esketamine + oral AD treatment groups and from 0.5% to 3.1% in the oral AD + placebo groups.
- Across the completed Phase 3 studies/study phases, the incidence of TEAEs leading to discontinuation of study medication ranged from 1.1% to 9.5% in the esketamine + oral AD treatment groups and from 1.4% to 3.1% in the oral AD + placebo groups.

Safety Topics of Interest

- *Suicidal Ideation and Behavior:* Evaluation of C-SSRS scores and TEAEs of suicidal ideation and behavior in the Phase 2 and 3 clinical studies in patients with TRD did not suggest that esketamine is associated with increased risk of suicidal ideation and behavior. Most patients stayed within the same suicidality category based on C-SSRS score throughout the Phase 3 studies. There were 3 cases of completed suicide in the completed and ongoing Phase 2 and 3 studies in patients with TRD among 1861 unique patients treated with esketamine (1045 patient-years of exposure). In the controlled Phase 3 studies, the overall incidence of suicidality-related TEAEs was similar for the esketamine + oral AD and oral AD + placebo groups.
- *Dissociation:* Consistent with the observation of peak plasma esketamine levels at approximately 40 minutes after dose administration, dissociative/perceptual changes captured using the CADSS had an onset shortly after the start of the dose, peaked by 40 minutes postdose, and typically resolved within 1.5 hours. Peak mean CADSS scores attenuated with repeated dosing. Reported TEAEs associated with these symptoms were primarily transient. Most events of dissociation were mild or moderate in severity. There were no serious adverse events of dissociation.
- *Effects on Blood Pressure:* Transient increases in systolic and diastolic blood pressure were observed following administration of esketamine nasal spray, with maximum elevations in the clinical studies observed within 40 minutes of dosing (consistent with peak plasma elevations) and values returning to, or close to, pretreatment levels by 1.5 hours after dose administration.
  - The largest mean of the maximum blood pressure increases across dosing days compared to predose values in the short-term Phase 3 studies were:
    - Systolic blood pressure: 13.3 to 16.0 mm Hg in the esketamine + oral AD groups and 6.1 to 11.1 mm Hg in the oral AD + placebo groups
    - Diastolic blood pressure: 8.7 to 9.5 mm Hg in the esketamine + oral AD groups and 4.9 to 6.8 mm Hg in the oral AD + placebo groups
  - Changes in blood pressure observed in the 56 mg and 84 mg esketamine dose groups did not demonstrate a dose-response relationship.
  - A similar pattern for transient increases in blood pressure were observed in patients ≥65 years.
  - In the long-term safety study SUSTAIN-2, there were no cumulative effects of the changes in blood pressure, and the pattern of transient blood pressure increases remained consistent over time for patients 18-64 years and those ≥65 years.
  - TEAEs related to increased blood pressure were reported at higher frequencies following treatment with esketamine + oral AD compared to oral AD + placebo in the controlled Phase 3 studies/study phases. Across all Phase 3 studies, there were 4 patients with a severe TEAE related to increased blood pressure (1 case of hypertensive crisis and 3 cases of blood pressure increased); two patients experienced a serious adverse event related to increased blood pressure (1 case of hypertensive crisis and 1 case of blood pressure increased).

- *Sedation and Somnolence:* Based on the pattern of responses on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) in the Phase 2 and 3 studies, sedative effects of esketamine were generally mild, had an onset shortly after the nasal spray dosing peaking at 30 to 45 minutes postdose, and typically resolved by 1 to 1.5 hours postdose. The reported TEAE data for sedation and somnolence were consistent with MOAA/S findings. Across the Phase 2 and 3 TRD studies, TEAEs of somnolence or sedation were primarily mild or moderate in intensity and nonserious. Most reported TEAEs of somnolence or sedation occurred on the day of dosing in the short-term and long-term Phase 3 studies/study phases and of these, most resolved spontaneously the same day. There was 1 serious adverse event of sedation.
- *Effects on Cognition:* In the short-term Phase 3 studies, 4 weeks of treatment with esketamine + oral AD did not influence any aspect of cognition studied in adult patients with TRD and was not associated with any systematic changes in cognition in patients ≥65 years. In the long-term open-label safety study SUSTAIN-2, overall group mean performance on multiple cognitive domains including visual learning and memory, as well as spatial memory/executive function, either improved or remained stable postbaseline in adult patients. In the subset of patients ≥65 years of age from this open-label study, a slowing of reaction time was observed starting at Week 20 and through the end of the study; however, this appeared to represent an isolated observation related to processing speed and not a broad attentional impairment. Performance on all other cognitive tests remained stable in patients ≥65 years in this study.
- *Respiratory Rate and Oxygen Saturation:* Treatment with esketamine nasal spray had no clinically meaningful effects on respiratory rate or oxygen saturation as measured by pulse oximetry. There were no cases of respiratory depression or TEAEs that required cardiopulmonary resuscitation or other medical intervention reported in any esketamine-treated patient in the Phase 2 or 3 studies in TRD.
- *Interstitial Cystitis:* There were no cases of interstitial cystitis (including ulcerative cystitis) in any of the clinical trials with esketamine.

Abuse Potential

- While the potential for abuse, misuse, and diversion exists for esketamine due to its similar pharmacologic profile to ketamine, no evidence of abuse, misuse or overdose was observed in the esketamine development program with a TRD population (note, patients with moderate to severe substance use disorder were excluded from the studies), and possible diversion was minimal (<0.1% clinical supply kits unaccounted for in the Phase 3 studies).
- The potential for overdose and death with esketamine is low, given that distribution of the medication will be limited, there were no cases of respiratory depression observed in the clinical program, and each nasal spray device contains a low dose of esketamine (28 mg).
- There will be a comprehensive set of measures in place to mitigate the risk for abuse and misuse of this product, including the proposed REMS (certification of outpatient healthcare settings and pharmacies that dispense esketamine, controlled distribution program, and REMS communication materials), drug administration model, product labeling for esketamine nasal spray, extensive education and training program and resources, together with several features of the single-use disposable nasal spray device, which was designed to mitigate the risks of abuse and misuse.

11.4. Patient Preference Survey

A preference survey co-developed with Duke Clinical Research Institute was conducted with TRD patients (both those who participated in the esketamine clinical studies and those who did not) to assess their tradeoff preferences for key benefit and harm outcomes associated with TRD treatments, with a focus on the unique features of ketamine-based treatments. The main goal of the preference survey was to provide information on how patients with TRD would regard the tradeoff between potential benefits of esketamine (improved mood, how quickly the medication works) versus short-term issues associated with dosing (dissociation, dizziness, supervision by a healthcare professional, wait time of 2 hours after dosing, and restrictions on driving) and potential long-term safety issues observed with ketamine abuse (cystitis and memory/cognitive difficulties).

Results from patient preference surveys administered in esketamine-experienced respondents with TRD and ketamine/esketamine-naïve respondents who actively made tradeoff decisions had very similar preferences. Both groups placed a low importance on the occurrence of short-term unusual postdose sensations (i.e., dissociation and dizziness) and logistical drug administration issues (i.e., supervision by a healthcare professional, postdose wait time of 2 hours, and restrictions on driving until the next day), and esketamine-experienced respondents reported even less concern with these features compared to improvements in efficacy. In addition, respondents were willing to accept between 3% and 5% risk of permanent bladder/cystitis or permanent cognitive and memory impairment in exchange for an improvement in MADRS total score from severe (40) to moderate (20).

Further information about the patient preference survey is provided in Appendix 16.

11.5. Quantitative Benefit-risk Assessment in TRD Clinical Studies

A structured approach was applied to the selection and analysis of those endpoints in the Phase 3 esketamine program that have an important effect on the benefit-risk balance. Proportions of beneficial events were compared to proportions of harmful events. Assessments were conducted for induction treatment (using data from the short-term treatment studies TRANSFORM-1, 2, and 3) and for maintenance treatment (using data from the maintenance of effect study SUSTAIN-1). The open-label safety studies SUSTAIN-2 and SUSTAIN-3 are not used in these quantitative assessment as they do not have comparator arms.

Efficacy endpoints (benefits) during the induction phase included the proportions of responders and remitters at Day 28. The beneficial endpoints for the maintenance phase were the proportion of stable remitters or stable responders in SUSTAIN-1 who remained relapse free. Remission and response are secondary efficacy endpoints not associated with formal statistical testing. They are used for benefit-risk rather than the primary efficacy endpoint of change in MADRS total score because they are clinically meaningful endpoints that enable comparing proportions of beneficial events to those of harmful events. All remitters are also responders, given study inclusion criteria, so these endpoints are neither additive nor mutually-exclusive but rather are alternative characterizations of efficacy.

Safety endpoints (risks) included death, incident suicidal ideation and the most commonly observed adverse drug reactions. These common ADRs are defined in Section 8.3.2 and include dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increase, anxiety, and vomiting. These common ADRs include the TEAEs of special interest other than suicidality (addressed separately with suicidal ideation and death), cystitis (no cystitis events occurred) and abuse potential (addressed separately) or tachycardia. The degrees of severity examined for these ADRs were whether they resulted in discontinuation and whether they were assessed as severe by the investigator. All severe common ADRs were also characterized based on time of onset and resolution relative to the dosing day. Specifically, severe common ADRs with (1) onset and resolution on a dosing day, (2) onset on a dosing day and resolution on a non-dosing day and (3) onset on a non-dosing day. Interstitial cystitis and changes in cognition were also considered as risks, though as noted above, there were no cases of interstitial cystitis (Section 8.13) and the only between treatment difference in all the cognitive tests performed was a slowing of reaction time in the absence of any other change in cognitive performance in older patients observed in the long-term safety study SUSTAIN-2 (Section 8.8). This observation could not be attributed to study medication and the clinical relevance and consequences have not been established. Overdose, abuse or drug-seeking behavior was not observed in any clinical study (Section 9), and abuse potential is addressed in the comprehensive risk mitigation program (Section 10.1).

For the benefit-risk assessment, risk differences are used since risk differences for efficacy endpoints can be compared more directly to risk differences for safety endpoints. The risk difference for an event can be interpreted as the additional number of patients in a population of 100 who would experience that event when treated with esketamine + oral AD compared to their being treated with oral AD + placebo. A negative value indicates that there were more occurrences of an outcome in the population treated with oral AD + placebo, and a positive value indicates more occurrences in a population treated with esketamine + oral AD. Note that these benefit-risk analyses are not intended for hypothesis testing. While risk differences are shown with 95% CIs, no statistical tests for these endpoints were specified nor was any multiplicity adjustment applied.

For TRANSFORM-1, 2, and 3, treatment comparisons were performed using the full analysis set for each study separately. For SUSTAIN-1, comparisons were performed using the full "stable remitters" analysis and full "stable responders" analysis sets for efficacy endpoints and the safety (maintenance phase) analysis set for safety endpoints. Treatment comparisons are provided in Appendix 12.

Benefit-Risk Balance of Induction Treatment in Adults 18-64 Years of Age

Risk differences for key benefits and risks are shown for TRANSFORM-1 and 2 in Figure 36 and App 12 - Table 1 and App 12 - Table 2. Compared to oral AD + placebo, induction treatment with esketamine + oral AD resulted at Day 28 in:

- 17.3 (95% CI: 4.01; 30.60) more responders per 100 patients in the flexible-dose study TRANSFORM-2

- 15.2 (95% CI: 2.11; 28.22) and 14.2 (95% CI: 0.68; 27.67) more responders per 100 patients for esketamine doses of 56 and 84 mg, respectively, in TRANSFORM-1

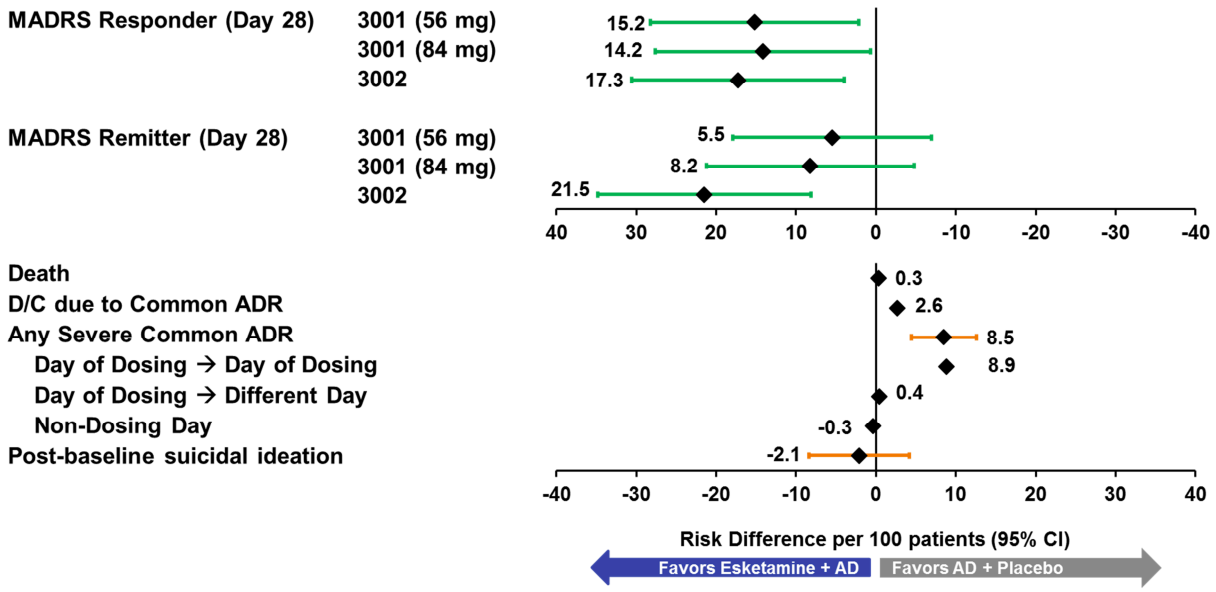
Compared to oral AD + placebo, esketamine + oral AD also resulted in a greater number of patients in remission at Day 28:

- 21.5 (95% CI: 8.17; 34.78) more remitters per 100 patients in TRANSFORM-2
- 5.5 (95% CI: -6.98; 17.94) and 8.2 (95% CI: -4.76; 21.20) more remitters per 100 patients for esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, respectively, in TRANSFORM-1

The overall rates of severe ADRs and ADRs leading to discontinuation were higher for the esketamine + oral AD groups than for the oral AD + placebo groups for TRANSFORM-1 and 2. Per 100 patients, esketamine + oral AD treatment resulted in 2.6 more discontinuations due to a common ADR, and 8.5 (95% CI: 4.41; 12.61) more severe common ADRs per 100 patients (Figure 36). These events are predominantly dissociation, vertigo and dizziness. Comparing the risk differences for severe common ADRs that occurred and resolved on the day of dosing (8.9, 95% CI: 5.31; 12.40) to those for severe common ADRs that occurred on day of dosing and resolved on a different day (0.4) or occurred on a non-dosing day (-0.3) suggests that the 8.5 additional severe common ADRs per 100 patients treated with esketamine + oral AD tend to be transient, occur primarily on the day of dosing, and resolve the same day (App 12 - Table 8).

There were no severe increases in blood pressure in either study (App 12 - Table 8). One death occurred in the esketamine arm of TRANSFORM-2 from multiple injuries sustained in a road traffic accident and was not considered related to treatment (Section 8.3.4.1). Incident postbaseline suicidal ideation was numerically balanced between study arms -2.1 (95% CI -8.40; 4.18) per 100 patients. There was also no difference between study arms in any of the cognitive tests performed during TRANSFORM-1 or 2 (Section 8.8).

Figure 36: Risk Differences per 100 Patients 18-64 Years of Age for Key Benefits and Risks of Esketamine + Oral AD versus Oral AD + Placebo for in Short-term Studies TRANSFORM-1 and 2: Full Analysis Set for Efficacy and Pooled Safety Endpoints (Observed Case Analysis)



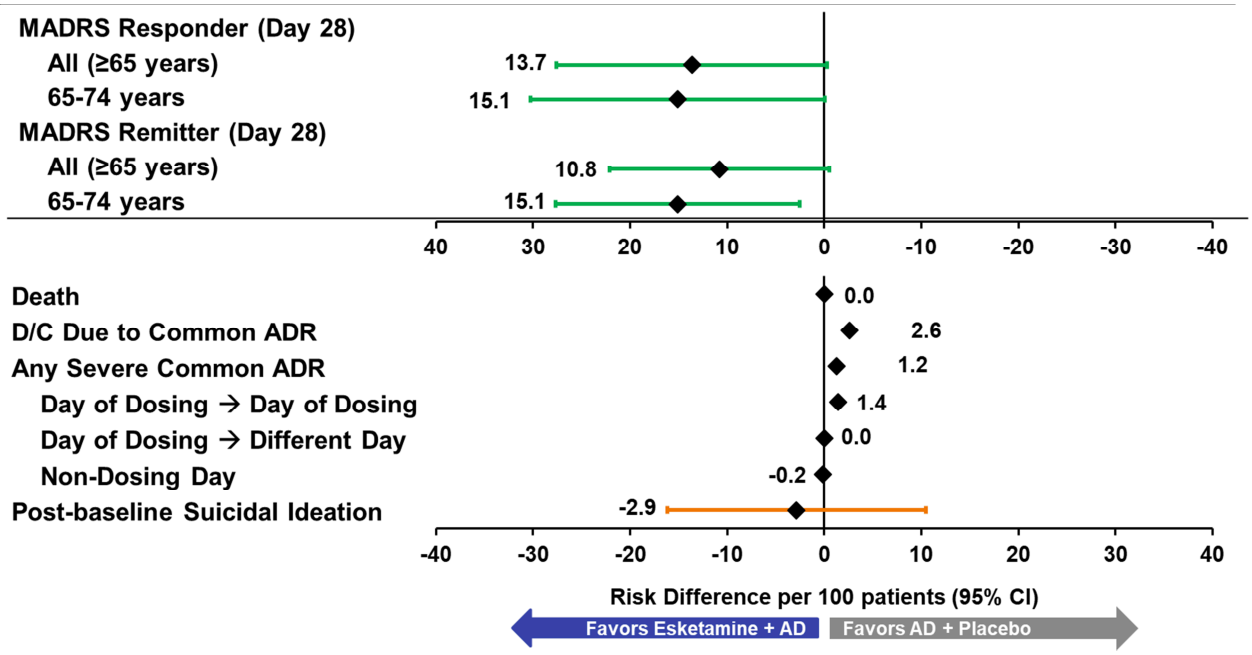
AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; C-SSRS=Columbia-Suicidality Severity Rating Scale; D/C=discontinuation; MADRS=Montgomery-Asberg Depression Rating Scale; TRD=treatment-resistant depression
Note: Diamonds represent point estimates and lines represent 95% CIs. No CI provided if the number of events is 0 or 1 in either group. Benefits are identified in green and harms in orange.
Note: x-axis is reversed for efficacy endpoints.
TRANSFORM-1 was a fixed-dose study with a 56 mg dose arm and an 84 mg dose arm); TRANSFORM-2 was a flexible-dose study with an esketamine (56 or 84 mg) dose arm.
MADRS Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28.
MADRS Remitter is defined as the proportion of patients achieving MADRS total score of ≤12 at Day 28.
The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting.
Proportion of patients who discontinued nasal spray treatment due to common ADR: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.
Postbaseline Suicidal Ideation = proportion of patients who had worsening in suicidality with postbaseline suicidal ideation based on the C-SSRS among patients with no suicidal ideation or behavior at baseline

Benefit-Risk Balance of Induction Treatment in Patients ≥65 Years of Age

The benefit-risk analysis for TRANSFORM-3 in patients ≥65 years of age showed a similar pattern to that presented for patients 18-64 years of age in TRANSFORM-1 and 2 (Figure 37 and App 12 - Table 3). Compared to oral AD + placebo, esketamine + oral AD resulted in 13.7 (95% CI: -0.28; 27.58) more responders and 10.8 (95% CI: -0.51; 22.09) more remitters per 100 patients at Day 28 (App 12 - Table 3). For those 65-74 years of age, both endpoints shifted slightly in favor of esketamine, with 15.1 (95% CI -0.08; 30.27) more responders and 15.1 (95% CI 2.53; 27.66) more remitters per 100 patients treated with esketamine + oral AD (App 12 - Table 4). There were too few patients to perform a similar assessment for those above 75 years of age (Section 7.3.1.1).

For the esketamine + oral AD group, there were 2.6 more discontinuations due to common ADRs per 100 patients and 1.2 more severe common ADRs per 100 patients. Comparing the risk differences for severe common ADRs that occurred and resolved on the day of dosing (1.4) to those that occurred on the day of dosing and resolved on a different day (0 in both arms) or occurred on a non-dosing day (-0.2) suggests that the 1.2 additional severe common ADRs per 100 patients treated with esketamine + oral AD tend to be transient, occur primarily on the day of dosing, and resolve the same day (App 12 - Table 3). One severe event of blood pressure increased occurred and resolved on the day of dosing in the esketamine + oral AD arm. There was no case of death and incident postbaseline suicidal ideation was numerically balanced between study arms: -2.9 (95% CI: -16.20; 10.45) per 100 patients.

Figure 37: Risk Differences per 100 Patients ≥65 Years of Age for Key Benefits and Risks of Esketamine + Oral AD versus Oral AD + Placebo for in Short-term Study TRANSFORM-3: Full Analysis Set for Efficacy and Safety Endpoints (Observed Case Analysis)



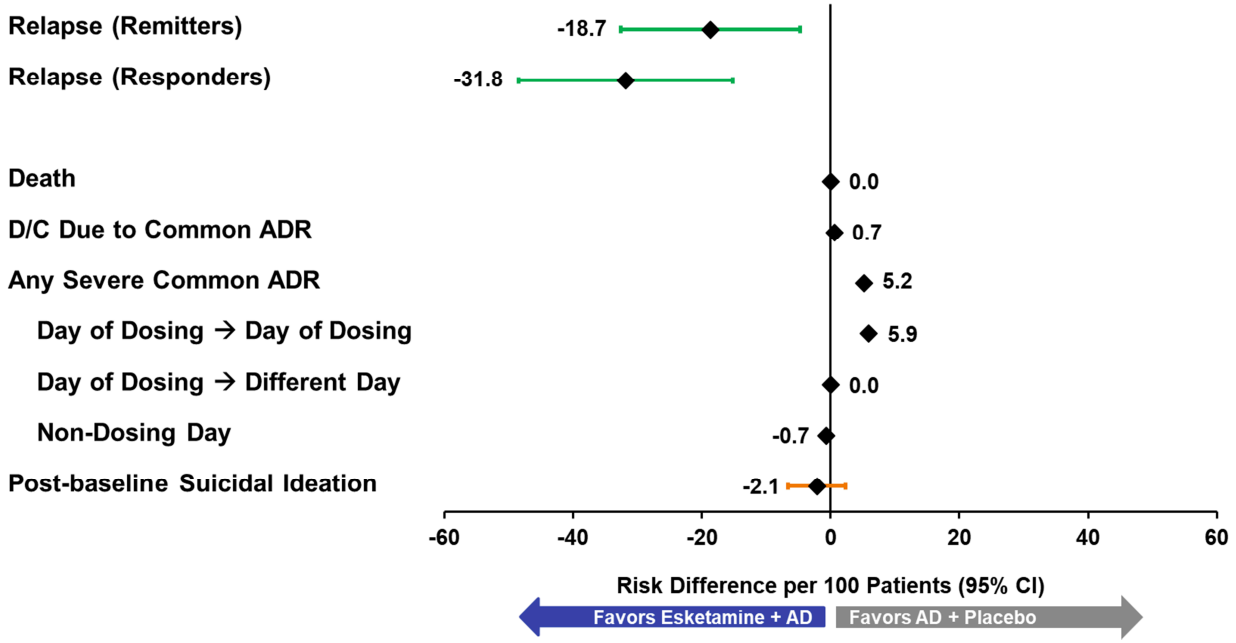
AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; C-SSRS=Columbia-Suicidality Severity Rating Scale; D/C=discontinuation; MADRS=Montgomery-Asberg Depression Rating Scale; TRD=treatment-resistant depression
Note: Diamonds represent point estimates and lines represent 95% CIs. No CI provided if the number of events is 0 or 1 in either group. Benefits are identified in green and harms in orange.
Note: x-axis is reversed for efficacy endpoints.
TRANSFORM-3 was a flexible-dose study with an esketamine (28, 56 or 84 mg) dose arm.
MADRS Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28.
MADRS Remitter is defined as the proportion of patients achieving MADRS total score of ≤12 at Day 28.
The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting.
Proportion of patients who discontinued nasal spray treatment due to common ADR: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.
Postbaseline Suicidal Ideation = proportion of patients who had worsening in suicidality with postbaseline suicidal ideation based on the C-SSRS among patients with no suicidal ideation or behavior at baseline

Benefit-Risk Balance of Maintenance Treatment

Among patients in SUSTAIN-1 who had achieved stable remission after 16 weeks treatment with esketamine + oral AD (stable remitters analysis set), randomized continuation with esketamine resulted in 18.7 (95% CI: 4.75; 32.62) fewer relapses per 100 patients compared to discontinuing esketamine (Figure 38 and App 12 - Table 5). Among patients who had achieved a stable response (but not remission) after 16 weeks treatment with esketamine + oral AD (stable responders analysis set), randomized continuation with esketamine resulted in 31.8 (95% CI: 15.16; 48.48) fewer relapses per 100 patients compared to discontinuing esketamine (Figure 38 and App 12 - Table 6). The primary reason for relapse was worsening depression manifested as a deteriorating MADRS total score, with few patients meeting criteria for relapse based on a clinically relevant event.

Safety endpoints for benefit-risk analysis of the maintenance phase of SUSTAIN-1 were examined using data from the safety (maintenance phase) analysis set (i.e., stable remitters and stable responders combined). There were 0.7 more common ADRs leading to discontinuation and 5.2 (95% CI: 0.83; 9.57) more severe common ADRs per 100 patients receiving esketamine + oral AD. Comparing the risk differences for severe common ADRs that occurred and resolved on the day of dosing (5.9) to those that occurred on day of dosing and resolved on a different day (0 in both arms) or occurred on a non-dosing day (-0.7) suggests that the 5.2 additional severe common ADRs per 100 patients treated with esketamine tend to be transient, occur primarily on the day of dosing, and resolve the same day in sustained use (App 12 - Table 7). There were no deaths; incident postbaseline suicide ideation showed no meaningful difference -2.1 (95% CI: -6.55; 2.29) per 100 patients, and there was no difference between treatment groups in any of the cognitive tests performed (Section 8.8).

Figure 38: Risk Differences per 100 Patients 18-64 Years of Age for Key Benefits and Risks of Esketamine + Oral AD versus Oral AD + Placebo for in SUSTAIN-1. Efficacy based on Full (Stable Remitters) Analysis Set and Full (Stable Responders) Analysis Set; Safety based on Safety (Maintenance Phase) Analysis Set



AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; C-SSRS=Columbia-Suicidality Severity Rating Scale; D/C=discontinuation; MADRS=Montgomery-Asberg Depression Rating Scale; TRD=treatment-resistant depression
Note: Diamonds represent point estimates and lines represent 95% CIs. Benefits are identified in green and harms in orange.
Note: No CI provided if the number of events is 0 or 1 in either group.
Relapse = Proportion of patients who relapse based on any predefined criteria of (1) MADRS total score ≥ 22 for two consecutive assessments separated by 5 to 15 days or (2) hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention.
Remitters include esketamine-treated patients who achieved MADRS total score of ≤12 at the end of the optimization phase who were randomized to double-blind treatment during the maintenance phase.
Responders include esketamine-treated patients who achieved at least 50% improvement in MADRS at the end of the optimization phase who were randomized to double-blind treatment during the maintenance phase.
The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting.
Proportion of patients who discontinued nasal spray treatment due to common ADR: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety, and vomiting.
Postbaseline Suicidal Ideation = proportion of patients who had worsening in suicidality with postbaseline suicidal ideation based on the C-SSRS among patients with no suicidal ideation or behavior at baseline.

11.6. Justification of Dose Recommendation

By having 3 doses and varying dose frequency available for esketamine nasal spray, treatment at the lowest possible effective dose and least frequent dosing schedule can be individualized for patients, including patients over 65 years of age.

The Sponsor's proposed dosage recommendations for esketamine nasal spray are shown below.

Dosage Recommendations for Esketamine Nasal Spray

Induction Phase	Maintenance Phase
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly**
Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment	Periodically reexamine the need for continued treatment.

* For patients ≥65 years Day 1 starting dose is 28 mg.
** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

While the results from the esketamine 84 mg dose group in the short-term fixed-dose Phase 3 study TRANSFORM-1 did not reach statistical significance, there were improvements in depressive symptoms in the group of patients who were treated with the 84 mg dose. The evidence across the clinical development program supports including the 84 mg dose of esketamine as a treatment option for patients with TRD.

The Phase 1 pharmacokinetics studies showed higher doses of esketamine nasal spray result in higher plasma levels of esketamine. The plasma esketamine C_{max} and AUC increased in a dose-proportional manner after administration of 56 mg and 84 mg nasal esketamine.

Data from the Phase 2 dose-response study SYNAPSE provides evidence of a relationship between the dose of esketamine nasal spray (28, 56, and 84 mg) and the magnitude of improvement in depressive symptoms after 1 week of treatment (Section 5.2.1 and Figure 8). While there were a limited number of patients in the study, there were substantial improvements in depressive symptoms in patients with TRD who were treated with the 84 mg dose, and the results support including the 84 mg dose as a treatment option.

The benefit of having 2 doses of esketamine, 56 and 84 mg, available as options for treatment is supported by the finding that the majority of patients in the esketamine + oral AD group of the short-term flexible-dose studies TRANSFORM-2 and 3 optimized to the 84-mg dose by the end of the double-blind induction phase (TRANSFORM-2: 66.7%; TRANSFORM-3: 64.5%). Over 50% of patients were optimized to the 84 mg dose by Day 8 in TRANSFORM-2 and by Day 11 in TRANSFORM-3. The same was true for the maintenance of effect study SUSTAIN-1, in which 56% of stable remitters and 68% of stable responders were receiving the 84 mg esketamine dose at the start of the maintenance phase. In the long-term open-label study SUSTAIN-2, 50% of patients received the 84-mg dose at the end of the optimization/maintenance phase.

Furthermore, in the flexible-dose study TRANSFORM-2, a descriptive analysis by esketamine dose during the last 2 weeks of treatment showed numerically greater response and remission rates at Day 28 in patients who received the 84-mg dose after Day 15 compared with those who received the 56-mg dose during the same period.

In TRANSFORM-1, the overall rates of TEAEs and severe TEAEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups, and most TEAEs across both dose groups were mild or moderate in severity, occurred on the day of dosing, and resolved the same day. Except for TEAEs of dissociation (which occurred at a higher rate in the esketamine 84 mg group than the 56 mg group), and severe TEAEs of dissociation and nausea (which occurred at a higher rate in the esketamine 84 mg group), there were no clear dose-related differences in safety and tolerability. The transient increases in blood pressure appeared to be similar in both dose groups, and the most common adverse events resolved in a similar time frame in both dose groups.

In addition, there are examples of other marketed antidepressants with multiple doses available that have not shown a clear dose response in clinical studies (e.g., fluoxetine/olanzapine combination, brexpiprazole and aripiprazole).

Importantly, as the population of patients with TRD is heterogenous, some patients may require higher doses to relieve depressive symptoms as suggested by the results from the flexible-dose Phase 3 studies, and it would be useful for clinicians to have more than one dose available to optimize treatment.

11.7. Benefit-risk Conclusions

The totality of evidence supports a positive benefit-risk balance for esketamine nasal spray as a new treatment for adults with TRD.

Remission is a significant improvement leading to near absence of disease symptoms. Response is a 50% or greater reduction in symptoms as measured by the MADRS total score. In the context of the high medical need and poor quality of life for TRD patients, 5 to 21 additional patients remitting or 14 to 17 additional patients responding per 100 treated, with symptom relief starting to manifest in some patients within days, is a considerable benefit that outweighs the adverse reactions, predominantly dissociation, vertigo and dizziness. The benefit seen with continued maintenance treatment of 19 to 32 fewer relapses per 100 patients (who have achieved stable remission or response) over longer-term therapy also outweighs the few severe common adverse reactions. The single death across the 4 controlled Phase 3 studies, three deaths in the uncontrolled open-label safety studies, and one death in the follow-up phase of the Phase 2 dose-response study SYNAPSE were not considered related to treatment by the study investigator, and the cumulative exposure to esketamine across studies was much larger than exposure to placebo. Notably, the all-cause mortality rate in a study of TRD patients in the Medicare system[38] was higher than that observed in the clinical studies with esketamine in TRD patients.

The safety experience with esketamine indicated that most of the adverse reactions seen with the drug, including those of common events such as dissociative symptoms, dizziness/vertigo, increased blood pressure, and sedation, occurred shortly after dosing while the patient was under the supervision of a healthcare professional, and resolved the same day. The benefits of esketamine are considered to outweigh the risks of the infrequent severe or treatment-limiting side effects in the TRD population. While the potential for abuse exists with esketamine, a

comprehensive set of risk mitigation initiatives, including a proposed REMS (with a certification requirement for outpatient healthcare settings and pharmacies that dispense esketamine, controlled distribution program, and REMS communication materials), will be in place at the time of product launch to lessen the potential for abuse and misuse. Patient preference study findings indicate that patients with TRD, both with and without esketamine treatment experience, place a higher value on improved depression symptoms over those of short-term unusual postdose sensations (e.g., dissociation and dizziness) and drug administration logistics (e.g., supervision by a healthcare professional) or hypothesized extreme safety risks associated with ketamine abuse (e.g., bladder or memory problems).

With a comprehensive risk mitigation program, which includes education about dosing under the supervision of a healthcare professional, esketamine has the potential to improve the treatment landscape for TRD, based on the rapid and durable efficacy observed in clinical studies. Esketamine is therefore anticipated to address a major public health interest and has the potential to provide important benefits in establishing a new standard of care for achieving meaningful clinical response and remission among adults with TRD.

REFERENCES

1. Ablow K. Ketamine: a miracle antidepressant? Fox News Health; Jan 31, 2012. http://www.foxnews.com/health/2012/01/31/ketamine-miracle-antidepressant.html. Accessed 13 November 2018.
2. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152.
3. Amos TB, Tandon N, Lefebvre P, et al. Direct and indirect cost burden and change of employment status in treatment-resistant depression: a matched-cohort study using a US commercial claims database. J Clin Psychiatry. 2018;79(2):17m11725.
4. Andrade C. Ketamine for depression: clinical summary of issues related to efficacy, adverse events, and mechanism of action. J Clin Psychiatry. 2017;78(4):415-419.
5. Baker SC, Shabir S, Gerogopoulos NT, et al. Ketamine-induced apoptosis in normal human urothelial cells. Am J Pathol. 2016;186(5):1267-1277.
6. Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. J Affect Disord. 2013;148(1):129-135.
7. Barbuti M, Pacchiarotti I, Vieta E, et al. Antidepressant-induced hypomania/mania in patients with major depression: Evidence from the BRIDGE-II-MIX study. J Affect Disord. 2017;219:187-192.
8. Bauer M, Severus E, Möller HJ, Young AH. WFSBP Task Force on Unipolar Depressive Disorders. Pharmacological treatment of unipolar depressive disorders: summary of WFSBP guidelines. Int J Psychiatry Clin Pract. 2017;3:1-11.
9. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000 Feb 15;47(4):351-4.
10. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci. 2003;58:249-265.
11. Borges S, Chen Y-C, Laughren TP, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry. 2014;75(3):205–214.
12. Boulenger J-P, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. J Psychopharmacol. 2012;26(11):1408-1416.
13. Bräu ME, Sander F, Vogel W, Hempelmann G (1997). Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. Anesthesiology, 86: 394-404.
14. Brioch K. Committee for Medicinal Products for Human Use (CHMP) assessment on efficacy of antidepressants. Eur Neuropsychopharmacol. 2009;19:305-308.
15. Bryson EO, Silverstein JH. Addiction and Substance Abuse in Anesthesiology. Anesthesiology. 2008;109(5):905-917.
16. 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 Jul 1;175(7):620-630.
17. Castle C, Gray A, Neehoff S, Glue P. Effect of ketamine dose on self-rated dissociation in patients with treatment refractory anxiety disorders. J Psychopharmacol. 2017;31(10):1306-1311.
18. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci Ther. 2010;16(5):322-325.
19. Chen, X., Shu, S., Bayliss, D.A., 2009. HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. Journal of neuroscience, 29, 600-609.
20. Chiu, C.T., Scheuing, L., Liu, G., Liao, H.M., Linares, G.R., Lin, D., Chuang, D.M., 2015. The mood stabilizer lithium potentiates the antidepressant-like effects and ameliorates oxidative stress induced by acute ketamine in a mouse model of stress. The international journal of neuropsychopharmacology18, 1-13.

21. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology Guidelines. J Psychopharmacol. 2015;29(5):459-525.

22. Coates, K.M., Flood, P., 2001. Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in Xenopus oocytes. British journal of pharmacology 134, 871-879.

23. Committee for Medicinal Products for Human Use. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression. 2013.

24. Cristancho MA, Thase ME. Drug safety evaluation of olanzapine/fluoxetine combination. Expert Opin Drug Saf. 2014;13(8):1133-1141.

25. Cymbalta® (duloxetine hydrochloride capsule, delayed release). Prescribing information. Eli Lilly and Company, Dec 2017.

26. Department of Veteran Affairs. VA/DOD clinical practice guideline for the management of major depressive disorder. 2016. https://www healthquality.va.gov/guidelines/MH/mdd/MDDFullFinal5192016.pdf. Accessed November 12, 2018.

27. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010;67:793-802.

28. DiBernardo A, Lin X, Zhang Q, Xiang J, Lu L, Jamieson C, Benson C, Lee K, Bodén R, Brandt L, Brenner P, Reutfors J, Li G. Humanistic outcomes in treatment resistant depression: a secondary analysis of the STAR*D study. BMC Psychiatry. 2018 Oct 29;18(1):352.

29. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depen. 2003;69:23-28.

30. Domino EF. Taming the ketamine tiger. Anesthesiology. 2010 Sep;113(3):678-84.

31. Dougherty DD, Rezai AR, Carpenter LL, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry. 2015;78(4):240-248.

32. Drug Enforcement Administration. Drugs of Abuse. A DEA resource guide, 2017 edition. Available at: https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf. Accessed on 2 May 2018.

33. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med. 2016;22(3):238-249.

34. Durieux, M.E., Nietgen, G.W., 1997. Synergistic inhibition of muscarinic signaling by ketamine stereoisomers and the preservative benzethonium chloride. Anesthesiology 86, 1326-1333.

35. Ebert, B., Mikkelsen, S., Thorkildsen, C., Borgbjerg, F.M., 1997. Norketamine, the main metabolite of ketamine, is a non-competitive NMDAR antagonist in the rat cortex and spinal cord. European journal of pharmacology 333, 99-104.

36. Faria V, Gingnell M, Hoppe JM, et al. Do you believe it? Suggestions influence the clinical and neural effects of escitalopram in social anxiety disorder: a randomized trial. BioMedicine. 2017; 24:179–188.

37. Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J Affect Dis. 2009;116:4-11.

38. Feldman RL, Dunner DL, Muller JS, Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. J Med Econ. 2013;16:62-74.

39. Finck, A.D., Ngai, S.H., 1982. Opiate receptor mediation of ketamine analgesia. Anesthesiology 56, 291-297.

40. Flood, P., Krasowski, M.D., 2000. Intravenous anesthetics differentially modulate ligand-gated ion channels. Anesthesiology 92, 1418-1425.

41. Friederich P, Dybek A, Urban BW (2000). Stereospecific interaction of ketamine with nicotinic acetylcholine receptors in human sympathetic ganglion-like SH-SY5Y cells. Anesthesiology, 93(3): 818-824.

42. Gale CR, Batty GD, Osborn DP, Tynelius P, Whitley E, Rasmussen F. Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men. Arch Gen Psychiatry. 2012 Aug;69(8):823-31.

43. Gerhard DM, Duman RS. Rapid-Acting Antidepressants: Mechanistic Insights and Future Directions. Curr Behav Neurosci Rep. 2018 Mar;5(1):36-47.

44. Goyal S, Ambekar A, Ray R. Ketamine dependence in an anesthesiologist: an occupational hazard? Indian J Psychol Med. 2014;36(3):335-337.

45. Hirota K1, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. Anesthesiology. 1999;90(1):174-82.

46. Hustveit, O., Maurset, A., Oye, I., 1995. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacology & toxicology 77, 355-359.

47. International Conference on Harmonisation Tripartite Guideline E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Recommended for Adoption at Step 4 of the ICH Process on 12 May 2005 by the ICH Steering Committee.

48. International Conference on Harmonisation Tripartite Guideline E14. Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Recommended for Adoption at Step 4 of the ICH Process on 12 May 2005 by the ICH Steering Committee - questions and answers. U.S. Department of Health and Human Services, Food and Drug Administration. June 2017.

49. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. Dialogues Clin Neurosci. 2015;17(2):111-126.

50. Kapur, S., Seeman, P., 2002. NMDAR antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Molecular Psychiatry 7, 837-844.

51. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540-560.

52. Khan A, Redding N, Brown WA. The persistence of the placebo response in antidepressant clinical trials. J Psychiatr Res. 2008 Aug;42(10):791-6.

53. Klepstad P1, Maurset A, Moberg ER, Oye I, 1990. Evidence of a role for NMDARs in pain perception. Eur J Pharmacol. 187(3):513-8.

54. Knöchel C, Alves G, Friedrichs B, et al. Treatment-resistant late-life depression: challenges and perspectives. Curr Neuropharmacol. 2015;13:577-591.

55. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.

56. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27(2):93-105.

57. Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. Br J Psychiatry. 2014;205(6):443-449.

58. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010 Aug 20;329(5994):959-64.

59. Li, N., Liu, R.J., Dwyer, J.M., Banasr, M., Lee, B., Son, H., Li, X.Y., Aghajanian, G., Duman, R.S., 2011. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biological psychiatry 69, 754-761.

60. Liao Y, Tang J, Corlett PR, Wang X, Yang M, Chen H, Liu T, Chen X, Hao W, Fletcher PC (2011). Reduced dorsal prefrontal gray matter after chronic ketamine use. Biological Psychiatry, 69: 42-48.

61. Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, Liu T, Chen X, Fletcher P, Hao W (2010). Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. Brain, 133: 2115-2122.

62. Liu J, Ji XQ, Zhu XZ (2006). Comparison of psychic emergence reactions after (±)-ketamine and (+)-ketamine in mice. Life Sciences, 78: 1839-1844.

63. Luckenbaugh DA, Niciu MJ, Ionescu DF, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? J Affect Disord. 2014;159:56-61.

64. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nature Med. 2001;7:541-547.

65. Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs. 2012;26:189-204.

66. Melander H, Salmonson T, Abadie E, van Zwieten-Boot B. A regulatory Apologia-A review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur Neuropsychopharmacol. 2008;18:623-627.

67. Mesas AE, Leon-Munoz LM, Rodriquez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr. 2011;94:1113–1126.

68. Moaddel, R., Abdrakhmanova, G., Kozak, J., Jozwiak, K., Toll, L., Jimenez, L., Rosenberg, A., Tran, T., Xiao, Y., Zarate, C.A., Wainer, I.W., 2013. Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in alpha7 nicotinic acetylcholine receptors. European journal of pharmacology 698, 228-234.

69. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134:382-389.

70. Montgomery SA, Moller H-J. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Intl Clin Psychopharmacol. 2009:24:111–118.

71. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. Addiction. 2010;105:121 133.

72. Morgan CJ, Rees H, Curran HV. Attentional bias to incentive stimuli in frequent ketamine users. Psychol Med. 2008;38:1331–1340.

73. Morgan CJA, Curran HV. Independent Scientific Committee on Drugs. Ketamine use: a review. Addiction. 2011;107:27-38.

74. Naismith SL, Norrie LM, Mowszowski L, Hickie IB. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog Neurobiol. 2012;98(1):99-143.

75. National Institute for Health and Care Excellence (NICE) Depression in adults: recognition and management Clinical guideline (CG90) 28 October 2009 (Updated April 2018). https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742638037 [Accessed 27 April 2018]

76. National Institute for Health and Care Excellence (NICE) Guidance on the use of electroconvulsive therapy Technology appraisal guidance (TA59), 2 May 2003.

77. National Institute for Health and Care Excellence (NICE) Vagus nerve stimulation for treatment-resistant depression. Interventional procedure guidance (IPG330) 16 December 2009.

78. Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015;172(10):950-966.

79. Nishimura M, Sato K. (1999) Ketamine stereoselectively inhibits rat dopamine transporter. Neuroscience Letters, 274: 131-134.

80. Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. Eur J Clin Nutrition. 1999;53:831-839.

81. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol. 2009;19(1):34-40.

82. Penning R, van Nuland M, Fliervoet LAL, et al. The pathology of alcohol hangover. Curr Drug Abuse Rev 2010;3:68-75.

83. Phillips JL, Batten LA, Tremblay P, Aldosary F, Blier P. A Prospective, Longitudinal Study of the Effect of Remission on Cortical Thickness and Hippocampal Volume in Patients with Treatment-Resistant Depression. Int J Neuropsychopharmacol. 2015 Mar 30;18(8).

84. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry. 2004;55:301-312.

85. Reynolds CF 3rd, Butters MA, Lopez O, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. Arch Gen Psychiatry. 2011 Jan;68(1):51-60.

86. Rickels K, Garcia-Espana F, Mandos L, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008;28(4):447–451.

87. Roberts R, Curran HV, Friston KJ, Morgan CJA (2014). Abnormalities in white matter microstructure associated with chronic ketamine use. Neuropsychopharmacology, 39: 329-338.

88. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905-1917.

89. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA. 2001;285:1299-1307.

90. Salloway S, Malloy P, Kohn R, Gillard E, Duffy J, Rogg J, Tung G, Richardson E, Thomas C, Westlake R. MRI and neuropsychological differences in early- and late-life-onset geriatric depression. Neurology. 1996 Jun;46(6):1567-74.

91. Sanacora G, Schatzberg AF. Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? Neuropsychopharmacology. 2015 Mar 13;40(5):1307.

92. Sasaki T, Andoh T, Watanabe I, Kamiya Y, Itoh H, Higashi T, Matsuura T (2000). Nonstereoselective inhibition of neuronal nicotinic acetylcholine receptors by ketamine isomers. Anesthesia Analgesia, 91: 741-748.

93. Sassano-Higgins S, Baron D, Juarez G, Esmaili N, Gold M. A review of ketamine abuse and diversion. Depress Anxiety. 2016;33:718-727.

94. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. Pharmacol Rev. 2015 Jul;67(3):697-730.

95. Sheahan CG, Mathews DM. Monitoring and delivery of sedation. Br J Anaesth. 2014 Dec;113 Suppl 2:ii37-47.

96. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11 Suppl 3:89-95.

97. Singh JB, Fedgchin M, Daly E, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. 2016;80:424-431.

98. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry. 2016;173:816-826.

99. Sinner B., Graf B.M. (2008) Ketamine. In: Schüttler J., Schwilden H. (eds) Modern Anesthetics. Handbook of Experimental Pharmacology, vol 182. Springer, Berlin, Heidelberg.

100. Smith DJ, Azzaro AJ, Zaldivar SB, Palmer S, Lee HS (1981). Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. Neuropharmacology, 20: 391-396.

101. Snyder PJ, Werth J, Giordani B, Caveney AF, Feltner D, Maruff P. A method for determining the magnitude of change across different cognitive functions in clinical trials: the effects of acute administration of two different doses alprazolam. Hum Psychopharmacol. 2005;20:263-273.

102. Solovich S. One time party drug hailed as miracle for treating severe depression. The Washington Post; Feb 1, 2016. https://www.washingtonpost.com/national/health-science/a-one-time-party-drug-is-helping-people-with-deep-depression/2016/02/01/d3e73862-b490-11e5-a76a-0b5145e8679a_story html?utm_term=.8947186a0207. Accessed 13 November 2018.

103. Stassen HH, Angst J, Hell D, Scharfetter C, Szegedi A. Is there a common resilience mechanism underlying antidepressant drug response? Evidence from 2848 patients. J Clin Psychiatry. 2007 Aug;68(8):1195-205.

104. Substance Abuse and Mental Health Services Administration. 2017. Results from the 2017 National Survey on Drug Use and Health: Detailed Tables. Tables 1.96B and 1.99B. Available at: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#lotsect1pe Accessed 7 January 2019.

105. Substance Abuse and Mental Health Services Administration. 2018. Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report. Accessed on 22 October 2018.

106. Turker S, Onur E, Ozer Y. Nasal route and drug delivery systems. Pharm World Sci. 2004;26:137-142.

107. United Nations Office on Drugs and Crime: World drug report 2010. Available at: https://www.unodc.org/documents/wdr/WDR_2010/World_Drug_Report_2010_lo-res.pdf. Accessed 31 July 2018.

108. United States Food and Drug Administration. Guidance for Industry: Assessment of Abuse Potential of Drugs (Jan 2017). Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

109. United States Food and Drug Administration. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (Aug 2012).

110. United States Food and Drug Administration. Major Depressive Disorder: Developing Drugs for Treatment. 2018.

111. Verster JC1, Mets MA. Psychoactive medication and traffic safety. Int J Environ Res Public Health. 2009;6(3):1041-1054.

112. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. 2014;171(4):404-415.

113. Wang C, Liu F, Patterson A, Paule MG, Slikker W (2013). Preclinical assessment of ketamine. CNS Neuroscience & Therapeutics, 19: 448-453.

114. Wassmer G. Planning and analyzing adaptive group sequential survival trials. Biom J. 2006;48(4): 714-729.

115. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 2008;192(1):52-58.

116. World Health Organization. 2017. "Depression: let's talk" says WHO, as depression tops list of causes of ill health. Available at: http://www.who.int/en/news-room/detail/30-03-2017--depression-let-s-talk-says-who-as-depression-tops-list-of-causes-of-ill-health. Accessed 12 November 2018.

117. Yamakura, T., Chavez-Noriega, L.E., Harris, R.A., 2000. Subunit-dependent inhibition of human neuronal nicotinic acetylcholine receptors and other ligand-gated ion channels by dissociative anesthetics ketamine and dizocilpine. Anesthesiology 92, 1144-1153.

118. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006 Aug;63(8):856-64.

119. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J Psychiatr Res. 2004 Nov-Dec;38(6):577-82.

List of Appendices

LIST OF APPENDICES

Appendix 1: Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale

Below is an excerpt from the publication describing the Structured Interview Guide for the Montgomery - Asberg Depression Rating Scale. The reference is as follows:

Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 2008;192(1):52-58.

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Structured Interview Guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA)

Interviewer

The questions in bold type for each item should be asked exactly as written. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for instance if information is unknown.

Notes

Time period. The ratings should be based on the patient's condition in the past week.

Change from baseline. In general, a symptom is rated as present only when it reflects a change from before the depression began. The interviewer should try to identify a 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the patient has dysthymia, the referent should be to the last time the person felt all right (i.e. not depressed or high) for at least a few weeks.

This interview guide is based on the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996 and 2005.

Structured Interview Guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA)

PT'S INITIALS: _____ PT'S ID: _____ INTERVIEWER: _____ TIME BEGAN SIGMA: _____ DATE: _____

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUT-PATIENT: Have you been working? (What kind of work do you do?) IF NOT: Why not?

In the past week, have you been feeling sad or unhappy?
(Depressed at all?) IF YES: Can you describe what this has been like for you?
(IF UNKNOWN: How bad has that been?)
IF DEPRESSED: Does the feeling lift at all if something good happens
How much does your mood lift? Does the feeling ever go away completely?
(What things have made you feel better?)
How often did you feel (depressed/OWN EQUIVALENT) this past week?
(IF UNKNOWN: How many days this week did you feel that way? How much of each day?)
In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you?
IF ACKNOWLEDGES DEPRESSED MOOD, TO GET CONTEXT ASK:
How long have you been feeling this way?

1. REPORTED SADNESS. Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances
1
2 Sad or low but brightens up without difficulty
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 Continuous or unvarying sadness, misery or despondency

RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.
In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?
How about when you've looked in the mirror? Did you look gloomy or depressed?
IF YES: How sad or depressed do you think you have looked?
How much of the time over the past week do you think you have looked depressed or down?
IF APPEARANCE WAS DEPRESSED IN PAST WEEK: Have you been able to laugh or smile at all during the past week? IF YES: How hard has it been for you to laugh or smile, even if you weren't feeling happy inside?

2. APPARENT SADNESS. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions and posture. Rate by depth and inability to brighten up.

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent

Have you felt tense or edgy in the past week? Have you felt anxious or nervous?
IF YES: Can you describe what that has been like for you? How bad has it been? (Have you felt panicky?)
What about feeling fearful that something bad is about to happen?
How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)
How much of the time have you felt this way over the past week?

3. INNER TENSION. Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension
1
2 Occasional feelings of edginess and ill-defined discomfort
3
4 Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty
5
6 Unrelenting dread or anguish. Overwhelming panic

How has your sleeping been in the past week? (How many hours have you been sleeping, compared with usual?)

Have you had trouble falling asleep? (How long has it been taking you to fall asleep this past week?)

Have you been able to stay asleep through the night? (Have you been waking up at all in the middle of the night? How long does it take you to go back to sleep?)

Has your sleeping been restless or disturbed?

4. REDUCED SLEEP. Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual
1
2 Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep
3
4 Sleep reduced or broken by at least 2 hours
5
6 Less than 2 or 3 hours sleep

How has your appetite been this past week?
(What about compared with your usual appetite?)
Have you been less interested in food? (How much less?)
Does food taste as good as usual? IF LESS: How much less?
Have you had to force yourself to eat?
Have other people had to urge you to eat?

5. REDUCED APPETITE. Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite
1
2 Slightly reduced appetite
3
4 No appetite. Food is tasteless
5
6 Needs persuasion to eat at all

Appendix (continued)

Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a newspaper or magazine? Do you need to read things over and over again?)

How often has that happened in the past week? Has this caused any problems for you? IF YES: Can you give me some examples?

Has your trouble concentrating been so bad at any time in the past week that it has been difficult to follow a conversation? (IF YES: How bad has that been? How often has that happened this past week?)

NOTE: ALSO CONSIDER BEHAVIOUR DURING INTERVIEW.

6. CONCENTRATION DIFFICULTIES. Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentration
1
2 Occasional difficulties in collecting one's thoughts
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
5
6 Unable to read or converse without great difficulty

Have you had any trouble getting started at things in the past week? IF YES: What things?

Have you had to push yourself to do things? IF YES: What things? How hard have you had to push yourself? Are you OK once you get started or is it still more of an effort to get something done? What about getting started at simple routine everyday things (like getting dressed)?

Have you done everyday things more slowly than usual? (Have you been sluggish?) IF YES: Like what, for example? How bad has that been?

7. LASSITUDE. Representing a difficulty getting started, or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness
1
2 Difficulties in starting activities
3
4 Difficulties in simple routine activities, which are carried out with effort
5
6 Complete lassitude. Unable to do anything without help

Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How bad has that been? How much less interested in (those things) are you now compared with before?

Have you been less able to enjoy the things you usually enjoy? Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)

How do you feel towards your family and friends? Is that different from usual? IF REDUCED: Do you feel less than you used to towards them?

8. INABILITY TO FEEL. Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people
1
2 Reduced ability to enjoy usual interests
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends

Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?

Have you been feeling guilty about anything in the past week? What about feeling as if you have done something bad or sinful? IF YES:

What have your thoughts been? How often have you felt that way?

ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.

9. PESSIMISTIC THOUGHTS. Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable

This past week, have you felt like life isn't worth living? IF YES: Tell me about that. IF NO: What about feeling as if you're tired of living?

This week, have you thought that you would be better off dead? IF YES: Tell me about that.

Have you had thoughts of hurting or even killing yourself this past week? IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)

10. SUICIDAL THOUGHTS. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.

0 Enjoys life or takes it as it comes
1
2 Weary of life. Only fleeting suicidal thoughts
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide

TOTAL MADRS SCALE SCORE: _____

Appendix 2: Treatment Algorithm: Frequency of Administration of Nasal Spray During the Optimization and Maintenance Phases of SUSTAIN-1

The treatment algorithm for nasal spray dosing during the optimization and maintenance phases in SUSTAIN-1 are described below.

Optimization Phase

Transferred-entry patients continued the same double-blind nasal spray study medication at the same dose from the double-blind induction phase of TRANSFORM-1 or TRANSFORM-2. Direct-entry patients continued the same open-label esketamine treatment at the same dose from the open-label induction phase.

During the optimization phase, the Montgomery-Asberg Depression Rating Scale (MADRS) was performed weekly by an independent, remote rater, and this MADRS total score was used for nasal spray treatment session frequency assignment every 4 weeks. For all patients, the frequency of nasal spray treatment sessions was reduced from the twice-weekly frequency used in the induction phase to weekly for the first 4 weeks of the optimization phase (Week 5 to Week 8).

There were 2 fixed time points (Week 8 and Week 12) during the optimization phase at which an adjustment to the frequency could be made.

Patients with a MADRS total score >12 at Week 8 (or the last MADRS total score available) were to continue to receive weekly nasal spray treatment sessions for the remainder of the optimization phase. If the MADRS total score was ≤12 at Week 8 (or the last MADRS total score available), the frequency of nasal spray treatment sessions was reduced to every other week for the next 4 weeks (i.e., Week 10 and Week 12).

If the MADRS total score was >12 at Week 12 (or last MADRS total score available), the frequency of nasal spray treatment sessions was to be increased to weekly for the remainder of the optimization phase (through Week 16) without further change to the treatment session frequency. If the MADRS total score was ≤12 at Week 12 (or last MADRS total score available), the patient was to remain on a nasal spray treatment session frequency of every other week for the next 4 weeks (i.e., through Week 16).

Maintenance Phase

All patients received double-blind nasal spray study medication in this phase, and MADRS was assessed weekly by an independent, remote rater.

Patients who were currently receiving nasal spray treatment sessions on a weekly basis stayed at the same weekly treatment session frequency for the first 4 weeks of this phase. For patients who were currently receiving nasal spray treatment sessions every other week, if the MADRS total score was >12 at Week 16, the frequency of treatment sessions was to be increased to weekly for the next 4 weeks. If the MADRS total score was ≤12 at Week 16, the patient was to stay at the same every-other-week treatment session frequency for the next 4 weeks.

Thereafter, changes to the nasal spray treatment session frequency occurred at 4-week intervals (Week 20, 24, 28, 32, 36, 40, 44 and every 4 weeks until the end of the phase), if applicable, based on the MADRS total score:

- If the MADRS total score was ≤12 at that week (or the last MADRS score available prior to that week):
  - If the frequency was weekly, the frequency was to be changed to every other week.
  - If the frequency was every other week, there was to be no change in frequency.

- If the MADRS total score was >12 at that week (or the last MADRS score available prior to that week):
  - If the frequency was weekly, there was to be no change in frequency.
  - If the frequency was every other week, the frequency was to be changed to weekly.

A maximum of 3 changes in nasal spray treatment session frequency from weekly to every other week was permitted during the maintenance phase. After this time, if a given patient was unable to sustain improvement on every-other-week dosing they were to remain on a weekly dosing frequency for the duration of the maintenance phase.

Appendix 3: SUSTAIN-1: Additional Information Regarding Disposition, Demographics, and Baseline Characteristics

Details about the characteristics of the study population in SUSTAIN-1 are presented below.

Maintenance Phase

At the beginning of the maintenance phase, eligible patients were randomized if they met the criteria for stable remission and stable response (but not remission). The efficacy populations in SUSTAIN-1 included 176 patients in the full (stable remitters) analysis set of the maintenance phase, which was the primary efficacy set, and 121 patients were included in the full (stable responders) analysis set, which was a secondary efficacy set.

The demographic and baseline characteristics for patients in the full (stable remitters) analysis set are shown in App 3 - Table 1.

App 3 - Table 1: Demographic and Baseline (Induction Phase) Characteristics (SUSTAIN-1: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
Age (years)			
Mean (SD)	45.4 (12.12)	46.2 (11.16)	45.8 (11.64)
Age category (years), n (%)			
18-44	38 (42.2%)	37 (43.0%)	75 (42.6%)
45-64	52 (57.8%)	49 (57.0%)	101 (57.4%)
Sex, n (%)			
Female	58 (64.4%)	59 (68.6%)	117 (66.5%)
Race, n (%)			
Black or African American	4 (4.4%)	6 (7.0%)	10 (5.7%)
White	80 (88.9%)	76 (88.4%)	156 (88.6%)
American Indian or Alaskan native	0	1 (1.2%)	1 (0.6%)
Other	2 (2.2%)	1 (1.2%)	3 (1.7%)
Multiple	1 (1.1%)	0	1 (0.6%)
Not Reported	3 (3.3%)	2 (2.3%)	5 (2.8%)
Ethnicity, n (%)			
Hispanic or Latino	14 (15.6%)	12 (14.0%)	26 (14.8%)
Not Hispanic or Latino	73 (81.1%)	72 (83.7%)	145 (82.4%)
Not Reported	3 (3.3%)	2 (2.3%)	5 (2.8%)
Region, n (%)			
Europe	52 (57.8%)	50 (58.1%)	102 (58.0%)
North America	22 (24.4%)	20 (23.3%)	42 (23.9%)
Other	16 (17.8%)	16 (18.6%)	32 (18.2%)
Class of oral antidepressant, n (%)			
SNRI	62 (68.9%)	58 (67.4%)	120 (68.2%)
SSRI	28 (31.1%)	28 (32.6%)	56 (31.8%)
Oral antidepressant, n (%)			
Duloxetine	47 (52.2%)	38 (44.2%)	85 (48.3%)
Escitalopram	13 (14.4%)	14 (16.3%)	27 (15.3%)
Sertraline	15 (16.7%)	14 (16.3%)	29 (16.5%)
Venlafaxine extended release (XR)	15 (16.7%)	20 (23.3%)	35 (19.9%)

AD=antidepressant; Esk=esketamine; SD=standard deviation; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor

The baseline psychiatric history for patients in the full (stable remitters) analysis set are shown in App 3 - Table 2 and App 3 - Table 3.

App 3 - Table 2: Baseline (Induction Phase) Psychiatric History (SUSTAIN-1: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
Age when diagnosed with MDD (years)			
Mean (SD)	32.5 (11.42)	33.4 (11.41)	32.9 (11.39)
Baseline MADRS total score			
Mean (SD)	37.4 (5.20)	37.6 (4.66)	37.5 (4.93)
Baseline SDS total score			
Mean (SD)*	23.5 (3.85)	23.8 (3.97)	23.7 (3.90)
Baseline PHQ-9 total score			
Mean (SD)	19.2 (4.16)	19.8 (3.43)	19.5 (3.82)
Duration of current episode (weeks)			
Mean (SD)	112.2 (171.30)	110.5 (147.41)	111.4 (159.62)
Family history of depression, n (%)			
Yes	39 (43.3%)	36 (41.9%)	75 (42.6%)

AD=antidepressant; Esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PHQ-9=9-item Patient Health Questionnaire; SD=standard deviation; SDS=Sheehan Disability Scale
* Intranasal Esk + Oral AD: N=88; Oral AD + Intranasal Placebo: N=80; Total: N=168
MADRS total score (clinician-rated measure of depression severity ranging from 0 to 60) ≥35 signals severe depression
SDS total score (patient-reported measure of mental health-related functional impairment) ranges from 0 (not impaired) to 30 (extremely impaired)
PHQ-9 total score (patient-reported measure of depression severity ranging from 0 to 27) ≥20 signals severe depression

App 3 - Table 3: Number of Antidepressant Medications With Nonresponse Prior to Study Entry (SUSTAIN-1: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
Number of previous antidepressant medications with nonresponse, n (%)			
2	60 (66.7%)	53 (61.6%)	113 (64.2%)
3 or more	27 (30.0%)	28 (32.6%)	55 (31.3%)

AD=antidepressant; Esk=esketamine
Of the 8 patients not summarized in the table, 5 were determined to have had nonresponse to at least 2 oral antidepressants based on other data in the database, and the remaining 3 (all of whom were direct-entry patients) had nonresponse to 1 oral antidepressant.

The demographic and baseline characteristics for patients in the full (stable responders) analysis set are shown in App 3 - Table 4.

App 3 - Table 4: Demographic and Baseline (Induction Phase) Characteristics (SUSTAIN-1: Full (Stable Responders) Analysis Set)

	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)	Total (N=121)
Age (years)			
Mean (SD)	47.2 (11.00)	46.7 (9.76)	47.0 (10.37)
Age category (years), n (%)			
18-44	23 (37.1%)	24 (40.7%)	47 (38.8%)
45-64	39 (62.9%)	35 (59.3%)	74 (61.2%)
Sex, n (%)			
Female	38 (61.3%)	42 (71.2%)	80 (66.1%)
Race, n (%)			
Asian	0	1 (1.7%)	1 (0.8%)
Black or African American	2 (3.2%)	1 (1.7%)	3 (2.5%)
White	57 (91.9%)	55 (93.2%)	112 (92.6%)
Other	3 (4.8%)	1 (1.7%)	4 (3.3%)
Multiple	0	1 (1.7%)	1 (0.8%)
Ethnicity, n (%)			
Hispanic or Latino	8 (12.9%)	9 (15.3%)	17 (14.0%)
Not Hispanic or Latino	54 (87.1%)	50 (84.7%)	104 (86.0%)
Region, n (%)			
Europe	34 (54.8%)	35 (59.3%)	69 (57.0%)
North America	18 (29.0%)	16 (27.1%)	34 (28.1%)
Other	10 (16.1%)	8 (13.6%)	18 (14.9%)
Class of oral antidepressant, n (%)			
SNRI	35 (56.5%)	36 (61.0%)	71 (58.7%)
SSRI	27 (43.5%)	23 (39.0%)	50 (41.3%)
Oral antidepressant, n (%)			
Duloxetine	27 (43.5%)	30 (50.8%)	57 (47.1%)
Escitalopram	17 (27.4%)	10 (16.9%)	27 (22.3%)
Sertraline	10 (16.1%)	13 (22.0%)	23 (19.0%)
Venlafaxine extended release (XR)	8 (12.9%)	6 (10.2%)	14 (11.6%)

AD=antidepressant; Esk=esketamine; SD=standard deviation; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor

See App 3 - Table 5 and App 3 - Table 6 for the baseline psychiatric history for the full (stable responders) analysis set.

App 3 - Table 5: Baseline (Induction Phase) Psychiatric History (SUSTAIN-1: Full (Stable Responders) Analysis Set)

	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)	Total (N=121)
Age when diagnosed with MDD (years)			
Mean (SD)	36.2 (13.25)	34.0 (10.54)	35.1 (12.01)
Baseline MADRS total score			
Mean (SD)	40.1 (5.56)	38.9 (4.92)	39.5 (5.27)
Baseline SDS total score			
Mean (SD)*	24.8 (3.56)	24.0 (3.67)	24.4 (3.62)
Baseline PHQ-9 total score			
Mean (SD)	20.5 (4.12)	20.4 (4.15)	20.4 (4.12)
Duration of current episode (weeks)			
Mean (SD)	121.6 (193.85)	141.8 (254.43)	131.4 (224.71)
Family history of depression, n (%)			
Yes	30 (48.4%)	21 (35.6%)	51 (42.1%)

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PHQ-9=9-item Patient Health Questionnaire; SD=standard deviation; SDS=Sheehan Disability Scale
* Intranasal Esk + Oral AD: N=60; Oral AD + Intranasal Placebo: N=58; Total: N=118
MADRS total score (clinician-rated measure of depression severity ranging from 0 to 60) ≥35 signals severe depression
SDS total score (patient-reported measure of mental health-related functional impairment) ranges from 0 (not impaired) to 30 (extremely impaired)
PHQ-9 total score (patient-reported measure of depression severity ranging from 0 to 27) ≥20 signals severe depression

App 3 - Table 6: Number of Antidepressant Medications With Nonresponse Prior to Study Entry (SUSTAIN-1: Full (Stable Responders) Analysis Set)

	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)	Total (N=121)
Number of previous antidepressant medications with nonresponse, n (%)			
2	34 (54.8%)	31 (52.5%)	65 (53.7%)
3 or more	27 (43.5%)	27 (45.8%)	54 (44.6%)

AD=antidepressant; Esk=esketamine
Of the 2 patients not summarized in the table, 1 patient was determined to have had nonresponse to at least 2 oral antidepressants based on other data in the database, and 1 (direct-entry) patient had nonresponse to 1 oral antidepressant.

Appendix 4: SUSTAIN-2: Additional Information Regarding Demographics, and Baseline Characteristics

Further details regarding the demographic and baseline characteristics of patients enrolled in SUSTAIN-2 reported at the start of the induction phase are presented in App 4 - Table 1.

App 4 - Table 1: Demographic and Baseline (Induction Phase) Characteristics (SUSTAIN-2: All Enrolled Analysis Set)

	Intranasal Esk + Oral AD (N=802)
Age (years)	
Mean (SD)	52.2 (13.69)
Age category (years), n (%)	
18-44	225 (28.1%)
45-64	399 (49.8%)
65-74	159 (19.8%)
>=75	19 (2.4%)
Sex, n (%)	
Female	502 (62.6%)
Race, n (%)	
Asian	81 (10.1%)
Black or African American	15 (1.9%)
White	686 (85.5%)
Other	8 (1.0%)
Multiple	8 (1.0%)
Not Reported	4 (0.5%)
Ethnicity, n (%)	
Hispanic or Latino	149 (18.6%)
Not Hispanic or Latino	640 (79.8%)
Not Reported	10 (1.2%)
Unknown	3 (0.4%)
Region, n (%)	
Europe	322 (40.1%)
North America	147 (18.3%)
Other	333 (41.5%)
Class of oral antidepressant, n (%)*	
SNRI	407 (50.8%)
SSRI	394 (49.2%)
Oral antidepressant, n (%)*	
Duloxetine	251 (31.3%)
Escitalopram	237 (29.6%)
Sertraline	157 (19.6%)
Venlafaxine extended release (XR)	156 (19.5%)

AD=antidepressant; Esk=esketamine; SD=standard deviation; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor
* A total of 801 patients were evaluated.

The baseline psychiatric history of the patients enrolled in SUSTAIN-2 is summarized in App 4 - Table 2 and App 4 - Table 3.

App 4 - Table 2: Baseline (Induction Phase) Psychiatric History (SUSTAIN-2: All Enrolled Analysis Set)

	Intranasal Esk + Oral AD (N=802)
Age when diagnosed with MDD (years)	
Mean (SD)	35.7 (13.75)
Baseline MADRS total score	
Mean (SD)	31.4 (5.39)
Baseline SDS total score	
Mean (SD)*	22.2 (5.42)
Baseline PHQ-9 total score	
Mean (SD)	17.3 (5.01)
Duration of current episode (weeks)	
Mean (SD)	160.5 (261.80)
Family history of depression, n (%)	
Yes	346 (43.1%)

AD=antidepressant; Esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PHQ-9=9-item Patient Health Questionnaire; SD=standard deviation; SDS=Sheehan Disability Scale
* N=722
Baseline (Induction Phase) is the last observation prior to or on the start date of induction phase for direct-entry and transferred-entry non-responder patients and is baseline (Induction Phase) from TRANSFORM-3 for the transferred-entry responder patients.
MADRS total score (clinician-rated measure of depression severity ranging from 0 to 60) ≥35 signals severe depression
SDS total score (patient-reported measure of mental health-related functional impairment) ranges from 0 (not impaired) to 30 (extremely impaired)
PHQ-9 total score (patient-reported measure of depression severity ranging from 0 to 27) ≥20 signals severe depression

App 4 - Table 3: Number of Antidepressant Medications With Nonresponse Prior to Study Entry (SUSTAIN-2: Full (Induction Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=779)
Number of previous antidepressant medications with nonresponse, n (%)	
2	452 (58.0%)
3 or more	314 (40.3%)

AD=antidepressant; Esk=esketamine
Of the 13 patients not summarized in the table, 7 (5 of whom were transferred-entry non-responders) were determined to have had nonresponse to at least 2 oral antidepressants based on other data in the database, and 6 (all of whom were transferred-entry non-responders) took 1 oral antidepressant.

Appendix 5: Summary of Published Information on Clinically Meaningful Improvement in Assessment of Antidepressant Efficacy

Assessment of Antidepressant Efficacy

For assessment of antidepressant efficacy, the current standard is based on clinician-rated outcome measures. Currently 2 rating scales are accepted by health authorities: the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale, 17-item version (HAM-D). The primary endpoint most often used is difference in change in total scores of MADRS or HAM-D between new antidepressant and comparator at endpoint.

The average treatment effect by HAM-D was -3.0 (SD=2.4) in studies conducted before 1995 and then was -1.8 (SD=1.0) in studies conducted since 1995.[7] The average 2-point difference between antidepressants and placebo translates into a clinically meaningful treatment difference for well accepted antidepressants with proven efficacy.[10]

This clinically meaningful difference of 2 points applies equally to both the HAM-D and MADRS, albeit most of the older studies used the HAM-D as the primary scale. In studies which have used both HAM-D and MADRS scales, the differences at endpoint between drug and comparator is approximately 2 points for both scales[10] and this is widely believed by academics to be sufficient as a criterion establishing obvious clinically meaningful benefit,[10] and also accepted by European Health Authorities.[9]

The data from some of the recently approved antidepressants for adjunctive treatment of depression and treatment-resistant depression are summarized in App 5 - Table 1 and App 5 - Table 2, as examples of change in MADRS total scores.

App 5 - Table 1: Summary Statistics of Treatment Effect Sizes for Approved Antidepressant Drugs Based on Change in MADRS Total Score

	Difference From Reference	
Study Medication	**MADRS Mean**	**Median (Range)**
Quetiapine	-2.67	-2.79 (-3.05; -1.90)
Aripiprazole	-3.17	-3.00 (-3.70; -2.80)
Brexpiprazole	-1.94	-1.52 (-3.12; -1.19)
Vortioxetine	-3.23	-2.50 (-7.10, -0.50)
Olanzapine + fluoxetine	-2.54	-1.40 (-6.90; -0.20)

MADRS=Montgomery-Asberg Depression Rating Scale

App 5 - Table 2: Treatment Effect Size for MADRS Total Score Reported in Individual Published Studies of Approved Antidepressant Drugs

Study Medication	Study	Treatment Arm	MADRS Difference From Placebo
Quetiapine	Bauer et al.[2]	150 mg	-3.05
		300 mg	-2.73
	El Khalili et al.[6]	150 mg	-1.90
		300 mg	-3.00
	Bauer et al.[1]	150 mg	-2.50
		300 mg	-2.85
Aripiprazole	Berman et al.[4]	2-20 mg	-3.00
	Marcus et al.[8]	2-20 mg	-2.80
	Berman et al.[3]	2-20 mg	-3.70
Brexpiprazole	Thase et al.[14]	1 mg	-1.19
		3 mg	-1.52
	Thase et al.[13]	2 mg	-3.12
Vortioxetine	11492A[15]	5 mg	-5.9
		10 mg	-5.7
	13267A[15]	15 mg	-5.5
		20 mg	-7.1
	315[15]	15 mg	-1.5
		20 mg	-2.8
	316[15]	10 mg	-2.2
		20 mg	-3.6
	11984A[15]	5 mg	-1.7
		10 mg	-1.5
	317[15]	10 mg	-0.8
		15 mg	-0.5
		Reference Treatment Arm	MADRS Difference From Reference
Olanzapine + fluoxetine	Thase et al.[12]	Fluoxetine	-5.60
		Olanzapine	-6.90
	Thase et al.[12]	Fluoxetine	-1.40
		Olanzapine	-0.70
	Shelton et al.[11]	Fluoxetine	-0.20
		Olanzapine	-1.76
		Nortriptyline	-1.25

MADRS=Montgomery-Asberg Depression Rating Scale

Differences in Response Rates

Coauthors from the Medical Products Agency, Sweden (MPA), from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), from the Agence Francaise de Securité Sanitaire des Produits de Santé, France (AFSSAPS), and from the Medicines Evaluation Board, Netherlands (MEB) have argued that differences in MADRS or HAM-D total scores versus placebo are important, but that differences in response rates should also be demonstrated.[9]

The United Kingdom's National Institute of Clinical Excellence (NICE) uses a 10% difference in response rate to assess for clinically meaningful difference between 2 new antidepressant treatments.[10] An assessment on efficacy of antidepressants by the CHMP set a 16% difference in response rates between antidepressant and placebo to be a clinically meaningful difference, and noted that the difference in response rates for most approved antidepressants was between 13.1% and 19.5%.[5]

References

1. Bauer M, El-Khalili N, Datto C, Szamosi J, Eriksson H. A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. J Affect Disord. 2010;127(1-3):19-30.
2. Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009;70(4):540-549.
3. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009;14(4):197-206.
4. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-53.
5. Broich K; Committee for Medicinal Products for Human Use. Committee for Medicinal Products for Human Use (CHMP) assessment on efficacy of antidepressants. Eur Neuropsychopharmacol. 2009;19:305-308.
6. El-Khalili N, Joyce M, Atkinson S, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13(7):917-932.
7. Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. 2011;72(4):464-72.
8. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008;28(2):156 165.
9. Melander H, Salmonson T, Abadie E, van Zwieten-Boot B. A regulatory Apologia - a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur Neuropsychopharmacol. 2008;18:623-627.
10. Montgomery SA, Moller HJ. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Int Clin Psychopharmacol. 2009;24:111-118.
11. Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry. 2005;66(10):1289-1297.
12. Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry. 2007;68(2):224-36.
13. Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224-1231.
14. Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J Clin Psychiatry. 2015;76(9):1232-1240.
15. Zhang J, Mathis MV, Sellers JW, et al. The US Food and Drug Administration's perspective on the new antidepressant vortioxetine. J Clin Psychiatry. 2015 Jan;76(1):8-14.

Appendix 6: Subgroup Analyses of the Primary Endpoint in the Short-term Phase 3 Studies

For the 3 short-term studies, the subpopulations of the 342 patients in TRANSFORM-1, the 223 patients in TRANSFORM-2, and the 137 patients in TRANSFORM-3 were compared for the primary efficacy outcomes (i.e., the change in Montgomery-Asberg Depression Rating Scale [MADRS] total score after twice-weekly esketamine dosing for 28 days), with the following results:

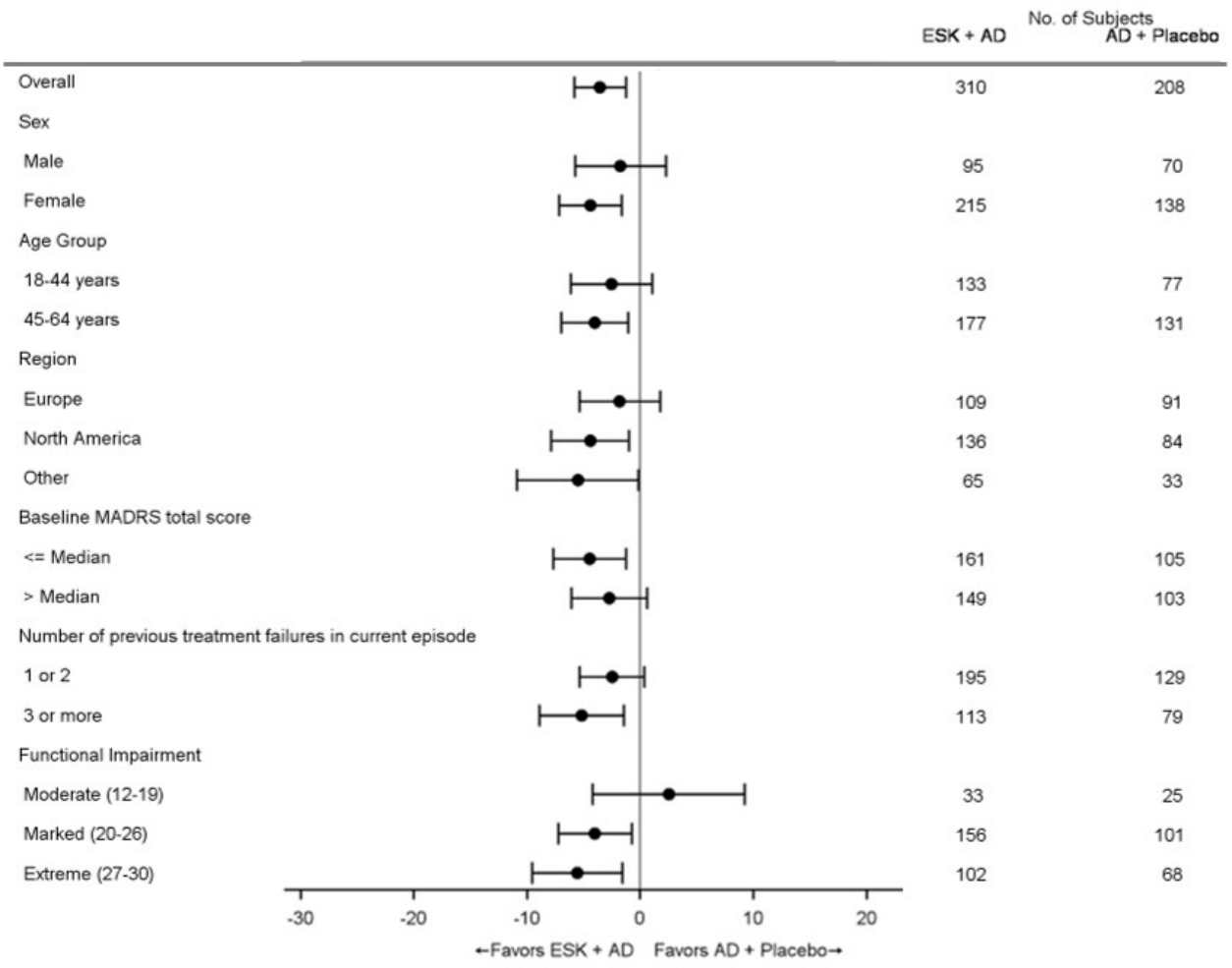
- Age subpopulations: Efficacy results were generally consistent in favoring esketamine for both patients aged <65 years and patients aged ≥65 years, and for both patients aged 18 to 44 years and patients aged 45 to 64 years. For patients ages 65 to 74 years versus patients ≥75 years, the very small sample size of the latter limited any meaningful conclusions. Overall, the results indicated the potential for benefit in the vulnerable and difficult-to-treat population ≥65 years.
- Subgroup analyses in the pooled adult population for TRANSFORM-1/2 showed no major differences in the results as a function of age, sex, race, baseline MADRS total score, number of previous treatment failures, functional impairment by Sheehan Disability Scale (SDS) total score, country, region, class of oral antidepressant (AD), or oral AD class history.

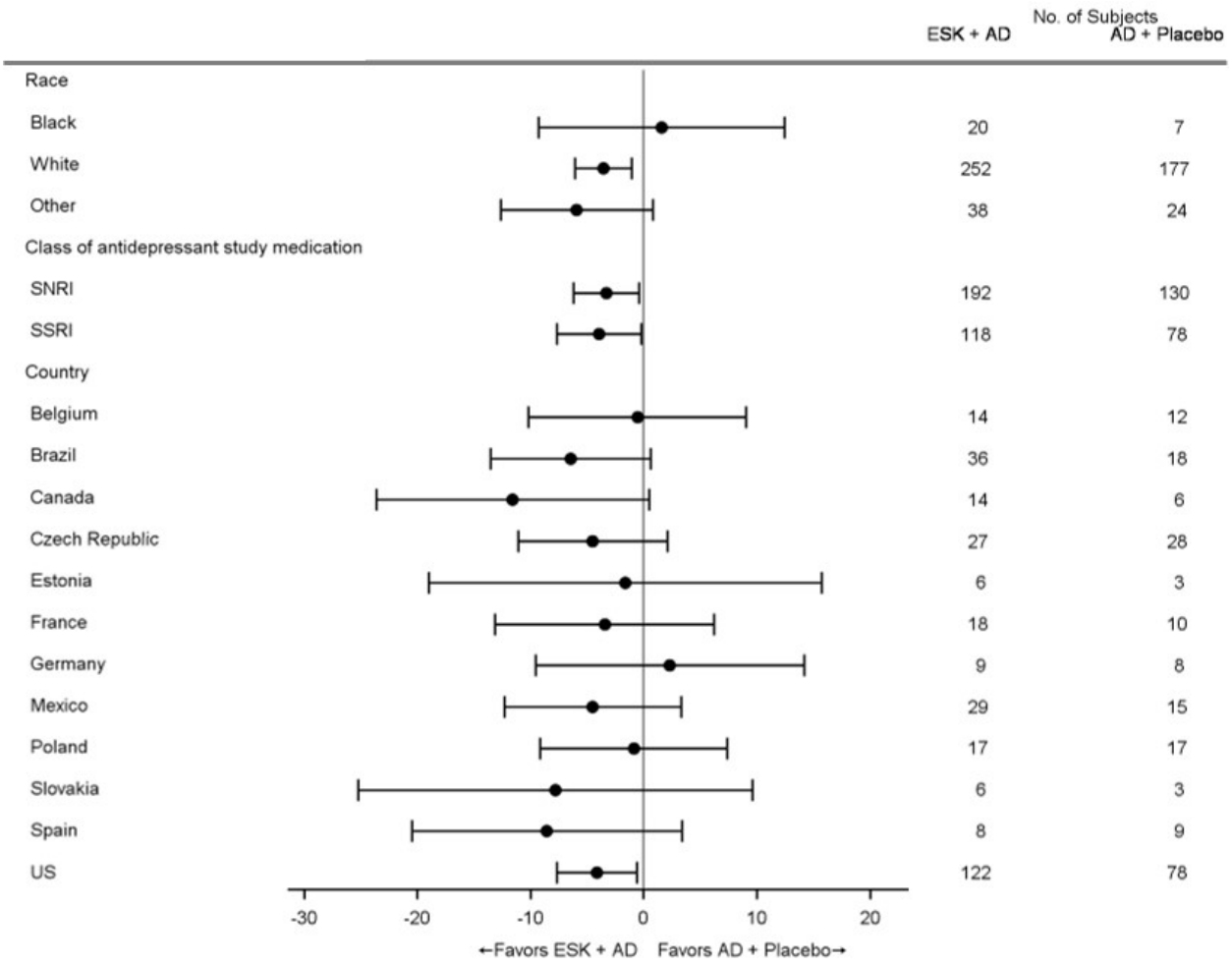
Subgroup Analysis of Pooled Results from Patients 18-64 Years of Age in TRANSFORM-1 and 2

In the exploratory pooled analysis of TRANSFORM-1 and 2, forest plots were generated to show the least-squares mean treatment differences of change from baseline (95% CI) to Day 28 or endpoint for the following demographic variables: age, sex, race, baseline MADRS total score, number of previous treatment failures, functional impairment by SDS total score, country, region, class of oral antidepressant (AD), or oral AD class history. Results are shown for subpopulations with at least 6 patients per variable in App 6 - Figure 1.

Esketamine + oral AD was generally favored over oral AD + placebo in the various demographic subpopulations in the pooled adult studies TRANSFORM-1/2. Some exceptions occurred in subpopulations with numbers of patients that were small; for example, for Black race with 20 patients in the esketamine group but 7 patients in the oral AD + placebo group. Some exceptions were driven by results of one study but not the other; for example, for baseline functional impairment, esketamine was favored in all 3 categories in TRANSFORM-1 and 2 categories (marked and extreme impairment) in TRANSFORM-2. Moreover, these potential exceptions in race and functional impairment in the short-term studies were not observed in the long-term study.

App 6 - Figure 1: MADRS Total Score: Forest Plot by MMRM (Observed Case) for Prespecified Subpopulations: Least-squares Mean Treatment Difference of Change From Baseline (95% CI) to Day 28 of the Double-blind Induction Phases Studies TRANSFORM-1/2 (Full Analysis Set)





AD=antidepressant; CI=confidence interval; Esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SDS=Sheehan Disability Scale; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; US=United States.
Notes: Subpopulations with 5 or fewer patients are not included.

Subgroup Analysis of Patients ≥65 Years of Age in TRANSFORM-3

Patients Aged 65 to 74 Years Versus Patients ≥75 years

In the short-term study of older patients (TRANSFORM-3), the MADRS total scores were analyzed for the subpopulations of patients aged 65 to 74 years and ≥75 years. Highlights of the subpopulations analysis by age are shown in App 6 - Table 1.

- Number of patients: At baseline, the subpopulation sizes were 116 patients 65 to 74 years and 21 patients ≥75 years. Due to the small number of patients ≥75 years, the results should be interpreted with caution.
- Severity at baseline: The mean MADRS total scores were slightly higher, indicating a more severe baseline condition, for patients ≥75 years (at approximately 37 points) than for the patients 65 to 74 years (at approximately 34 or 35 points).

- Results: With oral AD + placebo, improvements were approximately similar between patients aged 65 to 74 years and patients ≥75 years, with all showing approximately 5 to 7 points of improvement in mean MADRS total scores. With esketamine + oral AD, the differences versus oral AD + placebo were clinically meaningful for patients 65 to 74 years but were not consistent for patients ≥75 years. The difference in least-squares mean changes (95% CI) by MMRM at Day 28, results were -4.9 (-8.96; -0.89) for patients 65 to 74 years and -0.4 (-10.38; +9.50) for patients ≥75 years. Overall for the patients aged ≥75 years, the small sample size limited any meaningful conclusions.

App 6 - Table 1: MADRS Total Score for Patients Aged 65 to 74 years and Patients Aged ≥75 years: Change From Baseline to Day 28 by MMRM (Observed Case) in the Double-blind Induction Phase of TRANSFORM-3 (Full Analysis Set)

	To Day 28, by MMRM	
	Esketamine (28, 56, or 84 mg) + Oral AD (N=72)	**Oral AD + Placebo (N=65)**
Patients 65 to 74 years		
Baseline		
N	59	57
Mean (standard deviation)	35.1 (6.13)	34.4 (5.88)
Day 28 or endpoint		
N	53	53
Mean (standard deviation)	24.1 (12.68)	28.3 (9.52)
Change, baseline to Day 28 or endpoint		
N	53	53
Mean (standard deviation)	-10.9 (12.90)	-6.2 (9.06)
Statistical analysis [a]		
Difference (standard error)	-4.9 (2.04)	
95% confidence interval on difference	-8.96; -0.89	
Patients ≥75 years		
Baseline		
N	13	8
Mean (standard deviation)	37.3 (4.61)	37.1 (9.75)
Day 28 or endpoint		
N	10	7
Mean (standard deviation)	32.2 (11.01)	31.6 (14.46)
Change, baseline to Day 28 or endpoint		
N	10	7
Mean (standard deviation)	-5.1 (11.14)	-7.0 (7.72)
Statistical analysis [a]		
Difference (standard error)	-0.4 (5.02)	
95% confidence interval on difference	-10.38; 9.50	

AD=antidepressant; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures

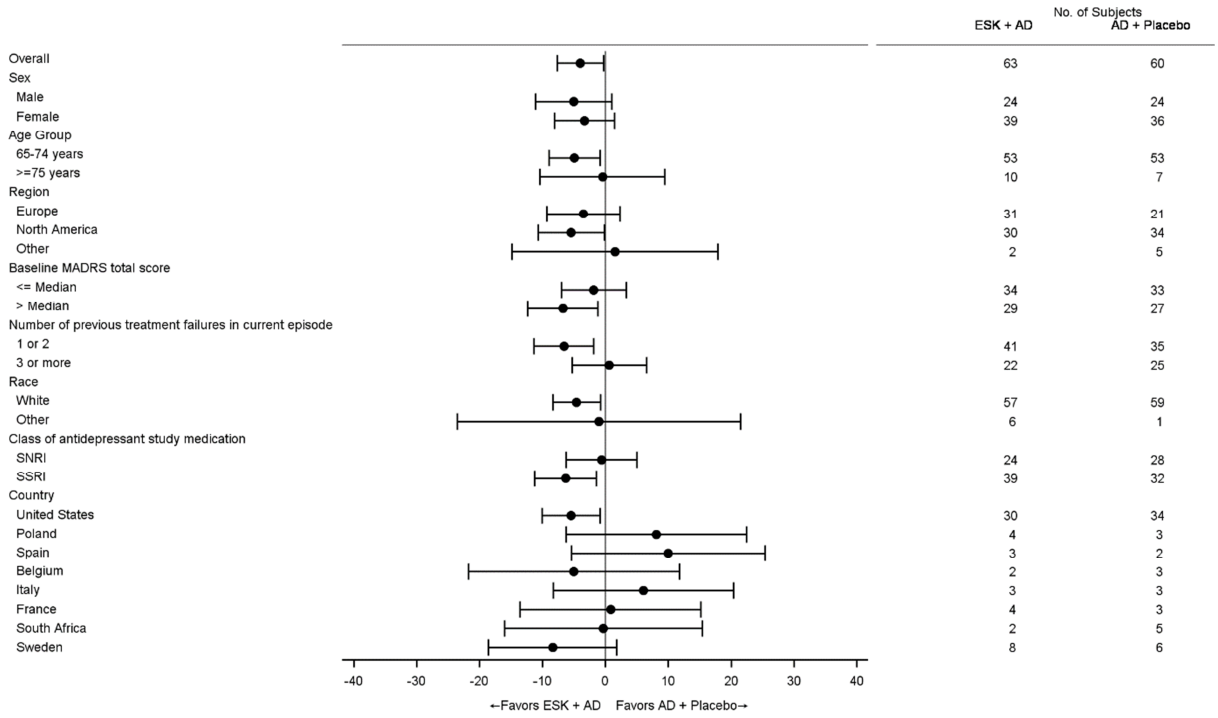
[a] The difference is the result of the least-squares means for esketamine + AD minus AD + placebo. The MMRM is based on change from baseline as the response variable and the fixed effect model terms for treatment (esketamine + oral AD or oral AD + placebo), day, region, class of oral AD (serotonin and norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI]), age group, treatment-by-day, treatment-by-age group, treatment-by-age group, and treatment-by-day-by-age group, and baseline value as a covariate. A negative difference favors esketamine, and the results were not adjusted for sample size re-estimation.

Notes: The MADRS total score ranges from 0 to 60 points; a higher score indicates a more severe condition, and a negative change in score indicates improvement. The age categories apply to study entry.

Results from Subgroup Analyses of Other Demographic Variables in TRANSFORM-3

Results for the other prespecified demographic variables in TRANSFORM-3 are shown in App 6 - Figure 2 (i.e., gender, race, geographic region, country, number of previous treatment failures in current episode, baseline MADRS total score [above median versus at or below median], and class of oral AD initiated at randomization [SNRI or SSRI]). Results generally favored esketamine over placebo; some exceptions occurred in subpopulations with numbers of patients that were too small to support any conclusions.

App 6 - Figure 2: Forest Plot for MADRS Total Score: Least-squares Mean Treatment Difference of Change From Baseline (95% CI) to Day 28 MMRM (Observed Case) by Subgroup; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)

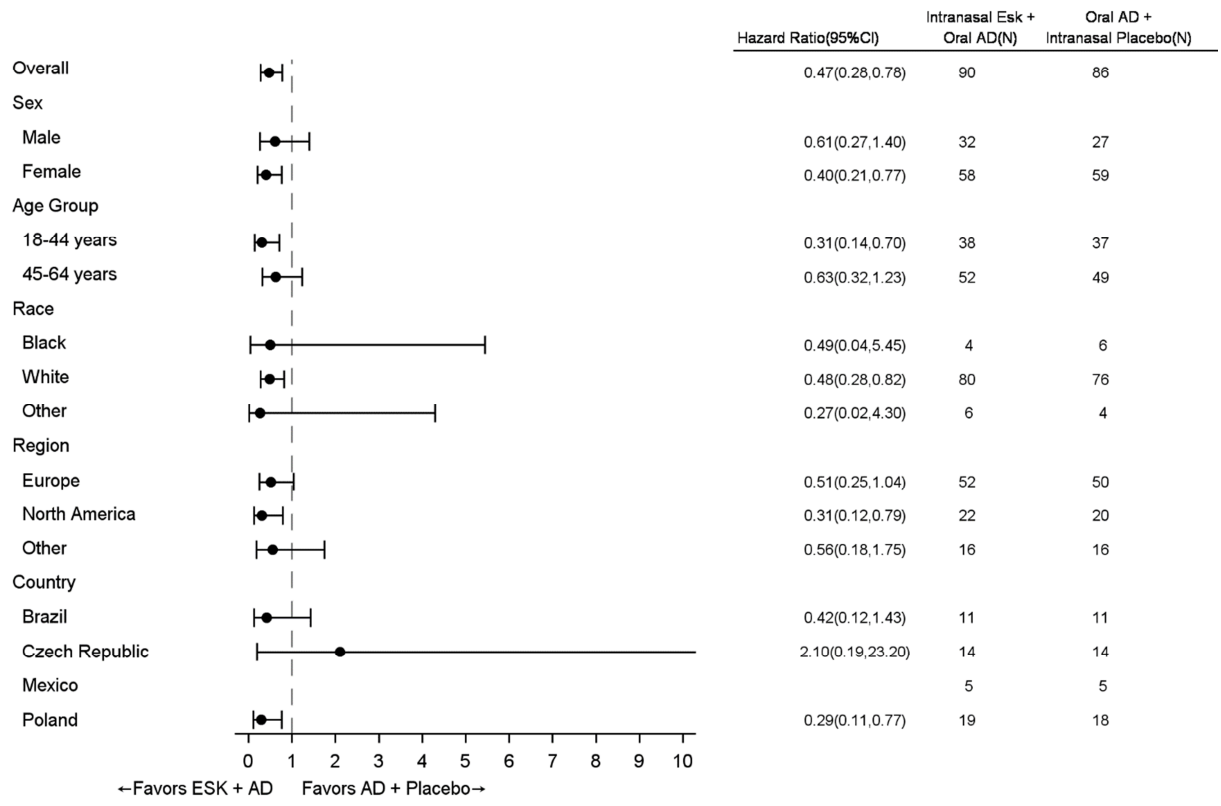


AD=antidepressant; CI=confidence interval; ESK=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effects model using repeated measures; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor
Notes: Subgroups with fewer than 5 patients not presented. Results are not adjusted for sample size re-estimation.

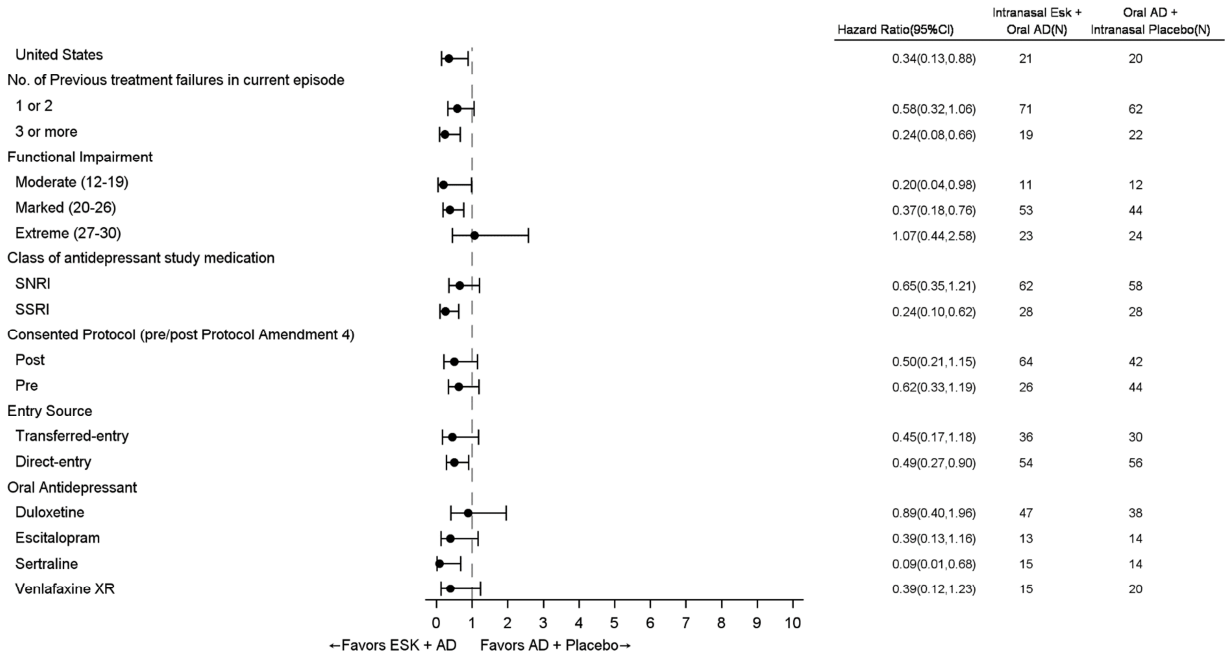
Appendix 7: Subgroup Analyses of the Primary Endpoint in the Maintenance of Effect Study

In SUSTAIN-1, subgroup analyses were performed using the Cox proportional hazards model. The model included treatment and 1 subgroup and treatment-by-subgroup at a time. A forest plot with the corresponding hazard ratios and 95% CI is shown in App 7 - Figure 1. In general, the results favored esketamine + oral antidepressant treatment groups for the subgroups.

App 7 - Figure 1: Forest Plot of Hazard Ratio by Subgroup: Cox Regression (SUSTAIN-1: Full (Stable Remitters) Analysis Set)



App 7 - Figure 1: Forest Plot of Hazard Ratio by Subgroup: Cox Regression (SUSTAIN-1: Full (Stable Remitters) Analysis Set)



AD=antidepressant; CI=confidence interval; Esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor
Notes: Hazard ratio estimates for subgroups with no event in either arm not displayed.
Subgroups with fewer than 5 patients not presented.
All patients had to have non-response to at least 2 antidepressants per protocol; some patients required confirmation of non-response to the second antidepressant during the screening/prospective observational period
In Amendment 4 to the SUSTAIN-3 protocol, the definition of stable remission was modified. Before Amendment 4 was adopted, stable remission was defined as MADRS total score ≤12 for the last 4 weeks of the optimization phase. In Amendment 4, the definition of stable remission was revised to allow a single excursion of the MADRS total score or one missed MADRS assessment at Week 13 or Week 14 on the basis that it could be due to a life event and not the underlying illness.

Appendix 8: Treatment-emergent Adverse Events in at Least 5% of Patients in SUSTAIN-1

Induction Phase

App 8 - Table 1: Treatment-emergent Adverse Events in at Least 5% of Patients; Open-label Induction Phase (SUSTAIN-1: Safety (Induction Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=437)
Total no. subjects with TEAE	336 (76.9%)
Nervous system disorders	248 (56.8%)
Dizziness	98 (22.4%)
Dysgeusia	90 (20.6%)
Somnolence	65 (14.9%)
Headache	60 (13.7%)
Paraesthesia	48 (11.0%)
Sedation	44 (10.1%)
Dizziness postural	33 (7.6%)
Hypoaesthesia	30 (6.9%)
Psychiatric disorders	164 (37.5%)
Dissociation	84 (19.2%)
Anxiety	33 (7.6%)
Gastrointestinal disorders	151 (34.6%)
Nausea	94 (21.5%)
Hypoaesthesia oral	32 (7.3%)
Vomiting	29 (6.6%)
Ear and labyrinth disorders	109 (24.9%)
Vertigo	99 (22.7%)
Respiratory, thoracic and mediastinal disorders	90 (20.6%)
Nasal discomfort	29 (6.6%)
Throat irritation	26 (5.9%)
Eye disorders	63 (14.4%)
Vision blurred	45 (10.3%)
Investigations	44 (10.1%)
Blood pressure increased	34 (7.8%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Optimization Phase

App 8 - Table 2: Treatment-emergent Adverse Events in at Least 5% of Patients; Optimization Phase (SUSTAIN-1: Safety (Optimization Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=455)
Total no. subjects with TEAE	335 (73.6%)
Nervous system disorders	212 (46.6%)
Dysgeusia	79 (17.4%)
Somnolence	63 (13.8%)
Dizziness	61 (13.4%)
Headache	57 (12.5%)
Dizziness postural	26 (5.7%)
Hypoaesthesia	24 (5.3%)
Paraesthesia	24 (5.3%)
Psychiatric disorders	136 (29.9%)
Dissociation	73 (16.0%)
Gastrointestinal disorders	116 (25.5%)
Nausea	48 (10.5%)
Hypoaesthesia oral	34 (7.5%)
Ear and labyrinth disorders	101 (22.2%)
Vertigo	91 (20.0%)
Respiratory, thoracic and mediastinal disorders	73 (16.0%)
Nasal discomfort	26 (5.7%)
Investigations	48 (10.5%)
Blood pressure increased	26 (5.7%)
Eye disorders	46 (10.1%)
Vision blurred	30 (6.6%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Maintenance Phase

App 8 - Table 3: Treatment-emergent Adverse Events in at Least 5% of Patients in Either Treatment Group; Maintenance Phase (SUSTAIN-1: Safety (Maintenance Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=152)	Oral AD + Intranasal Placebo (N=145)
Total no. subjects with TEAE	125 (82.2%)	66 (45.5%)
Nervous system disorders	83 (54.6%)	31 (21.4%)
Dysgeusia	41 (27.0%)	10 (6.9%)
Somnolence	32 (21.1%)	3 (2.1%)
Dizziness	31 (20.4%)	7 (4.8%)
Headache	27 (17.8%)	14 (9.7%)
Paraesthesia	11 (7.2%)	0
Dizziness postural	10 (6.6%)	3 (2.1%)
Sedation	10 (6.6%)	1 (0.7%)
Hypoaesthesia	9 (5.9%)	0
Psychiatric disorders	60 (39.5%)	15 (10.3%)
Dissociation	35 (23.0%)	0
Anxiety	12 (7.9%)	6 (4.1%)
Confusional state	9 (5.9%)	0
Gastrointestinal disorders	53 (34.9%)	11 (7.6%)
Nausea	25 (16.4%)	1 (0.7%)
Hypoaesthesia oral	20 (13.2%)	0
Vomiting	10 (6.6%)	1 (0.7%)
Paraesthesia oral	8 (5.3%)	1 (0.7%)
Ear and labyrinth disorders	43 (28.3%)	9 (6.2%)
Vertigo	38 (25.0%)	8 (5.5%)
Eye disorders	32 (21.1%)	1 (0.7%)
Vision blurred	24 (15.8%)	1 (0.7%)
Diplopia	9 (5.9%)	0
Infections and infestations	32 (21.1%)	25 (17.2%)
Viral upper respiratory tract infection	11 (7.2%)	12 (8.3%)
Respiratory, thoracic and mediastinal disorders	29 (19.1%)	11 (7.6%)
Nasal discomfort	11 (7.2%)	4 (2.8%)
Throat irritation	8 (5.3%)	1 (0.7%)
Investigations	19 (12.5%)	10 (6.9%)
Blood pressure increased	10 (6.6%)	5 (3.4%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Appendix 9: Treatment-emergent Adverse Events in at Least 5% of Patients in SUSTAIN-2

All Enrolled Patients

App 9 - Table 1: Treatment-emergent Adverse Events in at Least 5% of Patients; Induction and Optimization/Maintenance Phases (SUSTAIN-2: All Enrolled Analysis Set)

	Intranasal Esk + Oral AD (N=802)
Total no. subjects with TEAE	723 (90.1%)
Nervous system disorders	528 (65.8%)
Dizziness	264 (32.9%)
Headache	201 (25.1%)
Somnolence	134 (16.7%)
Dysgeusia	95 (11.8%)
Hypoaesthesia	95 (11.8%)
Sedation	71 (8.9%)
Dizziness postural	67 (8.4%)
Paraesthesia	58 (7.2%)
Psychiatric disorders	385 (48.0%)
Dissociation	221 (27.6%)
Anxiety	72 (9.0%)
Insomnia	65 (8.1%)
Gastrointestinal disorders	373 (46.5%)
Nausea	201 (25.1%)
Vomiting	87 (10.8%)
Hypoaesthesia oral	73 (9.1%)
Diarrhoea	60 (7.5%)
Infections and infestations	279 (34.8%)
Viral upper respiratory tract infection	82 (10.2%)
Urinary tract infection	65 (8.1%)
Influenza	43 (5.4%)
General disorders and administration site conditions	187 (23.3%)
Fatigue	63 (7.9%)
Musculoskeletal and connective tissue disorders	154 (19.2%)
Back pain	41 (5.1%)
Investigations	144 (18.0%)
Blood pressure increased	76 (9.5%)
Ear and labyrinth disorders	126 (15.7%)
Vertigo	88 (11.0%)
Eye disorders	105 (13.1%)
Vision blurred	60 (7.5%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Induction Phase

App 9 - Table 2: Treatment-emergent Adverse Events in at Least 5% of Patients; Induction Phase (SUSTAIN-2: Full (Induction Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=779)
Total no. subjects with TEAE	653 (83.8%)
Nervous system disorders	446 (57.3%)
Dizziness	228 (29.3%)
Headache	137 (17.6%)
Somnolence	94 (12.1%)
Hypoaesthesia	79 (10.1%)
Dysgeusia	77 (9.9%)
Dizziness postural	54 (6.9%)
Sedation	51 (6.5%)
Paraesthesia	46 (5.9%)
Psychiatric disorders	310 (39.8%)
Dissociation	182 (23.4%)
Anxiety	51 (6.5%)
Insomnia	41 (5.3%)
Gastrointestinal disorders	277 (35.6%)
Nausea	157 (20.2%)
Hypoaesthesia oral	63 (8.1%)
Vomiting	56 (7.2%)
General disorders and administration site conditions	135 (17.3%)
Fatigue	40 (5.1%)
Ear and labyrinth disorders	96 (12.3%)
Vertigo	68 (8.7%)
Investigations	81 (10.4%)
Blood pressure increased	53 (6.8%)
Eye disorders	76 (9.8%)
Vision blurred	49 (6.3%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Optimization/Maintenance Phase

App 9 - Table 3: Treatment-emergent Adverse Events in at Least 5% of Patients; Optimization/Maintenance Phase (SUSTAIN-2: Full (Optimization/Maintenance Phase) Analysis Set)

	Intranasal Esk + Oral AD (N=603)
Total no. subjects with TEAE	516 (85.6%)
Nervous system disorders	321 (53.2%)
Dizziness	135 (22.4%)
Headache	115 (19.1%)
Somnolence	85 (14.1%)
Dysgeusia	54 (9.0%)
Dizziness postural	41 (6.8%)
Hypoaesthesia	40 (6.6%)
Infections and infestations	238 (39.5%)
Viral upper respiratory tract infection	70 (11.6%)
Urinary tract infection	48 (8.0%)
Influenza	40 (6.6%)
Upper respiratory tract infection	35 (5.8%)
Gastrointestinal disorders	218 (36.2%)
Nausea	84 (13.9%)
Vomiting	45 (7.5%)
Diarrhoea	39 (6.5%)
Psychiatric disorders	217 (36.0%)
Dissociation	113 (18.7%)
Insomnia	35 (5.8%)
Musculoskeletal and connective tissue disorders	111 (18.4%)
Back pain	34 (5.6%)
Investigations	98 (16.3%)
Blood pressure increased	47 (7.8%)
Ear and labyrinth disorders	68 (11.3%)
Vertigo	43 (7.1%)

AD=antidepressant; Esk=esketamine; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Appendix 10: Grouping of Preferred Terms for the Analysis of Adverse Drug Reactions

App 10 - Table 1: Grouping of Preferred Terms for the Analysis of Adverse Drug Reactions

Grouped ADR term:	MedDRA Preferred Terms (terms included only if reported in esketamine Phase 2 and Phase 3 studies):
Tachycardia	Sinus Tachycardia; Tachycardia; Heart rate increased; Extrasystole
Anxiety	Anxiety; Anticipatory anxiety; Anxiety disorder; Generalized anxiety disorder; Agitation; Fear; Nervousness; Tension; Panic attack; Panic disorder; Panic reaction; Feeling jittery; Irritability; Psychogenic tremor
Dizziness	Dizziness; Dizziness postural; Procedural dizziness; Dizziness exertional
Vertigo	Vertigo; Vertigo positional
Sedation	Sedation; Somnolence; Altered state of consciousness; Depressed level of consciousness; Hypersomnia; Stupor
Dissociation	Dissociation; Depersonalisation/derealisation disorder; Derealisation; Dissociative disorder; Flashback; Hallucination; Hallucination, auditory; Hallucination, visual; Illusion; Somatic hallucination; Hyperacusis; Tinnitus; Diplopia; Vision blurred; Ocular discomfort; Photophobia; Visual impairment; Dysaesthesia, Oral dysaesthesia; Paraesthesia, Paraesthesia oral, Pharyngeal paraesthesia; Time perception altered; Daydreaming; Delusional perception; Feeling hot; Feeling cold; Feeling of body temperature change
Headache	Headache, Sinus headache
Hypoaesthesia	Hypoaesthesia; Hypoaesthesia oral; Hypoaesthesia teeth; Pharyngeal hypoaesthesia; Intranasal hypoaesthesia
Blood pressure increased	Blood pressure increased; Blood pressure systolic increased; Blood pressure diastolic increased; Hypertension; Hypertensive heart disease; Hypertensive crisis
Lethargy	Lethargy; Fatigue; Listless
Dysgeusia	Dysgeusia; Hypogeusia
Tremor	Tremor; Intention tremor
Pollakiuria	Pollakiuria; Micturition disorder
Dysarthria	Dysarthria; Speech disorder; Slow speech
Nasal discomfort	Nasal discomfort; Nasal crusting; Nasal dryness; Nasal pruritus

ADR=adverse drug reaction

Appendix 11: Preferred Terms Used to Search for Adverse Events of Special Interest

App 11 - Table 1: Search Terms for Events of Special Interest in Phase 2 and 3 Studies of Esketamine in TRD

Category of events	MedDRA Preferred Terms
TEAEs Suggestive of Abuse Potential	Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug use disorder, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome
Increased Blood Pressure	Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Hypertensive crisis, Hypertensive emergency, Hypertension
Increased Heart Rate	Heart rate increased, Tachycardia
Transient Dizziness/Vertigo	Dizziness, Dizziness exertional, Dizziness postural, Procedural dizziness, Vertigo, Vertigo labyrinthine, Vertigo positional, Vertigo CNS origin
Impaired Cognition	Cognitive disorder, Minor cognitive motor disorder
Cystitis	Allergic cystitis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom
Anxiety	Anticipatory anxiety, Anxiety, Anxiety disorder
Events potentially related to suicidality	Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self-injurious behavior, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt

CNS=central nervous system; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
NOTE: Preferred terms are based on MedDRA versions up to and including Version 20.0.

Appendix 12: Additional Information Regarding Quantitative Benefit-risk Assessment

App 12 - Table 1: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-1)

	Esketamine		Placebo	Treatment Difference (Esketamine - placebo)			
	Intranasal esk 56 mg + oral AD	Intranasal esk 84 mg + oral AD	Oral AD + Intranasal placebo	(Intranasal esk 56 mg + oral AD) - (Oral AD + Intranasal placebo)		(Intranasal esk 84 mg + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=115	N=114	N=113				
MADRS (Day 28)							
Responder (a)	54.1	53.1	38.9	15.2 (2.11; 28.22)	6.6	14.2 (0.68; 27.67)	7.1
Remitter (b)	36.0	38.8	30.6	5.5 (-6.98; 17.94)	18.2	8.2 (-4.76; 21.20)	12.2
Responder (without remission) (c)	18.0	14.3	8.3	9.7 (0.80, 18.50)	10	6.0 (-2.70, 14.6)	17
Safety	N=115	N=114	N=113				
Any Severe TEAE (d)	13.9	17.5	7.1	6.8 (-1.06; 14.73)	14.6	10.5 (2.03; 18.90)	9.6
Any Severe TEAE Starting and Resolving on Dosing Day	10.4	14.9	1.8	8.7 (2.57; 14.76)	11.5	13.1 (6.17; 20.12)	7.6
Any Severe TEAE Starting on Dosing and Resolving on a Different Day	3.5	2.6	0.9	2.6	38.6	1.7	57.3
Any Severe TEAE Starting on Non-Dosing Day	3.5	6.1	4.4	-0.9 (-6.01; 4.11)	-105.7	1.7 (-4.10; 7.53)	58.3
Discontinue from study medications due to a Common ADR (e)	0	5.3	0	0	-	5.3	19.0
Any Severe Common ADR	11.3	14.0	4.4	6.9 (-0.04; 13.80)	14.5	9.6 (2.19; 17.03)	10.4
Severe Dissociation	2.6	7.0	0	2.6	38.3	7.0	14.3
Severe Dizziness	3.5	3.5	0.9	2.6	38.6	2.6	38.1
Severe Nausea	0	3.5	0	0	-	3.5	28.5
Severe Sedation	0	2.6	0	0	-	2.6	38.0
Severe Headache	1.7	0.9	1.8	-0.0 (-3.44; 3.38)	-3248.8	-0.9	-112.0
Severe Vertigo	1.7	3.5	0	1.7	57.5	3.5	28.5
Severe Dysgeusia	2.6	0.9	0	2.6	38.3	0.9	114.0
Severe Hypoaesthesia	0	1.8	0	0	-	1.8	57.0
Severe Blood Pressure Increased	0	0	0	0	-	0	-
Severe Anxiety	1.7	1.8	2.7	-0.9 (-4.72; 2.89)	-109.2	-0.9 (-4.72; 2.92)	-111.1
Severe Vomiting	0	2.6	0	0	-	2.6	38.0

App 12 - Table 1: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-1)

	Esketamine		Placebo	Treatment Difference (Esketamine - placebo)			
	Intranasal esk 56 mg + oral AD	Intranasal esk 84 mg + oral AD	Oral AD + Intranasal placebo	(Intranasal esk 56 mg + oral AD) - (Oral AD + Intranasal placebo)		(Intranasal esk 84 mg + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH	Risk Difference/100 patients (95% CI)	NNT/NNH
Any Severe Common ADR Starting and Resolving on Dosing Day	9.6	13.2	0.9	8.7	11.5	12.3	8.1
Severe Dissociation	2.6	7.0	0	2.6	38.3	7.0	14.3
Severe Dizziness	3.5	3.5	0	3.5	28.8	3.5	28.5
Severe Nausea	0	2.6	0	0	-	2.6	38.0
Severe Sedation	0	2.6	0	0	-	2.6	38.0
Severe Headache	0	0	0	0	-	0	-
Severe Vertigo	1.7	3.5	0	1.7	57.5	3.5	28.5
Severe Dysgeusia	2.6	0.9	0	2.6	38.3	0.9	114.0
Severe Hypoaesthesia	0	1.8	0	0	-	1.8	57.0
Severe Blood Pressure Increased	0	0	0	0	-	0	-
Severe Anxiety	1.7	1.8	0.9	0.9	117.1	0.9	115.0
Severe Vomiting	0	2.6	0	0	-	2.6	38.0
Any Severe Common ADR Starting on Dosing Day and Resolving on a Different Day	0.9	0	0.9	0	-6497.5	-0.9	-113.0
Severe Dissociation	0.9	0	0	0.9	115.0	0	-
Severe Dizziness	0	0	0	0	-	0	-
Severe Nausea	0	0	0	0	-	0	-
Severe Sedation	0	0	0	0	-	0	-
Severe Headache	0	0	0	0	-	0	-
Severe Vertigo	0	0	0	0	-	0	-
Severe Dysgeusia	0.9	0	0	0.9	115.0	0	-
Severe Hypoaesthesia	0	0	0	0	-	0	-
Severe Blood Pressure Increased	0	0	0	0	-	0	-
Severe Anxiety	0	0	0.9	-0.9	-113.0	-0.9	-113.0
Severe Vomiting	0	0	0	0	-	0	-
Any Severe Common ADR Starting on Non-Dosing Day	1.7	1.8	2.7	-0.9 (-4.72; 2.89)	-109.2	-0.9 (-4.72; 2.92)	-111.1
Severe Dissociation	0	0	0	0	-	0	-
Severe Dizziness	0	0	0.9	-0.9	-113.0	-0.9	-113.0
Severe Nausea	0	0.9	0	0	-	0.9	114.0
Severe Sedation	0	0	0	0	-	0	-
Severe Headache	1.7	0.9	1.8	-0.0 (-3.44; 3.38)	-3248.8	-0.9	-112.0
Severe Vertigo	0	0	0	0	-	0	-
Severe Dysgeusia	0	0	0	0	-	0	-

App 12 - Table 1: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-1)

	Esketamine		Placebo	Treatment Difference (Esketamine - placebo)			
	Intranasal esk 56 mg + oral AD	Intranasal esk 84 mg + oral AD	Oral AD + Intranasal placebo	(Intranasal esk 56 mg + oral AD) - (Oral AD + Intranasal placebo)		(Intranasal esk 84 mg + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH	Risk Difference/100 patients (95% CI)	NNT/NNH
Severe Hypoaesthesia	0	0	0	0	-	0	-
Severe Blood Pressure Increased	0	0	0	0	-	0	-
Severe Anxiety	0	0	0.9	-0.9	-113.0	-0.9	-113.0
Severe Vomiting	0	0	0	0	-	0	-
Death	0	0	0	0	-	0	-
Patients with no suicidal ideation/behavior at baseline	N=87	N=78	N=77				
Postbaseline suicidal ideation	13.8	10.3	16.9	-3.1 (-14.16; 7.98)	-32.4	-6.6 (-17.37; 4.11)	-15.1

AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression

(a) Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28

(b) Remitter is defined as the proportion of patients achieving MADRS total score of ≤ 12 at Day 28. (Note, all patients had baseline MADRS ≥ 28.)

(c) Responder (without remission) is defined as the proportion of patients achieving at least 50% improvement in MADRS and MADRS total score >12 at Day 28

(d) Proportion of patients with treatment-emergent adverse event with severity of severe during double-blind induction phase

(e) The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting

Notes: No CI provided if the number of events is 0 or 1 in either group.

MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.

NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 2: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-2)

	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=114	N=109		
MADRS (Day 28)				
Responder (a)	69.3	52.0	17.3 (4.01; 30.60)	5.8
Remitter (b)	52.5	31.0	21.5 (8.17; 34.78)	4.7
Responder (without remission) (c)	16.8	21.0	-4.2 (-15.00, 6.60)	-24
Safety	N=114	N=109		
Any Severe TEAE (d)	13.2	2.8	10.4 (3.48; 17.33)	9.6
Any Severe TEAE Starting and Resolving on Dosing Day	8.8	1.8	6.9 (1.17; 12.71)	14.4
Any Severe TEAE Starting on Dosing and Resolving on a Different Day	3.5	0	3.5	28.5
Any Severe TEAE Starting on Non-Dosing Day	3.5	2.8	0.8 (-3.81; 5.32)	132.2
Discontinue from study medications due to a Common ADR (e)	2.6	0	2.6	38.0
Any Severe Common ADR	9.6	1.8	7.8 (1.84; 13.79)	12.8
Severe Dissociation	3.5	0	3.5	28.5
Severe Dizziness	0.9	0	0.9	114.0
Severe Nausea	0.9	0	0.9	114.0
Severe Sedation	0	0.9	-0.9	-109.0
Severe Headache	0.9	0	0.9	114.0
Severe Vertigo	3.5	0	3.5	28.5
Severe Dysgeusia	1.8	0	1.8	57.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	1.8	0.9	0.8	119.5
Severe Vomiting	1.8	0	1.8	57.0
Any Severe Common ADR Starting and Resolving on Dosing Day	7.9	1.8	6.1 (0.51; 11.61)	16.5
Severe Dissociation	2.6	0	2.6	38.0
Severe Dizziness	0.9	0	0.9	114.0
Severe Nausea	0.9	0	0.9	114.0
Severe Sedation	0	0.9	-0.9	-109.0
Severe Headache	0	0	0	-
Severe Vertigo	2.6	0	2.6	38.0
Severe Dysgeusia	1.8	0	1.8	57.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0.9	0.9	0	-2485.2
Severe Vomiting	1.8	0	1.8	57.0

App 12 - Table 2: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-2)

Any Severe Common ADR Starting on Dosing Day and Resolving on a Different Day	1.8	0	1.8	57.0
Severe Dissociation	0.9	0	0.9	114.0
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0.9	0	0.9	114.0
Severe Vertigo	0.9	0	0.9	114.0
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	0	0	-
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting on Non-Dosing Day	0.9	0.9	0	-2485.2
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0.9	0.9	0	-2485.2
Severe Vomiting	0	0	0	-
Death	0.9	0	0.9	114.0
Patients with no suicidal ideation/behavior at baseline	N=89	N=85		
Postbaseline suicidal ideation	6.7	8.2	-1.5 (-9.32; 6.34)	-66.9

AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
(a) Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28
(b) Remitter is defined as the proportion of patients achieving MADRS total score of ≤ 12 at Day 28. (Note, all patients had baseline MADRS ≥ 28)
(c) Responder (without remission) is defined as the proportion of patients achieving at least 50% improvement in MADRS and MADRS total score >12 at Day 28
(e) Proportion of patients with treatment-emergent adverse event with severity of severe during double-blind induction phase
(d) The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting
Notes: No CI provided if the number of events is 0 or 1 in either group.
MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.
NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 3: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-3)

	All Ages			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=72	N=65		
MADRS (Day 28)				
Responder (a)	27.0	13.3	13.7 (-0.28; 27.58)	7.3
Remitter (b)	17.5	6.7	10.8 (-0.51; 22.09)	9.3
Responder (without remission) (c)	9.5	6.7	2.9 (-6.80; 12.50)	34
Safety	N=72	N=65		
Any Severe TEAE (d)	4.2	1.5	2.6	38.0
Any Severe TEAE Starting and Resolving on Dosing Day	1.4	0	1.4	72.0
Any Severe TEAE Starting on Dosing and Resolving on a Different Day	0	0	0	-
Any Severe TEAE Starting on Non-Dosing Day	2.8	1.5	1.2	80.7
Discontinue from study medications due to a Common ADR (e)	4.2	1.5	2.6	38.0
Any Severe Common ADR	2.8	1.5	1.2	80.7
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	1.4	0	1.4	72.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	1.4	0	1.4	72.0
Severe Anxiety	0	1.5	-1.5	-65.0
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting and Resolving on Dosing Day	1.4	0	1.4	72.0
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	1.4	0	1.4	72.0
Severe Anxiety	0	0	0	-
Severe Vomiting	0	0	0	-

App 12 - Table 3: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-3)

	All Ages			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Any Severe Common ADR Starting on Dosing Day and Resolving on a Different Day	0	0	0	-
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	0	0	-
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting on Non-Dosing Day	1.4	1.5	-0.1	-668.6
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	1.4	0	1.4	72.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	1.5	-1.5	-65.0
Severe Vomiting	0	0	0	-

App 12 - Table 3: Treatment Comparison of Efficacy and Safety; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-3)

	All Ages			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Death	0	0	0	-
Patients with no suicidal ideation/behavior at baseline	N=58	N=54		
Postbaseline suicidal ideation	13.8	16.7	-2.9 (-16.20; 10.45)	-34.8

AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression
(a) Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28
(b) Remitter is defined as the proportion of patients achieving MADRS total score of ≤ 12 at Day 28. (Note, all patients had baseline MADRS ≥ 28)
(c) Responder (without remission) is defined as the proportion of patients achieving at least 50% improvement in MADRS and MADRS total score >12 at Day 28
(d) Proportion of patients with treatment-emergent adverse event with severity of severe during double-blind induction phase
(e) The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting
Notes: No CI provided if the number of events is 0 or 1 in either group.
MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.
NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 4: Treatment Comparison of Efficacy: Ages 65-74 years; Observed Case; Double-Blind Induction Phase; Full Analysis Set (TRANSFORM-3)

	Age 65 to 74 years			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=59	N=57		
MADRS (Day 28)				
Responder (a)	28.3	13.2	15.1 (-0.08; 30.27)	6.6
Remitter (b)	20.8	5.7	15.1 (2.53; 27.66)	6.6

AD=antidepressant; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit

(a) Responder is defined as the proportion of patients achieving at least 50% improvement in MADRS at Day 28

(b) Remitter is defined as the proportion of patients achieving MADRS total score of ≤ 12 at Day 28. (Note, all patients had baseline MADRS ≥ 28)

Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.

NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 5: Treatment Comparison of Efficacy; Double-Blind Maintenance Phase; Full Stable Remitters Analysis Set (SUSTAIN-1)

	Stable Remitters			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=90	N=86		
Relapse (all) (a)	26.7	45.3	-18.7 (-32.62; -4.75)	-5.4

AD=antidepressant; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit

(a) Proportion of patients who relapse based on MADRS or Hospitalization. In the case that both relapse criteria are met, the earlier date will be defined as the date of relapse for this patient. Patients with MADRS total score ≥ 22 for two consecutive assessments separated by 5 to 15 days. Patients with hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention.

Notes: No CI provided if the number of events is 0 or 1 in either group.

MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.

NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 6: Treatment Comparison of Efficacy; Double-Blind Maintenance Phase; Full Stable Responders Analysis Set (SUSTAIN-1)

	Stable Responders			
	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNT/NNH
Efficacy	N=62	N=59		
Relapse (all) (a)	25.8	57.6	-31.8 (-48.48; -15.16)	-3.1

AD=antidepressant; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; NNT; number needed to treat to benefit

(a) Proportion of patients who relapse based on MADRS or Hospitalization. In the case that both relapse criteria are met, the earlier date will be defined as the date of relapse for this patient. Patients with MADRS total score ≥ 22 for two consecutive assessments separated by 5 to 15 days. Patients with hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness such as suicide attempt, completed suicide, or hospitalization for suicide prevention.

Notes: No CI provided if the number of events is 0 or 1 in either group.

MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement.

NNT and NNH are the inverse of the risk difference. A positive NNT favors esketamine. A negative NNH favors esketamine.

App 12 - Table 7: Treatment Comparison of Safety; Double-Blind Maintenance Phase; Full Analysis Set (SUSTAIN-1)

	Intranasal esk + oral AD Risk /100 patients	Oral AD + Intranasal placebo Risk /100 patients	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo) Risk Difference/100 patients (95% CI)	NNH
Safety	N=152	N=145		
Any Severe TEAE (a)	7.9	4.1	3.8 (-1.62; 9.13)	26.6
Any Severe TEAE Starting and Resolving on Dosing Day	6.6	0	6.6	15.2
Any Severe TEAE Starting on Dosing and Resolving on a Different Day	0	0	0	-
Any Severe TEAE Starting on Non-Dosing Day	1.3	4.1	-2.8 (-6.54; 0.89)	-35.4
Discontinue from study medications due to a Common ADR (b)	0.7	0	0.7	152.0
Any Severe Common ADR	6.6	1.4	5.2 (0.83; 9.57)	19.2
Severe Dissociation	0.7	0	0.7	152.0
Severe Dizziness	0.7	0	0.7	152.0
Severe Nausea	0.7	0	0.7	152.0
Severe Sedation	2.0	0	2.0	50.7
Severe Headache	0.7	1.4	-0.7	-138.6
Severe Vertigo	1.3	0	1.3	76.0
Severe Dysgeusia	1.3	0	1.3	76.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	1.3	0	1.3	76.0
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting and Resolving on Dosing Day	5.9	0	5.9	16.9
Severe Dissociation	0.7	0	0.7	152.0
Severe Dizziness	0.7	0	0.7	152.0
Severe Nausea	0.7	0	0.7	152.0
Severe Sedation	2.0	0	2.0	50.7
Severe Headache	0	0	0	-
Severe Vertigo	1.3	0	1.3	76.0
Severe Dysgeusia	1.3	0	1.3	76.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	1.3	0	1.3	76.0
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting on Dosing Day and Resolving on a Different Day	0	0	0	-

App 12 - Table 7: Treatment Comparison of Safety; Double-Blind Maintenance Phase; Full Analysis Set (SUSTAIN-1)

	Intranasal esk + oral AD Risk /100 patients	Oral AD + Intranasal placebo Risk /100 patients	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo) Risk Difference/100 patients (95% CI)	NNH
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0	0	0	-
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	0	0	-
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting on Non-Dosing Day	0.7	1.4	-0.7	-138.6
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0.7	1.4	-0.7	-138.6
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	0	0	-
Severe Vomiting	0	0	0	-
Death	0	0	0	-
Patients with no suicidal ideation/behavior at baseline	N=126	N=133		
Postbaseline suicidal ideation	2.4	4.5	-2.1 (-6.55; 2.29)	-46.9

AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression

(a) Proportion of patients with treatment-emergent adverse event with severity of severe during double-blind induction phase

(b) The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting

Note: No CI provided if the number of events is 0 or 1 in either group.

NNH is the inverse of the risk difference. A negative NNH favors esketamine

App 12 - Table 8: Treatment Comparison of Safety; Double-Blind Induction Phase (Pooled Studies TRANSFORM-1 and 2: Full Analysis Set)

	Intranasal esk + oral AD Risk /100 patients	Oral AD + Intranasal placebo Risk /100 patients	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo) Risk Difference/100 patients (95% CI)	NNH
Safety	N=343	N=222		
Any Severe TEAE (a)	14.9	5.0	9.9 (5.19; 14.64)	10.1
Any Severe TEAE Starting and Resolving on Dosing Day	11.4	1.8	9.6 (5.78; 13.36)	10.5
Any Severe TEAE Starting on Dosing and Resolving on a Different Day	3.2	0.5	2.8	36.3
Any Severe TEAE Starting on Non-Dosing Day	4.4	3.6	0.8 (-2.50; 4.04)	129.9
Discontinue from study medications due to a Common ADR (b)	2.6	0	2.6	38.1
Any Severe Common ADR	11.7	3.2	8.5 (4.41; 12.61)	11.8
Severe Dissociation	4.4	0	4.4	22.9
Severe Dizziness	2.6	0.5	2.2	46.0
Severe Nausea	1.5	0	1.5	68.6
Severe Sedation	0.9	0.5	0.4	235.7
Severe Headache	1.2	0.9	0.3 (-1.42; 1.95)	377.0
Severe Vertigo	2.9	0	2.9	34.3
Severe Dysgeusia	1.7	0	1.7	57.2
Severe Hypoaesthesia	0.6	0	0.6	171.5
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	1.7	1.8	-0.1 (-2.29; 2.18)	-1903.7
Severe Vomiting	1.5	0	1.5	68.6
Any Severe Common ADR Starting and Resolving on Dosing Day	10.2	1.4	8.9 (5.31; 12.40)	11.3
Severe Dissociation	4.1	0	4.1	24.5
Severe Dizziness	2.6	0	2.6	38.1
Severe Nausea	1.2	0	1.2	85.8
Severe Sedation	0.9	0.5	0.4	235.7
Severe Headache	0	0	0	-
Severe Vertigo	2.6	0	2.6	38.1
Severe Dysgeusia	1.7	0	1.7	57.2
Severe Hypoaesthesia	0.6	0	0.6	171.5
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	1.5	0.9	0.6 (-1.22; 2.33)	179.6
Severe Vomiting	1.5	0	1.5	68.6

App 12 - Table 8: Treatment Comparison of Safety; Double-Blind Induction Phase (Pooled Studies TRANSFORM-1 and 2: Full Analysis Set)

	Intranasal esk + oral AD	Oral AD + Intranasal placebo	Treatment Difference (Intranasal esk + oral AD) - (Oral AD + Intranasal placebo)	
	Risk /100 patients	Risk /100 patients	Risk Difference/100 patients (95% CI)	NNH
Any Severe Common ADR Starting on Dosing Day and Resolving on a Different Day	0.9	0.5	0.4	235.7
Severe Dissociation	0.6	0	0.6	171.5
Severe Dizziness	0	0	0	-
Severe Nausea	0	0	0	-
Severe Sedation	0	0	0	-
Severe Headache	0.3	0	0.3	343.0
Severe Vertigo	0.3	0	0.3	343.0
Severe Dysgeusia	0.3	0	0.3	343.0
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0	0.5	-0.5	-222.0
Severe Vomiting	0	0	0	-
Any Severe Common ADR Starting on Non-Dosing Day	1.5	1.8	-0.3 (-2.51; 1.82)	-290.6
Severe Dissociation	0	0	0	-
Severe Dizziness	0	0.5	-0.5	-222.0
Severe Nausea	0.3	0	0.3	343.0
Severe Sedation	0	0	0	-
Severe Headache	0.9	0.9	-0.0 (-1.61; 1.56)	-3807.3
Severe Vertigo	0	0	0	-
Severe Dysgeusia	0	0	0	-
Severe Hypoaesthesia	0	0	0	-
Severe Blood Pressure Increased	0	0	0	-
Severe Anxiety	0.3	0.9	-0.6	-164.1
Severe Vomiting	0	0	0	-
Death	0.3	0	0.3	343.0
Patients with no suicidal ideation/behavior at baseline	N=254	N=162		
Postbaseline suicidal ideation	10.2	12.3	-2.1 (-8.40; 4.18)	-47.4

AD=antidepressant; ADR=adverse drug reaction; CI=confidence interval; esk=esketamine; MADRS=Montgomery-Asberg Depression Rating Scale; NNH=number needed to treat to harm; TEAE=treatment-emergent adverse event; TRD=treatment-resistant depression

(a) Proportion of patients with treatment-emergent adverse event with severity of severe during double-blind induction phase

(b) The following grouped terms with an incidence of >=10% in TRD patients treated with intranasal esketamine + oral AD and greater than oral AD + placebo are regarded as common ADRs: dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoaesthesia, blood pressure increased, anxiety and vomiting

Note: No CI provided if the number of events is 0 or 1 in either group.

NNH is the inverse of the risk difference. A negative NNH favors esketamine

Appendix 13: Statistical Methods

1. Overview

This statistical appendix contains analysis methods and results, including sensitivity analyses, for the primary and key secondary efficacy endpoints for the 4 Phase 3 double-blind trials in the esketamine program (TRANSFORM-1, 2, and 3, and SUSTAIN-1). Statistical references are provided at the end of this appendix.

2. Short-term Studies

2.1. Analysis Set

The efficacy analyses of data in the double-blind induction phase for each of the short-term studies were based on the full analysis set. The full analysis set was defined as all randomized patients who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase.

2.2. Primary Endpoint

The primary efficacy endpoint for each of the short-term studies was the change in MADRS total score from Day 1 to Day 28

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in these short-term studies, was defined by the following 3 components:

- **Population:** patients with TRD
- **Endpoint:** change from baseline to Day 28 in the MADRS total score
- **Measure of Intervention:** the effect of the initially randomized treatment together with the oral antidepressant that would have been observed had all patients remained on their randomized treatment throughout the double-blind induction phase.

The primary analysis was based on the full analysis set and the MADRS total scores collected during the double-blind induction phase.

The objective of these studies, as presented in the protocols, was to evaluate the efficacy of switching adult patients with TRD from a prior antidepressant treatment (to which they have not responded) to fixed or flexible-dose intranasal esketamine plus a newly-initiated oral antidepressant compared with switching to a newly-initiated oral antidepressant plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the MADRS total score from Day 1 (pre-randomization) to the end of the 4-week double-blind induction phase. In particular, the trials were intended to evaluate the effect of the drug when taken as intended in the protocol. Consequently, the following hypothetical strategy was employed for the intercurrent event of treatment discontinuation: had patients not discontinued treatment, their efficacy would have been similar to the efficacy of the patients from the same treatment group who did not discontinue treatment. As prespecified in the statistical analysis plan, the estimand variable was the change from baseline to Day 28 in the MADRS total score, consistent with the trial objectives. The summary measure was the difference in variable means.

3 Short-term Fixed-dose Study in Patients 18-64 Years of Age: TRANSFORM-1

3.1 Interim Analysis for Sample Size Re-estimation

A pre-planned interim analysis of efficacy data was conducted during the study, 4 weeks after randomizing 121 patients. The objective of the interim analysis was to re-estimate sample size or to stop the study for futility. An independent external statistical support group conducted the analysis and the Independent Data Monitoring Committee (unblinded to the data) reviewed the results and recommended to continue the study. Based on the predefined rules (App 13 - Table 1), the final sample size determined from the sample size re-estimation was 234, which was the minimum sample size for the study. The final sample size was communicated by the Independent Data Monitoring Committee (via the independent external statistical support group) to the interactive web response system vendor to ensure that the appropriate number of patients was enrolled in the study. None of the esketamine team members or staff members at the investigational sites were informed of any specific sample size adjustment resulting from the interim analysis until the final sample size was achieved. The Clinical Supplies group was informed of the decision made at the interim analysis to ensure only the required amount of study medication was packaged. Approximately 4 months after the data cutoff for the interim analysis, the Sponsor received notification from the interactive web response system vendor that the required number of patients had been randomized in the study, then the sites were informed to stop screening. Although the randomization cap was set at 234 patients, the Sponsor considered it an ethical obligation to clinical trial patients who either were already in the screening phase or had a screening visit scheduled, to proceed with screening and to participate in the study if all entry criteria were met. The additional time between site notification and closure (~ 3 days) was allowed based on the prior experience with screening closure in the Phase 3 program. This resulted in a total of 346 patients being randomized across participating countries and sites, bringing the total close to the maximum planned sample size of 348.

App 13 - Table 1: TRANSFORM-1 Rules for Sample Size Re-Estimation Based on Conditional Power for Each Treatment Comparison

	Conditional Power (%)		
Scenario	Comparison 1	Comparison 2	Re-estimated total sample size
1	$CP_1<10$	$CP_2<10$	Stop study
2a	$CP_1<10$	$10\leq CP_2\leq 30$	234
2b	$10\leq CP_1\leq 30$	$CP_2<10$	234
2c	$10\leq CP_1\leq 30$	$10\leq CP_2\leq 30$	234
3a	$CP_1\leq 30$	$30<CP_2<50$	348
3b	$30<CP_1<50$	$CP_2\leq 30$	348
3c	$30<CP_1<50$	$30<CP_2<50$	348
4a	$CP_1\leq 30$	$50\leq CP_2<80$	291
4b	$50\leq CP_1<80$	$CP_2\leq 30$	291
4c	$50\leq CP_1<80$	$50\leq CP_2<80$	291
5a	$CP_1\leq 30$	$CP_2\geq 80$	234
5b	$CP_1\geq 80$	$CP_2\leq 30$	234
5c	$CP_1\geq 80$	$CP_2\geq 80$	234
6a	$30<CP_1<50$	$50\leq CP_2$	348
6b	$50\leq CP_1$	$30<CP_2<50$	348
7a	$50\leq CP_1<80$	$CP_2\geq 80$	291
7b	$CP_1\geq 80$	$50\leq CP_2<80$	291

3.2 Level of Significance

A truncated fixed sequence parallel gatekeeping procedure[4,5] was applied to adjust for multiplicity and to strongly control type I error across the primary and the 3 key secondary efficacy endpoints (onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score), and the two dose-control comparisons.

The following was the order of testing of the endpoints: change in MADRS total score, onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score.

For all 4 endpoints, testing of the esketamine 56 mg dose group was conducted at the 2-sided 0.0425 level only if the 84-mg dose group was significant at the 2-sided 0.05 level for that endpoint. Testing of the endpoints was performed sequentially in the order indicated above for both dose groups only if the previous endpoint in the hierarchy was significant for both doses of esketamine (84 mg dose group at 2-sided 0.05 level, 56 mg dose group at 2-sided 0.0425 level). If only the 84-mg dose group was significant at the 2-sided 0.05 level for an endpoint, testing of the other endpoints down the hierarchy was conducted only for this dose group at the 2-sided 0.0075 level.

Analysis Methods

Mixed-effects Model Using Repeated Measures (MMRM)

The primary efficacy variable, change from baseline in MADRS total score at Day 28 in the double-blind induction phase, was analyzed using MMRM based on observed case data. The model included baseline MADRS total score as a covariate, and treatment, region, class of antidepressant (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects, and a random patient effect. The within-patient covariance between visits was estimated via an unstructured variance-covariance matrix. Comparison of each intranasal esketamine + oral antidepressant arm versus oral antidepressant + intranasal placebo was performed using the appropriate contrast. The MMRM analysis was performed for each stage separately (Stage 1- all data on patients used for sample size re-estimation at the interim analysis, and Stage 2- all data collected on the remaining patients), and a weighted combination test was performed using the test statistics obtained from the 2 stages.

Weighted Combination Test

To account for sample size reassessment, the weighted combination test was used for each comparison of interest. The combination test was defined by an approach which defined the test statistic as a weighted sum of the Stage 1 (before the interim analysis) and Stage 2 (after the interim analysis) test statistics.[3,6] The two stages were weighted equally in the combination test.

$$Z_C = \sqrt{0.5} \times Z_1 + \sqrt{0.5} \times Z_2$$

where $Z_1 = \Phi^{-1}(1-p_1)$ and $Z_2 = \Phi^{-1}(1-p_2)$ denoted the z-values corresponding to the 1-sided stage-wise p-values p_1 and p_2, respectively, for the hypothesis of interest based on the MMRM analysis of Stage 1 and Stage 2 data separately. The null hypothesis was rejected for large positive values of Z_C.

Results for the primary endpoint are shown in App 13 - Table 2 below. Using the weighted combination test, the difference between the intranasal esketamine 84 mg + oral antidepressant and the oral antidepressant+ intranasal placebo treatment groups was not statistically significant (2-sided p-value=0.088). Therefore, in accordance with the predefined testing sequence, the intranasal esketamine 56 mg + oral antidepressant treatment group could not be formally evaluated.

App 13 - Table 2: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=113)
Baseline			
N	115	114	113
Mean (SD)	37.4 (4.76)	37.8 (5.58)	37.5 (6.16)
Median (Range)	37.0 (27; 50)	37.5 (25; 51)	37.0 (18; 53)
Day 28			
N	111	98	108
Mean (SD)	18.5 (13.25)	19.4 (13.89)	22.8 (13.68)
Median (Range)	17.0 (0; 47)	18.0 (0; 46)	24.0 (0; 48)
Change from baseline to day 28			
N	111	98	108
Mean (SD)	-19.0 (13.86)	-18.8 (14.12)	-14.8 (15.07)
Median (Range)	-21.0 (-45; 11)	-20.0 (-43; 12)	-12.0 (-51; 21)
MMRM analysis (a)			
Diff. of LS means (Esk+AD minus AD+Placebo) (b)	-4.1	-3.2	
95% confidence interval on diff. (c)	-7.67; -0.49	-6.88; 0.45	
2-sided p-value (esk + AD minus AD + placebo) (d)	NA (e)	0.088	

AD=antidepressant; Diff=difference; Esk: esketamine; LS=least-squares; MMRM=mixed-effects model using repeated measures; NA=not applicable; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on mixed model for repeated measures (MMRM) with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk 56 mg + oral AD, intranasal esk 84 mg + oral AD, oral AD + intranasal placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
(b) Difference from placebo is the median unbiased estimate, which is a weighted combination of the least-squares means of the difference from placebo
(c) 2-sided confidence interval adjusted for sample size re-estimation
(d) P-value is based on the weighted combination test statistic
(e) The comparison between placebo and 56 mg cannot be formally evaluated since the comparison between 84 mg and placebo was not statistically significant.
Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.
Note: Negative change in score indicates improvement.

Sensitivity Analyses

Missing Data Sensitivity Analysis

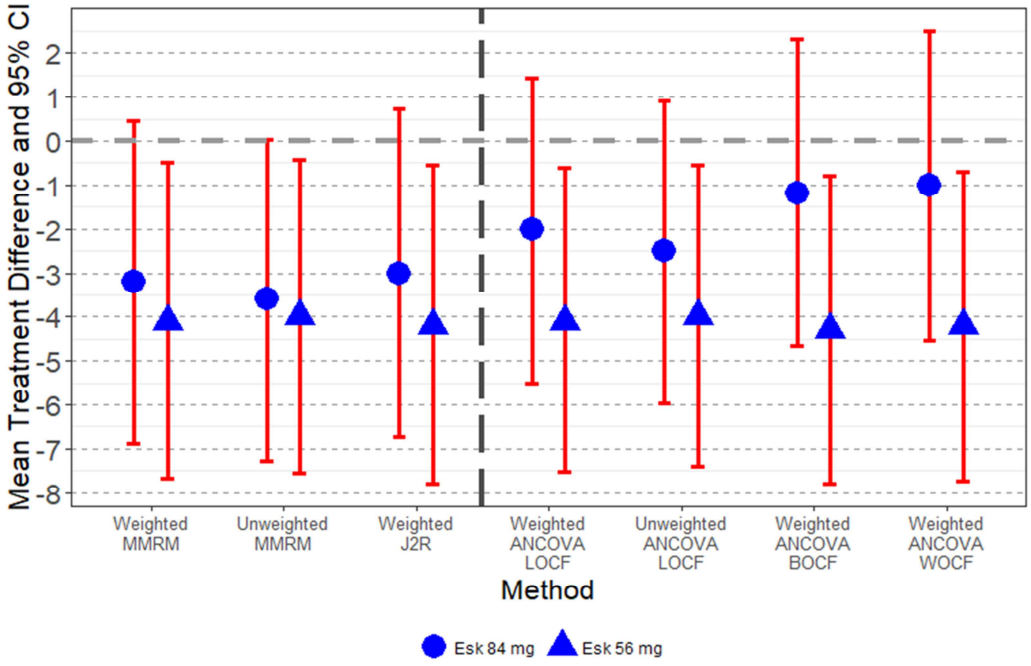
For the MMRM analysis, missing data was assumed to be missing at random. To evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption, a delta adjustment multiple imputation method was to be used for sensitivity analysis. Because the change in MADRS total score from baseline to Day 28 based on the weighted combination test was not statistically significant, sensitivity analysis to evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption was not performed.

A weighted jump to reference imputation was performed for a post hoc sensitivity analysis. This is the most conservative control based multiple imputation procedure. Additional sensitivity analyses were performed with a weighted analysis of covariance (ANCOVA) analysis of change in MADRS total score at endpoint using last observation carried forward (LOCF) (pre-planned), baseline observation carried

forward, and worst observation carried forward methods of imputation. The ANCOVA model included factors for treatment, region, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. In addition, an unweighted ANCOVA LOCF analysis was provided.

The results from these analyses were consistent with the primary MMRM analysis (App 13 - Figure 1).

App 13 - Figure 1: TRANSFORM-1 Primary, Sensitivity and Supplementary Analyses



ANCOVA: analysis of covariance; BOCF: baseline observation carried forward; LOCF: last observation carried forward; MMRM: mixed model of repeated measures; WOCF: worst observation carried forward

Exploring Differences by Stage

The characteristics of the current depression episode (e.g., prior use of oral antidepressants, severity of depression, duration of current episode) for patients included in Stage 1 and Stage 2 of the analysis were generally similar.

Treatment-by-stage interaction was explored for the primary endpoint using MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk 56 mg + oral AD, intranasal esk 84 mg + oral AD , oral AD + intranasal placebo), day, region, class of oral antidepressant (SNRI or SSRI), stage, treatment-by-day, treatment-by-stage, and treatment-by-day-by-stage, and baseline value as a covariate. A differential treatment effect was seen for Stage 1 compared with Stage 2. The LS mean (SE) treatment differences between the 2 intranasal esketamine + oral antidepressant treatment dose groups and the oral antidepressant + intranasal placebo treatment group were greater in Stage 2 compared to the treatment differences in Stage 1 (App 13 - Table 3). A plot of the LS mean changes for MADRS total score over time based on an MMRM observed case analysis for both stages during the double-blind induction phase is presented in App 13 - Figure 2.

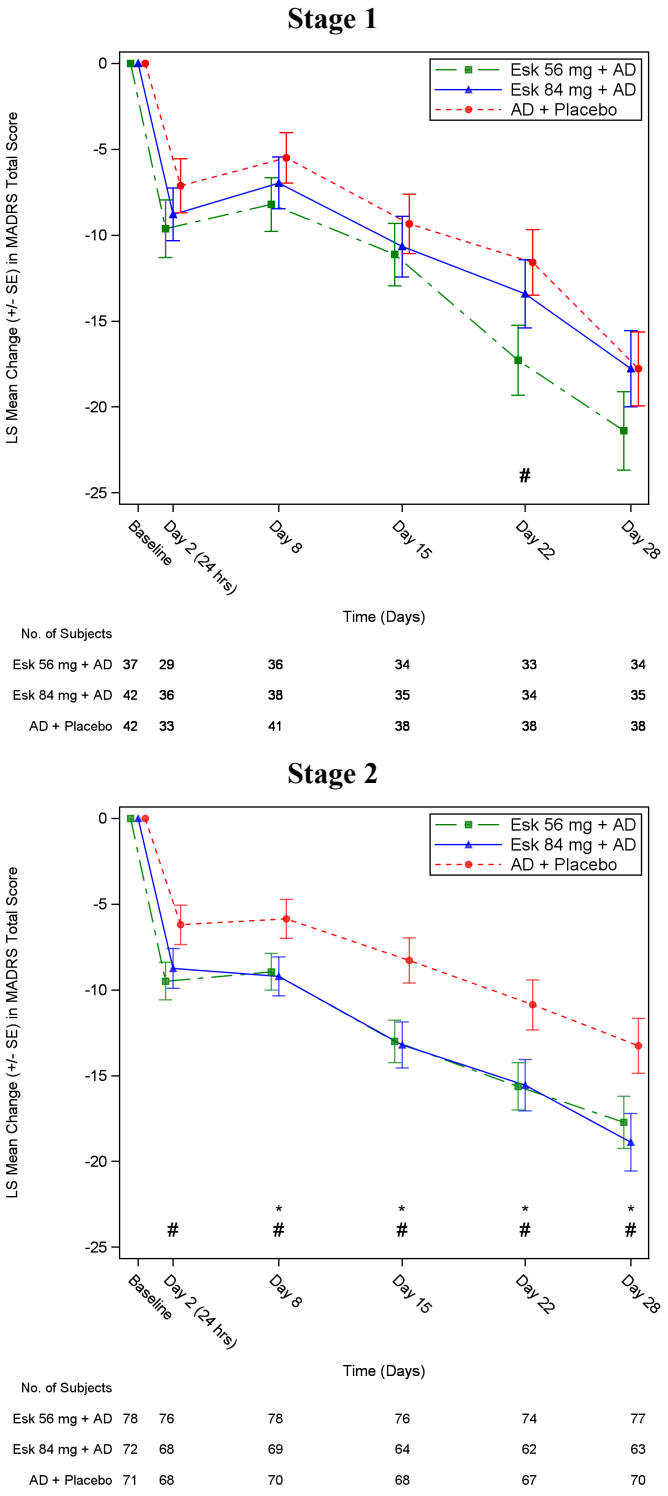
App 13 - Table 3: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case) by Stage; Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)

	Esk 56 mg + Oral AD	Esk 84 mg + Oral AD	Oral AD + Placebo
TRANSFORM-1			
Stage 1			
Mean change from baseline to Day 28	-21.5	-18.5	-17.6
Diff. of LS means (95% CI) (Esk+AD minus AD+Placebo) (a)	-3.6 (-9.76; 2.54)	0.0 (-6.05; 6.07)	
Stage 2			
Mean change from baseline to Day 28	-17.8	-18.9	-13.3
Diff. of LS means (95% CI) (Esk+AD minus AD+Placebo) (a)	-4.5 (-8.81; -0.12)	-5.6 (-10.16; -1.08)	

AD=antidepressant; CI=confidence interval; Diff=difference; Esk: esketamine; LS=least-squares; MMRM=mixed-effects model using repeated measures

(a) Results are not adjusted for multiple comparisons.
Note: Negative change in score indicates improvement.

App 13 - Figure 2: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM by Stage; Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)



AD=antidepressant; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SE=standard error; # Unadjusted 2-sided p<0.05 for intranasal esk 56 mg + oral AD vs oral AD + intranasal placebo ; * Unadjusted 2-sided p<0.05 for intranasal esk 84 mg + oral AD vs oral AD + intranasal placebo

While the study was ongoing, prior to and independent from the interim analysis, several key initiatives were implemented to further enhance the quality of study conduct, including:

- *Implementation of audio-recording for independent MADRS assessments:* To enhance remote rating quality and reliability, and to prevent rater drift, audio-recordings of the remote MADRS assessments was implemented. However, as the Sponsor had to first ensure that this technology is compliant with the information technology security requirements, this procedure could only be implemented uniformly approximately 1.5 years after study initiation.
- *Addition of new, experienced clinical sites:* In-depth site identification began prior to the interim analysis and resulted in over 40 new sites being added to the study.
- *Site education and training*: All clinical sites had thorough training on the protocol and study procedures at the beginning of the study. Following study initiation, it took time to identify challenges associated with the study, which then led to the development of enhanced education and training for all clinical sites. This included clinical site visits, telephone discussions with PI/site staff, and development of new training and recruitment materials.
- *Availability of the long-term esketamine open-label safety extension study (SUSTAIN-3)*: This study was made available to all randomized patients, regardless of response status at the end of the double-blind induction phase, after completion of the minimum duration of the follow-up phase, and is believed to have helped reduce potential bias for patients to be responders at the end of the study to continue access to study medication/participation. Patients not entering SUSTAIN-1 had the option to participate in the SUSTAIN-3 protocol after completion of the minimum time required in the follow-up phase.

These initiatives were considered to have the greatest impact on Stage 2 (those patients enrolled after the interim analysis was performed).

3.3. Major Secondary Endpoints

3.3.1. Onset of Clinical Response by Day 2 (24 Hours)

A patient was defined as having a clinical response by Day 2 (24 hours) if there was at least 50% improvement from baseline in the MADRS total score with onset by Day 2 (24 hours) that was maintained to Day 28. Patients were allowed one excursion (non-response) on Days 8, 15, or 22, however, the score on that day must have shown at least 25% improvement. Patients who did not meet these criteria, or discontinued during the study before Day 28 for any reason, were considered non-responders.

The proportion of patients who showed onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind induction phase in the esketamine + oral antidepressant arm was to be compared with the oral antidepressant + intranasal placebo arm using Fisher's exact test.

To account for sample size reassessment, a weighted combination test was used. The two stages were weighted equally in the combination test.

$$Z = \sqrt{0.5} \times Z_1 + \sqrt{0.5} \times Z_2$$

where Z_1 and Z_2 were the normal quantiles corresponding to 1-p_1 and 1-p_2, respectively; p_1 = 1-sided p-value from Fisher's exact test based on Stage 1 data, and p_2 = 1-sided p-value from Fisher's exact test based on Stage 2 data.

The difference in proportion of patients showing onset of clinical response by Day 2 between each intranasal esketamine + oral antidepressant group and oral antidepressant + intranasal placebo was

estimated by the weighted method. As shown in App 13 - Table 4, 10.4% of patients in the intranasal esketamine 56 mg + oral antidepressant and 8.8% of patients in the intranasal esketamine 84 mg + oral antidepressant treatment groups achieved clinical response with onset by Day 2 (24 hours) compared to 1.8% of patients in the oral antidepressant + intranasal placebo treatment group. This endpoint could not be formally evaluated since the primary endpoint was not statistically significant.

App 13 - Table 4: Onset of Clinical Response Based on Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Fisher's Exact Test; Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=113)
Onset of clinical response, n (%) (a)			
N	115	114	113
Yes	12 (10.4%)	10 (8.8%)	2 (1.8%)
No	103 (89.6%)	104 (91.2%)	111 (98.2%)
Difference of response rate from Placebo (b)	8.90	6.76	
Fisher's Exact test (c)			
2-sided p-value (esk+AD vs. AD+placebo)	NA (e)	NA (e)	
Odds ratio (95% CI) (d)	6.47(1.38,60.45)	5.34(1.09,50.91)	

AD=antidepressant; CI=confidence interval; Esk=esketamine; NA=not applicable

(a) Onset of clinical response is defined as at least 50% improvement from baseline in MADRS total score with onset by Day 2 that is maintained to Day 28. Patients are allowed one excursion (non-response) on Days 8, 15, or 22, provided the score is at least 25% improvement. Patients with missed assessments or discontinued early are not considered to have onset of clinical response.
(b) Weighted difference of the response rates estimated using asymptotic standard error and difference in response rates at each stage
(c) Fisher's Exact test for mean score difference between treatments. Results are weighted estimates.
(d) Unweighted estimate of the odds of achieving onset of clinical response on intranasal esk + oral AD divided by the odds of achieving onset of clinical response on oral AD + intranasal placebo.
(e) The onset of clinical response cannot be formally evaluated (for 84 mg or 56 mg) since previous endpoints in the testing hierarchy were not significant.

3.3.2. Sheehan Disability Scale (SDS)

Change from baseline in SDS total score at Day 28 in the double-blind induction phase was analyzed using the same model and weighted combination test described for the primary efficacy analysis in Section 3.2 (App 13 - Table 5). Based on the predefined testing sequence of key secondary endpoints, SDS total score could not be formally evaluated since previous endpoints in the testing hierarchy were not significant. However, results numerically favored the esketamine + oral AD treatment groups for the patient-reported outcomes related to functional impairment and associated disability (by SDS total score).

App 13 - Table 5: Sheehan Disability Scale (SDS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=113)
Baseline			
N	108	107	105
Mean (SD)	24.0 (4.12)	24.7 (4.58)	24.4 (3.86)
Median (Range)	24.0 (9; 30)	26.0 (6; 30)	25.0 (14; 30)
Day 28			
N	90	87	92
Mean (SD)	13.4 (9.76)	13.5 (10.07)	16.0 (9.82)
Median (Range)	13.5 (0; 30)	15.0 (0; 30)	15.5 (0; 30)
Change from baseline to day 28			
N	88	87	90
Mean (SD)	-11.0 (9.32)	-11.1 (10.04)	-8.4 (9.70)
Median (Range)	-10.5 (-30; 7)	-10.0 (-30; 15)	-6.0 (-30; 5)
MMRM analysis (a)			
Diff. of LS means (Esk+AD minus AD+Placebo) (b)	-2.5	-2.2	
95% confidence interval on diff. (c)	-5.25; 0.20	-4.91; 0.53	
2-sided p-value (esk + AD minus AD + placebo) (d)	NA (e)	NA (e)	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on mixed model for repeated measures (MMRM) with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk 56 mg + oral AD, intranasal esk 84 mg + oral AD, oral AD + intranasal placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
(b) Difference from placebo is the median unbiased estimate, which is a weighted combination of the least-squares means of the difference from placebo
(c) 2-sided confidence interval adjusted for sample size re-estimation
(d) P-value is based on the weighted combination test statistic
(e) The change in SDS total score cannot be formally evaluated (for 84 mg or 56 mg) since previous endpoints in the testing hierarchy were not significant.
Note: SDS total score ranges from 0 to 30; a higher score indicates greater impairment.
Note: Negative change in score indicates improvement.

3.3.2 Patient Health Questionnaire (PHQ-9)

Change from baseline in PHQ-9 total score at Day 28 in the double-blind induction phase was analyzed using the same model and weighted combination test described for the primary efficacy analysis in Section 3.2 (App 13 - Table 6). Based on the predefined testing sequence of key secondary endpoints, PHQ-9 total score could not be formally evaluated since previous endpoints in the testing hierarchy were not significant. However, results numerically favored the esketamine + oral AD treatment groups for the patient-reported outcomes related to depressive symptoms (by PHQ-9).

App 13 - Table 6: Patient Health Questionnaire (PHQ-9) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-1: Full Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=113)
Baseline			
N	115	114	113
Mean (SD)	20.3 (4.11)	20.7 (3.58)	20.8 (3.69)
Median (Range)	21.0 (7; 27)	21.0 (7; 27)	21.0 (12; 27)
Day 28			
N	110	99	108
Mean (SD)	9.3 (7.55)	9.2 (7.75)	11.7 (8.36)
Median (Range)	8.0 (0; 27)	8.0 (0; 27)	11.0 (0; 27)
Change from baseline to day 28			
N	110	99	108
Mean (SD)	-11.0 (8.07)	-11.7 (7.74)	-9.1 (8.35)
Median (Range)	-12.0 (-24; 6)	-13.0 (-25; 6)	-8.5 (-26; 4)
MMRM analysis (a)			
Diff. of LS means (Esk+AD minus AD+Placebo) (b)	-2.3	-2.2	
95% confidence interval on diff. (c)	-4.34; -0.31	-4.26; -0.20	
2-sided p-value (esk + AD minus AD + placebo) (d)	NA (e)	NA (e)	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on mixed model repeated measures (MMRM) with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk 56 mg + oral AD, intranasal esk 84 mg + oral AD, oral AD + intranasal placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
(b) Difference from placebo is the median unbiased estimate, which is a weighted combination of the least-squares means of the difference from placebo
(c) 2-sided confidence interval adjusted for sample size re-estimation
(d) P-value is based on the weighted combination test statistic
(e) The change in PHQ-9 total score cannot be formally evaluated (for 84 mg or 56 mg) since previous endpoints in the testing hierarchy were not significant.
Note: PHQ-9 total score ranges from 0 to 27; a higher score indicates greater depression.
Note: Negative change in score indicates improvement.

4 Short-term Flexible-dose Study in Patients 18-64 Years of Age: TRANSFORM-2

4.1 Level of Significance

Statistical analysis tests were conducted at a 2-sided 0.05 level of significance unless specified otherwise.

A serial gatekeeping (fixed sequence) approach was applied to adjust for multiplicity and to strongly control type I error across the primary and the 3 key secondary efficacy endpoints (onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score). The 3 key secondary endpoints were analyzed sequentially and were considered statistically significant at the 2-sided 0.05 level only if the endpoint is individually significant at the 2-sided 0.05 level and previous endpoints in the hierarchy were significant at the 2-sided 0.05 level, including the primary endpoint. If the primary endpoint is statistically significant, the selected secondary endpoints were assessed in the following order:

- Onset of clinical response by Day 2

- Change in SDS total score
- Change in PHQ-9 total score

4.2. Primary Endpoint Analysis

Analysis Methods

MMRM

The primary efficacy variable, change from baseline in MADRS total score at Day 28 in the double-blind induction phase, was analyzed using MMRM based on observed case data. The model included baseline MADRS total score as a covariate, and treatment, country, class of antidepressant (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects, and a random patient effect. The within-patient covariance between visits was estimated via an unstructured variance-covariance matrix. Comparison of the intranasal esketamine + oral antidepressant arm versus oral antidepressant + intranasal placebo was performed using the appropriate contrast.

Results of the MMRM analysis are found in App 13 - Table 7. The difference between treatment groups was statistically significant.

App 13 - Table 7: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-2: Full Analysis Set)

	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Baseline		
N	114	109
Mean (SD)	37.0 (5.69)	37.3 (5.66)
Median (Range)	37.0 (22; 48)	37.0 (21; 52)
Day 28		
N	101	100
Mean (SD)	15.5 (10.67)	20.6 (12.70)
Median (Range)	12.0 (1; 49)	19.0 (0; 49)
Change from baseline to day 28		
N	101	100
Mean (SD)	-21.4 (12.32)	-17.0 (13.88)
Median (Range)	-24.0 (-44; 13)	-18.5 (-43; 8)
MMRM analysis (a)		
Diff. of LS means (SE) (Esk+AD minus AD+Placebo)	-4.0 (1.69)	
95% confidence interval on diff.	-7.31; -0.64	
2-sided p-value	0.020	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on mixed model for repeated measures (MMRM) with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, country, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
Note: MADRS Total score ranges from 0 to 60; a higher score indicates a more severe condition.
Note: Negative change in score indicates improvement.

Sensitivity Analyses

Missing Data Sensitivity Analysis

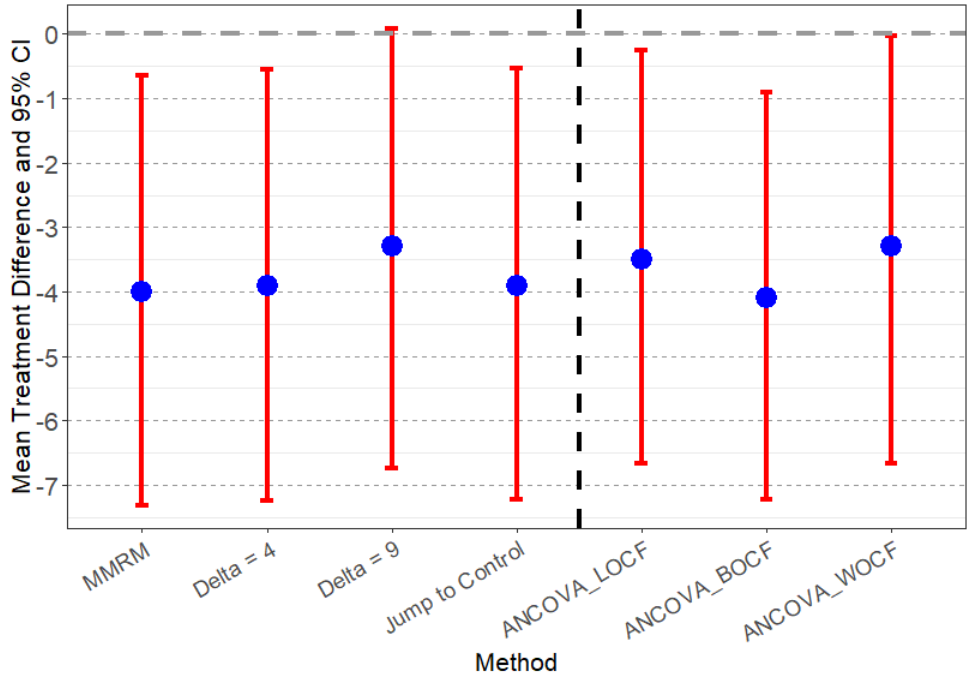
For the MMRM analysis, missing data was assumed to be missing at random. To evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption, a delta adjustment multiple imputation method was used for sensitivity analysis. This type of method is regarded to be an informative sensitivity analysis in clinical trials.[7,8]

Additionally, a jump to reference imputation was performed for a post hoc sensitivity analysis. This is the most conservative control based multiple imputation procedure.

Additional sensitivity analyses were performed with an ANCOVA analysis of change in MADRS total score at endpoint using LOCF (pre-planned), baseline observation carried forward, and worst observation carried forward methods of imputation. The ANCOVA model included factors for treatment, country, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. Comparison of the esketamine + oral antidepressant arm versus intranasal placebo + oral antidepressant was performed using the appropriate contrast.

The results from these analyses were consistent with the primary MMRM analysis (App 13 - Figure 3). For the delta adjustment multiple imputation method, the results indicate that if the missing at random assumption does not hold and the missing changes in MADRS total score for the intranasal esketamine + oral antidepressant group worsen after discontinuation, conclusions continue to favor intranasal esketamine + oral antidepressant over oral antidepressant + intranasal placebo up until the point that the missing changes in MADRS total scores for the intranasal esketamine + oral antidepressant group are 9.0 points (i.e., tipping point delta) worse after discontinuation than expected if they were missing at random.

App 13 - Figure 3: TRANSFORM-2 Primary, Sensitivity and Supplementary Analyses



ANCOVA: analysis of covariance; BOCF: baseline observation carried forward; LOCF: last observation carried forward; MMRM: mixed model of repeated measures; WOCF: worst observation carried forward

Initiatives to Enhance Quality of Study Conduct

Given that a differential treatment effect was seen for Stage 1 and Stage 2 in TRANSFORM-1 and TRANSFORM-3 and to further explore the impact of the initiatives to improve study execution and enhance quality on the results for the primary study endpoint, a post hoc analysis to mimic a similar by stage evaluation was done for TRANSFORM-2, although no interim analysis for sample size re-estimation was performed during this study. The analysis for TRANSFORM-2 evaluated whether similar differences between stages would have been observed had there been an interim analysis at 4 weeks after the 66th patient was randomized in the study. An MMRM analysis was done for each stage for the change from baseline in MADRS total score, with treatment, country, class of oral antidepressant (SSRI versus SNRI), day, and treatment-by-day interaction as fixed effects, and the baseline MADRS total score as a covariate. The results from this analysis are presented in App 13 - Table 8. Results were consistent with by stage analyses for TRANSFORM-1 and TRANSFORM-3 in showing a larger treatment group difference for patients who were enrolled later.

App 13 - Table 8: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline Over Time MMRM (Observed Case) by Stage; Double-blind Induction Phase (TRANSFORM-2: Full Analysis Set)

	Reference Group			Testing Group					Testing - Reference (a)(b)			
	Treatment	N	L.S. Mean	Treatment	N	L.S. Mean	M.S. Error	Error DF	L.S. Mean	95% CI	SE	2-sided P-value
MADRS total score												
Stage 1												
Day 2 (24 hrs)	Oral AD + placebo	31	-6.3	Esk + oral AD	32	-7.2	107.9	59	-0.9	(-6.07; 4.34)	2.60	0.741
Day 8	Oral AD + placebo	31	-4.0	Esk + oral AD	31	-6.5	94.9	59	-2.5	(-7.36; 2.42)	2.44	0.316
Day 15	Oral AD + placebo	32	-7.4	Esk + oral AD	31	-8.2	141.1	59	-0.7	(-6.68; 5.21)	2.97	0.806
Day 22	Oral AD + placebo	31	-10.3	Esk + oral AD	29	-13.4	140.7	59	-3.1	(-9.16; 2.90)	3.01	0.303
Day 28	Oral AD + placebo	30	-14.5	Esk + oral AD	27	-16.2	150.2	59	-1.7	(-8.00; 4.62)	3.15	0.594
Stage 2												
Day 2 (24 hrs)	Oral AD + placebo	71	-4.1	Esk + oral AD	77	-8.4	71.4	147	-4.2	(-6.97; -1.51)	1.38	0.003
Day 8	Oral AD + placebo	74	-5.2	Esk + oral AD	78	-8.2	66.7	147	-3.0	(-5.63; -0.41)	1.32	0.024
Day 15	Oral AD + placebo	70	-9.1	Esk + oral AD	76	-11.6	96.9	147	-2.4	(-5.62; 0.75)	1.61	0.132
Day 22	Oral AD + placebo	73	-12.1	Esk + oral AD	74	-16.1	126.6	147	-4.0	(-7.61; -0.32)	1.84	0.033
Day 28	Oral AD + placebo	70	-16.2	Esk + oral AD	74	-20.9	146.7	147	-4.7	(-8.67; -0.76)	2.00	0.020

AD=antidepressant; CI=confidence interval; Esk=esketamine; LS=least-squares; SE=standard error; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor
Note: The analysis is performed under the assumption that the interim analysis was conducted at the timepoint originally planned for the study, i.e., 4 weeks after randomizing 50% of the 132 patients in the study.
(a) Test for treatment effect is based on mixed model for repeated measures (MMRM) with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, country, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
(b) Results are not adjusted for the hypothetical sample size re-estimation
Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.
Note: Negative change in score indicates improvement.

4.3. Major Secondary Endpoints

4.3.1. Onset of Clinical Response by Day 2 (24 Hours)

A patient was defined as having a clinical response by Day 2 (24 hours) if there was at least 50% improvement (decrease) from baseline in the MADRS total score with onset by Day 2 (24 hours) that was maintained to Day 28. Patients were allowed one excursion (non-response) on Days 8, 15 or 22; however, the score must have shown at least 25% improvement. Patients who did not meet these criteria or discontinued before Day 28 for any reason were considered non-responders. Onset of clinical response was analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for country and class of oral antidepressant (SNRI or SSRI). As shown in App 13 - Table 9, there was no statistically significant difference between the treatment groups at the two-sided 0.05 level.

App 13 - Table 9: Onset of Clinical Response Based on Montgomery-Asberg Depression Rating Scale (MADRS) Total Score CMH Analysis; Double-blind Induction Phase (TRANSFORM-2: Full Analysis Set)

	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Onset of clinical response, n (%) (a)		
N	114	109
Yes	9 (7.9%)	5 (4.6%)
No	105 (92.1%)	104 (95.4%)
Generalized Cochran-Mantel-Haenszel test (b)		
2-sided p-value (esk+AD vs. AD+placebo)	0.321 (c)	
Odds ratio (95% CI) (d)	1.79(0.57,5.67)	

AD=antidepressant; CI=confidence interval; Esk=esketamine; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Onset of clinical response is defined as at least 50% improvement from baseline in MADRS total score with onset by Day 2 that is maintained to Day 28. Patients are allowed one excursion (non-response) on Days 8, 15 or 22, provided the score is at least 25% improvement. Patients with missed assessments or discontinued early are not considered to have onset of clinical response.

(b) Generalized Cochran-Mantel-Haenszel (CMH) test for mean score difference between treatments adjusting for country and class of oral antidepressant (SNRI or SSRI).

(c) The analysis can be considered statistically significant at the 2-sided 0.05 level only if the change in MADRS total score analysis is also significant. If not statistically significant, the onset of clinical response cannot be formally evaluated and the p-value should not be referenced.

(d) Odds of achieving onset of clinical response on intranasal esk + oral AD divided by the odds of achieving onset of clinical response on oral AD + intranasal placebo.

4.4 Sheehan Disability Scale

Change from baseline in SDS total score at Day 28 in the double-blind phase was evaluated based on the MMRM model as described for the primary efficacy analysis (Section 4.2). Based on the predefined testing sequence of key secondary endpoints, SDS total score could not be formally evaluated because there was not a statistically significant difference between treatment groups for onset of clinical response by Day 2 (24 hours). However, results numerically favored the esketamine + oral AD treatment groups for the patient-reported outcomes related to functional impairment and associated disability (by SDS total score); see App 13 - Table 10.

App 13 - Table 10: Sheehan Disability Scale (SDS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-2: Full Analysis Set)

	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Baseline		
N	111	104
Mean (SD)	24.0 (4.07)	24.2 (4.38)
Median (Range)	25.0 (11; 30)	25.0 (11; 30)
Day 28		
N	86	86
Mean (SD)	10.1 (7.71)	14.8 (9.07)
Median (Range)	9.0 (0; 29)	15.0 (0; 30)
Change from baseline to day 28		
N	86	85
Mean (SD)	-13.6 (8.31)	-9.4 (8.43)
Median (Range)	-14.0 (-30; 6)	-9.0 (-29; 6)
MMRM analysis (a)		
Diff. of LS means (SE) (Esk+AD minus AD+Placebo)	-4.0 (1.17)	
95% confidence interval on diff.	-6.28; -1.64	
2-sided p-value	NA (b)	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, country, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.
(b) The change in SDS total score cannot be formally evaluated since previous endpoints in the testing hierarchy were not significant.
Note: SDS total score ranges from 0 to 30; a higher score indicates greater impairment.
Note: Negative change in score indicates improvement.

4.5 Patient Health Questionnaire

Change from baseline in PHQ-9 total score at Day 28 in the double-blind phase was evaluated based on the MMRM model as described for the primary efficacy analysis (see Section 4.2). Based on the predefined testing sequence of key secondary endpoints, PHQ-9 total score could not be formally evaluated since previous endpoints in the testing hierarchy were not significant. However, results numerically favored the esketamine + oral AD treatment groups for the patient-reported outcomes related to depressive symptoms (by PHQ-9); see App 13 - Table 11.

App 13 - Table 11: Patient Health Questionnaire (PHQ-9) Total Score: Change From Baseline to Day 28 MMRM (Observed Case) Double-blind Induction Phase (TRANSFORM-2: Full Analysis Set)

	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Baseline		
N	114	109
Mean (SD)	20.2 (3.63)	20.4 (3.74)
Median (Range)	20.0 (5; 27)	21.0 (10; 27)
Day 28		
N	104	100
Mean (SD)	7.3 (5.74)	10.2 (7.68)
Median (Range)	5.5 (0; 27)	8.0 (0; 26)
Change from baseline to day 28		
N	104	100
Mean (SD)	-13.0 (6.42)	-10.2 (7.80)
Median (Range)	-14.0 (-26; 3)	-9.0 (-25; 6)
MMRM analysis (a)		
Diff. of LS means (SE) (Esk+AD minus AD+Placebo)	-2.4 (0.88)	
95% confidence interval on diff.	-4.18; -0.69	
2-sided p-value	NA (b)	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, country, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate.
A negative difference favors esketamine.
(b)The change in PHQ-9 total score cannot be formally evaluated since previous endpoints in the testing hierarchy were not significant.
Note: PHQ-9 total score ranges from 0 to 27; a higher score indicates greater depression.
Note: Negative change in score indicates improvement.

5. Short-term Flexible-dose Study in Patients 65 years of Age and Older: TRANSFORM-3

5.1. Interim Analysis for Sample Size Re-estimation

One unblinded interim efficacy analysis was conducted 4 weeks after 51 patients had been enrolled for sample size re-estimation. An independent external statistical support group conducted the analysis; the Independent Data Monitoring Committee reviewed unblinded results, recommended to continue the study, and provided the sample size (100 patients) based on the rules defined in the interim analysis statistical analysis plan (App 13 - Table 12). The decision was communicated by the Independent Data Monitoring Committee (via the statistical support group) to the interactive web response system vendor to ensure that the appropriate number of patients was enrolled in the study. None of the esketamine team members or staff members at the investigational sites were informed of any specific sample size adjustment resulting from the interim analysis until the final sample size was achieved. Once the Janssen team received notification from the interactive web response system vendor that the required number of patients had been randomized in the study, the sites were informed to stop screening. Although the cap was set at 100, the Sponsor considered it an ethical obligation to allow patients who either were already in the screening phase or had screening visits scheduled to proceed with screening and to participate in the study if all entry criteria were met. This resulted in a total of 138 patients being randomized into the

study. The Clinical Supplies group was informed of the decision made at the interim analysis to ensure only the required amount of study medication was packaged.

App 13 - Table 12: TRANSFORM-3 Rules for Sample Size Re-estimation Based on Conditional Power for the Treatment Comparison

Conditional Power (%)	p-value (1-sided)	Decision	Re-estimated total sample size
<1	>0.41	Stop study	
30<CP<50	--	Continue study	148
50≤CP<80	--	Continue study	124
1≤CP≤30 or CP≥80	--	Continue study	100

5.2 Level of Significance

Statistical analysis tests were conducted at a 2-sided 0.05 level of significance.

5.3 Primary Endpoint Analysis

Analysis Methods

MMRM

The primary efficacy variable, change from baseline in MADRS total score at Day 28 in the double-blind induction phase, was analyzed using the same MMRM analysis and weighted combination test described for TRANSFORM-1 in Section 3.2 Based on the weighted combination test, there was no statistically significant difference between treatment groups (two-sided p-value = 0.059). Results of the MMRM analysis are found in App 13 - Table 13.

App 13 - Table 13: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case); Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)

	Intranasal Esk + Oral AD (N=72)	Oral AD + Intranasal Placebo (N=65)
Baseline		
N	72	65
Mean (SD)	35.5 (5.91)	34.8 (6.44)
Median (Range)	36.0 (23; 50)	35.0 (19; 51)
Day 28		
N	63	60
Mean (SD)	25.4 (12.70)	28.7 (10.11)
Median (Range)	25.0 (0; 47)	30.0 (2; 44)
Change from baseline to day 28		
N	63	60
Mean (SD)	-10.0 (12.74)	-6.3 (8.86)
Median (Range)	-5.0 (-42; 10)	-4.5 (-33; 11)
MMRM analysis (a)		
Diff. of LS means (Esk+AD minus AD+Placebo) (b)	-3.6	
95% confidence interval on diff.(c)	-7.20; 0.07	
2-sided p-value(d)	0.059	

AD=antidepressant; Diff=difference; Esk=esketamine; LS=least-squares; MMRM= mixed-effects model using repeated measures; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

(a) Test for treatment effect is based on MMRM with change from baseline as the response variable and the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, region, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favors esketamine.

(b) Difference from placebo is the median unbiased estimate, which is a weighted combination of the least-squares means of the difference from placebo.

(c) 2-sided confidence interval adjusted for sample size re-estimation

(d) P-value is based on the weighted combination test statistic.

Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition.

Note: Negative change in score indicates improvement.

Sensitivity Analysis

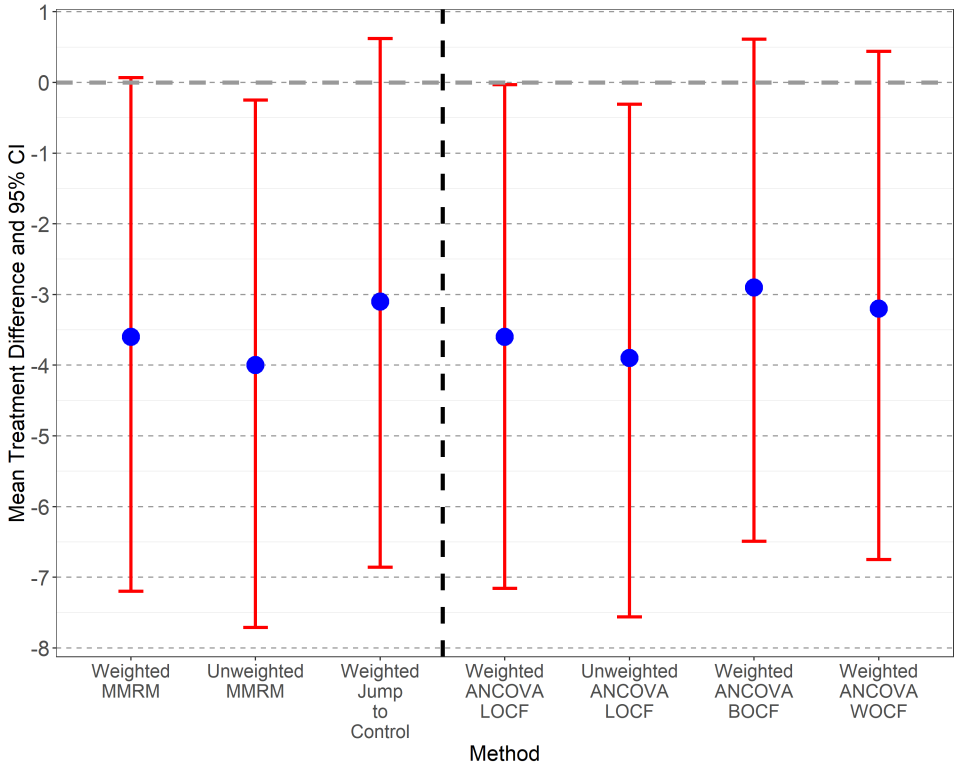
Missing Data Sensitivity Analysis

For the MMRM analysis, missing data was assumed to be missing at random. To evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption, a delta adjustment multiple imputation method was to be used for sensitivity analysis. Because the change in MADRS total score from baseline to Day 28 based on the weighted combination test was not statistically significant, this sensitivity analysis to evaluate the robustness of the MMRM analysis to increasing deviations from the missing at random assumption was not performed.

A jump to reference imputation was performed for a post hoc sensitivity analysis. This is the most conservative control based multiple imputation procedure (App 13 - Figure 4).

Sensitivity analyses were performed with a weighted combination ANCOVA analysis of change in MADRS total score at endpoint using LOCF (pre-planned), baseline observation carried forward, and worst observation carried forward methods of imputation. The ANCOVA models included factors for treatment, region, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. In addition, an unweighted ANCOVA LOCF analysis was provided (App 13 - Figure 4).

App 13 - Figure 4: TRANSFORM-3 Primary, Sensitivity and Supplementary Analyses



ANCOVA: analysis of covariance; BOCF: baseline observation carried forward; LOCF: last observation carried forward; MMRM: mixed model of repeated measures; WOCF: worst observation carried forward

Exploring Differences by Stage

The characteristics of the current depression episode (e.g., prior use of oral antidepressants, severity of depression, duration of current episode) for patients included in Stage 1 (before interim analysis) and Stage 2 (after interim analysis) of the analysis were generally similar.

A differential treatment effect on the primary endpoint for patients enrolled during Stage 1 and during Stage 2 was observed, with a larger LS mean treatment difference (favoring esketamine + oral AD over oral AD + placebo) observed for Stage 2 (App 13 - Table 14). The LS mean changes over time for each treatment group are provided in App 13 - Figure 5.

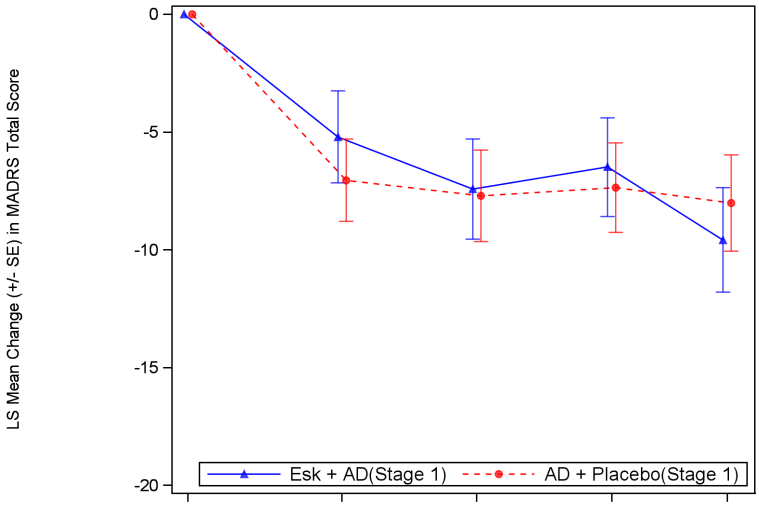
App 13 - Table 14: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change From Baseline to Day 28 MMRM (Observed Case) by Stage; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)

	Esk + Oral AD	Oral AD +Placebo
Stage 1		
Mean change from baseline to Day 28	-8.0	-6.6
Diff. of LS means (95% CI) (Esk+AD minus AD+Placebo)	-1.6 (-6.85; 3.70)	
Stage 2		
Mean change from baseline to Day 28	-11.2	-6.2
Diff. of LS means (95% CI) (Esk+AD minus AD+Placebo)	-5.6 (-10.78; -0.32)	

AD: antidepressant; CI: confidence interval; Esk: esketamine; LS: least-squares; MMRM=mixed-effects moded using repeated measures. Note: Negative change in score indicates improvement.

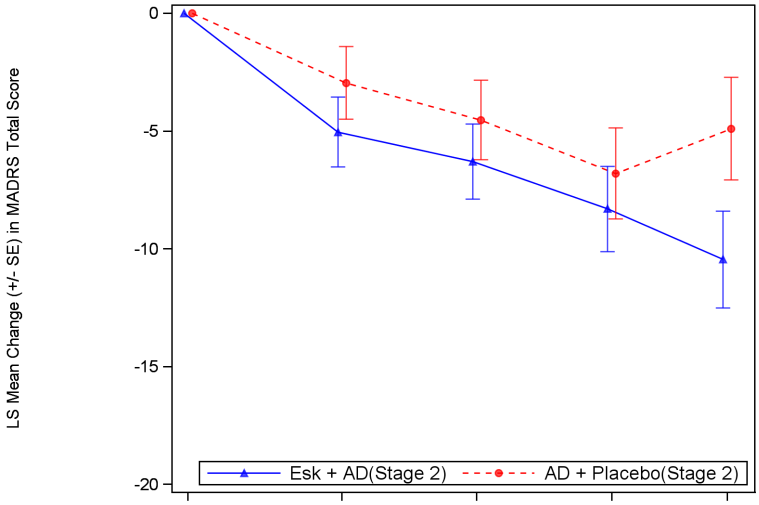
App 13 - Figure 5: Least-squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM by Stage; Double-blind Induction Phase (TRANSFORM-3: Full Analysis Set)

Stage 1



No. of Subjects					
Esk + AD(Stage 1)	25	24	24	21	23
AD + Placebo(Stage 1)	26	26	25	24	25

Stage 2



No. of Subjects					
Esk + AD(Stage 2)	47	42	44	39	40
AD + Placebo(Stage 2)	39	37	37	32	35

AD=antidepressant; Esk=esketamine; LS=least-squares; MMRM=mixed-effects model using repeated measures; SE=standard error;

In addition to amendments to the protocol, 4 key initiatives to improve study enrollment were implemented, prior to the interim analysis, all of which had a greater impact on the results in the latter part of the study (i.e., Stage 2):

- *Site Selection*: The initial sites selected for the study did not have specific experience with TRD patients 65 years and older. More patients from sites with expertise with patients 65 years and older participated in the study in Stage 2.
- *Sponsor Interaction with Sites*: The clinical discussions with the sites continued throughout the course of the study and, although initiated prior to the interim analysis, had the greatest impact after the interim analysis. This interaction contributed to the enrollment of patients meeting protocol requirements and a better understanding of the protocol, including dosing (see below), by investigators.
- *Remote Raters*: Remote raters (by telephone), required to provide effective blinding for this study, proved particularly challenging in the population ≥65 years of age because many of these patients minimized their symptoms to "strangers" over the phone and became frustrated with technical aspects of the telephone interview. The use of raters trained to interact effectively with patients ≥65 years of age may have improved reliability of the MADRS scores. This helped reduce the screen failure rate from 95% at the start of the study.
- *Dosing*: Dosing increases for intranasal study medication were slower and the overall doses were lower in Stage 1 compared to Stage 2 because early in the study, many investigators took the approach typically used in a population ≥65 years of age, starting with a low dose and increasing the dose more slowly (or not at all) than might be the case for younger adults. This effectively resulted in underdosing of many patients, especially during the initial 17 to 18 months of the study. The issue of potential underdosing was identified after assessing the first approximately 25 patients. Subsequently, biweekly to monthly clinical discussions with the investigators (see Sponsor Interaction with Sites section above for details) included explanation of the pharmacokinetic data and dosing; the impact of these calls occurred in the last 7 months of the study (Stage 2). Following these discussions many sites began to titrate up to more effective doses of esketamine.

6 Phase 3 Maintenance of Effect Study: SUSTAIN-1

6.1 Analysis Sets

There were 2 full analyses sets defined for the maintenance phase:

- Full (stable remitters): used to perform primary efficacy evaluation on randomized patients who were in stable remission at the end of the optimization phase and who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant during the maintenance phase. See Section 6.3 below for the definition of stable remitters.
- Full (stable responders): used to perform secondary efficacy evaluation on randomized patients who were stable responders (who were not stable remitters) at the end of the optimization phase and who received at least 1 dose of intranasal study medication and 1 dose of oral antidepressant during the maintenance phase. See Section 6.3 below for the definition of stable responders.

6.2. Level of Significance

A 2-stage group sequential design with 1 interim analysis was performed after 31 relapse events from randomized stable remitters who were treated with esketamine in the optimization phase. In either case of stopping at the interim analysis or continuing with sample size re-estimation, control of overall type I error was maintained.

At the time of the interim analysis, time to relapse was evaluated and compared between intranasal esketamine + oral antidepressant and intranasal placebo + oral antidepressant. The Wang-Tsiatis boundary[11] with shape parameter Δ=0.1 was used for detection of early efficacy.

Thirty-one relapses were included in the interim analysis therefore the interim efficacy analysis was performed at a significance level of 0.0097 (2-sided). Since the study was not stopped for efficacy at the interim analysis (two-sided p-value=0.03), the final number of relapses was determined by the sample size re-estimation (in the randomized patients with stable remission) that occurred during the maintenance phase. The sample size re-estimation determined that 59 relapse events would be required to ensure a conditional power at stage 2 of at least 90% based on the interim analysis data, using the approach proposed by Wassmer.[12] The final efficacy analysis was performed at a significance level of 0.046 (2-sided).

6.3 Primary and Secondary Endpoints and Analyses

In SUSTAIN-1, the primary endpoint was prespecified as the time from randomization to the first documentation of a relapse during the maintenance phase among patients who achieved stable remission at the end of optimization phase after 16 weeks of treatment with esketamine + oral AD, while the secondary endpoint was the time from randomization to the first documentation of a relapse in the maintenance phase for patients in stable response (not in remission) at the end of the optimization phase after 16 weeks of treatment with esketamine + oral AD. The definitions are provided below.

- At the end of the optimization phase:
  - *Stable remission:* A patient had a MADRS total score ≤12 points for at least 3 of the last 4 weeks of the optimization phase, but was permitted 1 excursion of a MADRS total score >12 points or 1 missing MADRS assessment at optimization Week 13 or 14 only. The patient's MADRS total score at Weeks 15 and 16 must have been ≤12 points. (This definition had been modified in Amendment 4 of the protocol; before then, the excursion or missing assessment had not been permitted, and the ≤12 points requirement had been imposed for all 4 of the last 4 weeks, not 3 of the 4 weeks.)
  - *Stable response:* A patient had a ≥50% reduction in the MADRS total score from baseline (Day 1 of induction phase; prerandomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but did not meet criteria for stable remission. For transferred-entry patients, Day 1 of the induction phase occurred in TRANSFORM-1 or 2. (This definition had been modified in Amendment 4 of the protocol; before then, stability had been required for the last 4 weeks [not the last 2 weeks], and had required at least 1 MADRS total score of >12 points in those 4 weeks for differentiation versus stable remission.)
- In the maintenance phase, relapse was defined as any of the following:
  - *Score:* MADRS total score ≥22 for 2 consecutive assessments separated by 5 to 15 days. The date of the second MADRS assessment was used for the date of relapse (based on counting processes for survival analysis).
  - *Event:* Hospitalization for worsening depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness, such as suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization was used for the date of relapse. Otherwise, the date of the event was used if the patient was not hospitalized.
  - *Score or event:* In case both relapse criteria were met, the earlier date was defined as the date of relapse for a patient.

The time to relapse and censoring are defined in App 13 - Table 15.

App 13 - Table 15: Time to Relapse / Censoring for the Primary Efficacy Endpoint

Patient status during maintenance phase	Time to relapse/Censoring	Censoring indicator
Randomized patients who relapse during maintenance phase	(Date of relapse – maintenance phase start date) + 1	No
Randomized patients who remained relapse free at the end of the maintenance phase	(End of maintenance phase date – maintenance phase start date) + 1	Yes
Early withdrawal/discontinued during the maintenance phase without relapse	(Date of early withdrawal – maintenance phase start date) + 1	Yes

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, was defined by the following variable and summary measure in the population, under the specified intervention effect:

- **Population:** patients with TRD who were in stable remission on intranasal esketamine at the end of the optimization phase
- **Variable:** time to relapse during the maintenance phase, while on their initially randomized treatment
- **Intercurrent Event:** the intercurrent event of treatment discontinuation is captured through the variable definition
- **Summary Measure:** Kaplan-Meier estimate of the survival function.

The primary analysis was based on the Full (stable remitters) analysis set.

Analysis Methods

Since the study was not terminated at the time of the interim analysis, the sample size (i.e., number of relapse events) was re-estimated to ensure a conditional power at stage 2 of at least 90% based on the interim analysis data, using the approach proposed by Wassmer.[12] The final analysis, given that a sample size re-estimation was performed, was based on a 2-stage group sequential survival design with the decision based on the log-rank test on accumulated information from both stages.

In this 2-stage group sequential design, the decision is based on the following test on accumulated data on both stages. Under the null hypothesis, the following test statistics are approximately standard normal. This test was performed on the Full (stable remitters) analysis set with the final number of events determined by the sample size re-estimation (59 events), including any additional events that occurred after the notification that the required number of events have been met and completion of the study. The final test statistic, Z_f, is a weighted combination of the 1-sided log-rank test statistics LR_1 and LR_2, $Z_f = \sqrt{\frac{30}{59}}\,\mathrm{LR}_1 + \sqrt{\frac{29}{59}}\left(\left(\sqrt{\frac{d_2}{d_2-d_{IA}}}\right)\mathrm{LR}_2 - \left(\sqrt{\frac{d_{IA}}{d_2-d_{IA}}}\right)\mathrm{LR}_1\right)$, where LR_2 was to be performed on the full analysis set and LR_1 on the Interim Full analysis set, d_{IA} = number of events observed in stage 1 and d_2=accumulated events for stage 1 and stage 2.

The treatment groups were compared using the weighted log-rank test statistic Z_f. Time to relapse was summarized (number of events, number of censored patients and quartiles of time to relapse). The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method. The estimate of the hazards ratio and its 95% confidence interval (CI) was based on Wassmer[12] and calculated using ADDPLAN Adaptive Designs - Plans and Analyses® software[1] and software R. Results are shown in Table 22 and Figure 25 (Section 7.3.2.1 in the main document). Based on the weighted combination log-rank test, the difference between treatment groups for the time to relapse was statistically significant (2-sided p=0.003) and was less than 0.046 (the threshold of statistical significance).

Evaluating Effects of Early Relapses

A concern cited in the interpretation of randomized withdrawal studies is that an increased rate of depression observed after discontinuing the antidepressant and switching to placebo could be a pharmacological consequence of antidepressant withdrawal.[2] All subjects in SUSTAIN-1 continued the oral antidepressant after randomization into the maintenance phase. A high early (in the first few weeks) rate of relapses in the arm randomized to discontinue esketamine could indicate a possible esketamine withdrawal effect.

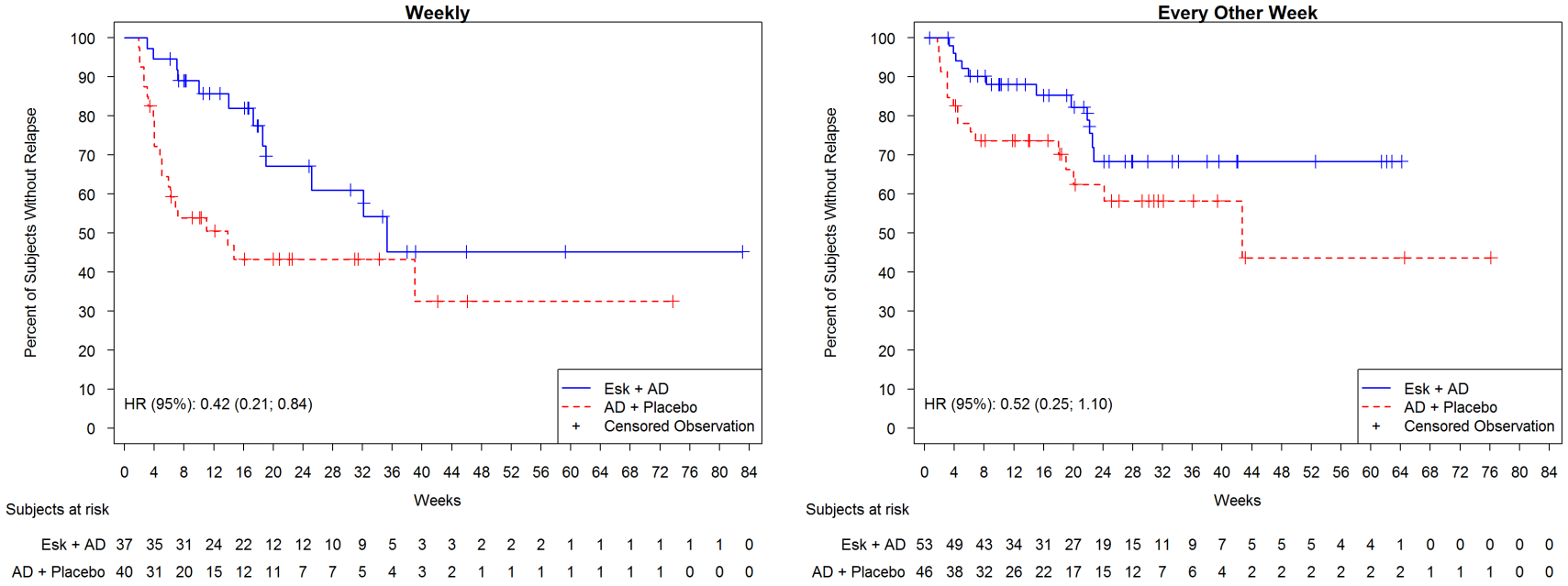
The results shown in Figure 25 (in the main document) demonstrate that patients who were randomized to continue esketamine were less likely to relapse than those who were randomized to discontinue esketamine. These results could be due to either a persistent treatment benefit or possible withdrawal effect, or both, as a high number of relapses was observed in the first few weeks after the start of the maintenance phase.

Alternatively, while the non-proportional hazards outcome observed in Figure 25 (in the main document) could be a consequence of a combination of persistent treatment effect and withdrawal effect, this outcome could also be explained by having a mixture of patient populations based on individual patient disease characteristics. To further explore this issue, an analysis by dosing frequency was performed.

Patients with TRD, have a higher likelihood of relapsing than those with MDD. Data from STAR*D study demonstrated that 65-70% of TRD patients relapse within 3 months of having achieved remission,[9] even while continuing the medication that they had improved on. This is a highly vulnerable group with significant interpatient variability. To address this interpatient variability, the protocol included an algorithm (Appendix 2) driven frequency of dosing to individualize to the patient's response. The aim of the dosing frequency algorithm was to reduce the frequency of dosing to every other week if the patient went into remission. If remission could not be maintained with this lower frequency, the dosing frequency was increased to weekly for 4 weeks and then reevaluated. This resulted in 56% of subjects in stable remission randomized while receiving esketamine at every-other-week frequency and 44% receiving weekly frequency. Essentially the group of patients dosed weekly could not sustain remission at every other week even after repeated attempts during the optimization phase. Thus, it would be expected (and as demonstrated during the optimization phase) that the group who required weekly dosing frequency to sustain improvement would be a vulnerable group who would be likely to relapse earlier than the group dosed every other week.

Based on the Kaplan-Meier analysis by dosing frequency shown in App 13 - Figure 6, there is evidence that the non-proportional hazards outcome seen in Figure 25 (in the main document) may in part be due to a mixture of populations based on individual patient disease characteristics. To be specific, the results from the cohort of patients dosed every other week (who clinically should be less vulnerable to early relapse upon discontinuation) are consistent with a proportional hazards effect on relapse rate with a hazard ratio of 0.52 favoring the arm randomized to continue esketamine. Results in this clinically less vulnerable cohort are statistically suggestive of persistent benefit of esketamine nasal spray in these patients. In contrast, results from the more vulnerable subjects who were not able to sustain remission unless given weekly treatment, suggest the observed effects may include both a persistent benefit of esketamine and an effect that is likely due to this more vulnerable group relapsing very quickly, as has been shown in electroconvulsive therapy.[10] Hence, the treatment effect observed in the patients who were dosed weekly (with a hazard ratio of 0.42) may be amplified by the presence of the more vulnerable patients. Overall, these results support continuing treatment with esketamine nasal spray for subjects who are in stable remission, with persistent efficacy of esketamine being an important contributor to having a lower relapse rate.

App 13 - Figure 6: Cumulative Proportion of Patients Who Remained Relapse Free by Dosing Frequency; Maintenance Phase (Kaplan-Meier Estimates) (SUSTAIN-1: Full (Stable Remitters) Analysis Set



AD=antidepressant; Esk=esketamine; HR=hazard ratio

6.4 Secondary Analysis

6.4.1 Time to Relapse in Stable Responders (who were not Remitters)

The time between randomization and the first documentation of a relapse in the maintenance phase was compared between treatment groups for patients in the Full (stable responders) analysis set. The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method and the treatment groups were compared using a 2-sided log-rank test.

The difference in the time to relapse between treatment groups was statistically significant based on the log-rank test (2-sided $p<0.001$). As shown in Table 23 (in Section 7.3.2.2 the main document), the estimated hazard ratio of intranasal esketamine + oral antidepressant relative to oral antidepressant + intranasal placebo based on the Cox proportional hazards model with treatment as a factor was, on average, 0.30 (95% CI: 0.16; 0.55). Kaplan-Meier curves of the time to relapse for the 2 treatment groups are presented in Figure 26 (in the main document).

References

1. ADDPLAN Adaptive Designs - Plans and Analyses®, ICON, Ireland, 2016; software available at http://www.iconplc.com/innovation/addplan.
2. Borges S, Chen YF, Laughren TP, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration, J Clin Psychiatry. 2014;75:205-214.
3. Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics. 1999 Sept; 55:853-857.
4. Dmitrienko A, Tamhane AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Stat Med. 2011 Jun 15; 30(13):1473-1488.
5. Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. Biom J. 2008 Oct;50(5):667-77.
6. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999; 55:1286–1290.
7. National Research Council, Panel on Handling Missing Data in Clinical Trials [2010], The prevention and treatment of missing data in clinical trials. Available: http://www nap.edu/catalog/12955 html
8. Permutt, T. Sensitivity analysis for missing data in regulatory submissions. Stat Med. 2015; Nov 15 (Epub ahead of print)
9. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905-1917.
10. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA. 2001;285:1299-1307.
11. Wang, S and Tsiatis, A. Approximately optimal one-parameter boundaries for group sequential trials. Biometrics 1987; 43:193-199.
12. Wassmer G. Planning and analyzing adaptive group sequential survival trials. Biometrical Journal 48(2006):4, 714-729.

Appendix 14: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term

App 14 - Table 1: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Total no. subjects with TEAE	69 (12.1%)	18 (3.7%)	252 (14.8%)
Psychiatric disorders	24 (4.2%)	9 (1.9%)	103 (6.0%)
Dissociation	13 (2.3%)	0	37 (2.2%)
Anxiety	5 (0.9%)	2 (0.4%)	20 (1.2%)
Depression	3 (0.5%)	3 (0.6%)	15 (0.9%)
Insomnia	2 (0.4%)	1 (0.2%)	8 (0.5%)
Suicidal ideation	1 (0.2%)	0	7 (0.4%)
Suicide attempt	0	0	7 (0.4%)
Confusional state	2 (0.4%)	0	4 (0.2%)
Panic attack	1 (0.2%)	2 (0.4%)	3 (0.2%)
Euphoric mood	0	0	2 (0.1%)
Fear	0	0	2 (0.1%)
Hallucination, visual	1 (0.2%)	0	2 (0.1%)
Irritability	0	0	2 (0.1%)
Affect lability	0	0	1 (0.1%)
Agitation	0	0	1 (0.1%)
Alcohol abuse	0	0	1 (0.1%)
Completed suicide	0	0	1 (0.1%)
Delirium	0	0	1 (0.1%)
Delusion	0	0	1 (0.1%)
Depersonalisation/derealisation disorder	0	0	1 (0.1%)
Depressed mood	0	0	1 (0.1%)
Depressive symptom	1 (0.2%)	0	1 (0.1%)
Disorientation	0	0	1 (0.1%)
Dissociative disorder	0	0	1 (0.1%)
Disturbance in sexual arousal	1 (0.2%)	0	1 (0.1%)
Dysphoria	0	0	1 (0.1%)
Fear of death	0	0	1 (0.1%)
Libido decreased	1 (0.2%)	0	1 (0.1%)
Logorrhoea	0	0	1 (0.1%)
Major depression	0	0	1 (0.1%)
Mania	1 (0.2%)	0	1 (0.1%)
Nervousness	1 (0.2%)	0	1 (0.1%)
Paranoia	0	0	1 (0.1%)
Screaming	0	0	1 (0.1%)
Sleep terror	0	0	1 (0.1%)
Soliloquy	0	0	1 (0.1%)
Tension	1 (0.2%)	1 (0.2%)	1 (0.1%)
Feeling of despair	0	1 (0.2%)	0
Nervous system disorders	33 (5.8%)	6 (1.2%)	98 (5.7%)
Dizziness	8 (1.4%)	1 (0.2%)	26 (1.5%)
Headache	5 (0.9%)	4 (0.8%)	20 (1.2%)
Dysgeusia	7 (1.2%)	0	19 (1.1%)
Somnolence	4 (0.7%)	1 (0.2%)	12 (0.7%)
Paraesthesia	1 (0.2%)	0	8 (0.5%)
Sedation	2 (0.4%)	0	8 (0.5%)
Dizziness postural	2 (0.4%)	0	3 (0.2%)
Hypoaesthesia	1 (0.2%)	0	3 (0.2%)
Psychomotor hyperactivity	1 (0.2%)	0	3 (0.2%)

App 14 - Table 1: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Coordination abnormal	0	0	2 (0.1%)
Dysarthria	2 (0.4%)	0	2 (0.1%)
Mental impairment	2 (0.4%)	0	2 (0.1%)
Sciatica	1 (0.2%)	0	2 (0.1%)
Syncope	1 (0.2%)	0	2 (0.1%)
Tunnel vision	2 (0.4%)	0	2 (0.1%)
Altered state of consciousness	1 (0.2%)	0	1 (0.1%)
Aphasia	1 (0.2%)	0	1 (0.1%)
Autonomic nervous system imbalance	0	0	1 (0.1%)
Carpal tunnel syndrome	1 (0.2%)	0	1 (0.1%)
Dizziness exertional	1 (0.2%)	0	1 (0.1%)
Generalised tonic-clonic seizure	0	0	1 (0.1%)
Head discomfort	1 (0.2%)	0	1 (0.1%)
Hypokinesia	0	0	1 (0.1%)
Lacunar stroke	0	0	1 (0.1%)
Lethargy	0	0	1 (0.1%)
Loss of consciousness	0	0	1 (0.1%)
Migraine	0	0	1 (0.1%)
Nystagmus	0	0	1 (0.1%)
Sinus headache	0	0	1 (0.1%)
Speech disorder	0	0	1 (0.1%)
Tension headache	0	0	1 (0.1%)
Unresponsive to stimuli	0	0	1 (0.1%)
Disturbance in attention	0	1 (0.2%)	0
Gastrointestinal disorders	10 (1.8%)	2 (0.4%)	42 (2.5%)
Nausea	6 (1.1%)	0	22 (1.3%)
Vomiting	5 (0.9%)	0	11 (0.6%)
Hypoaesthesia oral	1 (0.2%)	0	3 (0.2%)
Constipation	1 (0.2%)	0	2 (0.1%)
Diarrhoea	1 (0.2%)	0	2 (0.1%)
Salivary hypersecretion	2 (0.4%)	0	2 (0.1%)
Abdominal pain upper	0	0	1 (0.1%)
Colitis	0	0	1 (0.1%)
Colitis microscopic	0	0	1 (0.1%)
Dry mouth	0	0	1 (0.1%)
Food poisoning	0	0	1 (0.1%)
Gastrooesophageal reflux disease	0	0	1 (0.1%)
Large intestinal obstruction	0	0	1 (0.1%)
Pancreatitis	0	0	1 (0.1%)
Paraesthesia oral	0	0	1 (0.1%)
Retching	0	0	1 (0.1%)
Toothache	0	0	1 (0.1%)
Abdominal pain	0	1 (0.2%)	0
Dyspepsia	0	1 (0.2%)	0
Ear and labyrinth disorders	15 (2.6%)	0	32 (1.9%)
Vertigo	13 (2.3%)	0	28 (1.6%)
Motion sickness	1 (0.2%)	0	3 (0.2%)
Ear discomfort	0	0	2 (0.1%)
Hypoacusis	2 (0.4%)	0	2 (0.1%)
Tinnitus	1 (0.2%)	0	1 (0.1%)
General disorders and administration site conditions	11 (1.9%)	4 (0.8%)	24 (1.4%)
Fatigue	5 (0.9%)	0	7 (0.4%)
Feeling abnormal	2 (0.4%)	0	6 (0.4%)

App 14 - Table 1: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Chest discomfort	1 (0.2%)	0	3 (0.2%)
Chest pain	0	0	2 (0.1%)
Feeling drunk	1 (0.2%)	0	2 (0.1%)
Asthenia	0	0	1 (0.1%)
Chills	1 (0.2%)	1 (0.2%)	1 (0.1%)
Crying	0	1 (0.2%)	1 (0.1%)
Energy increased	1 (0.2%)	0	1 (0.1%)
Feeling cold	1 (0.2%)	0	1 (0.1%)
Feeling hot	1 (0.2%)	0	1 (0.1%)
Malaise	1 (0.2%)	0	1 (0.1%)
Pyrexia	0	1 (0.2%)	1 (0.1%)
Feeling of relaxation	0	1 (0.2%)	0
Gait disturbance	0	1 (0.2%)	0
Pain	0	1 (0.2%)	0
Therapeutic response unexpected	0	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	8 (1.4%)	0	20 (1.2%)
Nasal congestion	2 (0.4%)	0	5 (0.3%)
Nasal discomfort	2 (0.4%)	0	5 (0.3%)
Throat irritation	4 (0.7%)	0	5 (0.3%)
Oropharyngeal pain	1 (0.2%)	0	4 (0.2%)
Rhinorrhoea	1 (0.2%)	0	3 (0.2%)
Upper-airway cough syndrome	3 (0.5%)	0	3 (0.2%)
Rhinalgia	1 (0.2%)	0	2 (0.1%)
Acute respiratory failure	0	0	1 (0.1%)
Cough	0	0	1 (0.1%)
Dyspnoea	0	0	1 (0.1%)
Sneezing	1 (0.2%)	0	1 (0.1%)
Infections and infestations	1 (0.2%)	0	19 (1.1%)
Gastroenteritis	0	0	2 (0.1%)
Pneumonia	0	0	2 (0.1%)
Tooth infection	0	0	2 (0.1%)
Urinary tract infection	0	0	2 (0.1%)
Arthritis bacterial	0	0	1 (0.1%)
Gastroenteritis viral	0	0	1 (0.1%)
Gastrointestinal infection	0	0	1 (0.1%)
Hepatitis B	0	0	1 (0.1%)
Herpes zoster	0	0	1 (0.1%)
Mastoiditis	0	0	1 (0.1%)
Otitis media acute	0	0	1 (0.1%)
Pyelonephritis acute	0	0	1 (0.1%)
Rhinitis	1 (0.2%)	0	1 (0.1%)
Sepsis	0	0	1 (0.1%)
Sinusitis	0	0	1 (0.1%)
Upper respiratory tract infection	0	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	2 (0.4%)	2 (0.4%)	13 (0.8%)
Back pain	1 (0.2%)	0	5 (0.3%)
Arthralgia	0	0	2 (0.1%)
Muscular weakness	0	0	2 (0.1%)
Myalgia	1 (0.2%)	0	2 (0.1%)
Arthritis	0	0	1 (0.1%)
Neck pain	0	0	1 (0.1%)
Pain in extremity	0	0	1 (0.1%)
Musculoskeletal pain	0	1 (0.2%)	0
Spinal pain	0	1 (0.2%)	0

App 14 - Table 1: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Eye disorders	4 (0.7%)	0	11 (0.6%)
Vision blurred	2 (0.4%)	0	6 (0.4%)
Visual impairment	2 (0.4%)	0	4 (0.2%)
Metamorphopsia	0	0	1 (0.1%)
Injury, poisoning and procedural complications	2 (0.4%)	0	9 (0.5%)
Procedural pain	0	0	2 (0.1%)
Costochondral separation	0	0	1 (0.1%)
Hip fracture	1 (0.2%)	0	1 (0.1%)
Multiple injuries	1 (0.2%)	0	1 (0.1%)
Muscle strain	0	0	1 (0.1%)
Overdose	0	0	1 (0.1%)
Poisoning	0	0	1 (0.1%)
Road traffic accident	1 (0.2%)	0	1 (0.1%)
Toxicity to various agents	0	0	1 (0.1%)
Investigations	1 (0.2%)	0	5 (0.3%)
Blood pressure increased	1 (0.2%)	0	3 (0.2%)
Alanine aminotransferase increased	0	0	1 (0.1%)
Aspartate aminotransferase increased	0	0	1 (0.1%)
Gamma-glutamyltransferase increased	0	0	1 (0.1%)
Metabolism and nutrition disorders	0	0	5 (0.3%)
Gout	0	0	3 (0.2%)
Failure to thrive	0	0	1 (0.1%)
Hypomagnesaemia	0	0	1 (0.1%)
Renal and urinary disorders	2 (0.4%)	0	5 (0.3%)
Pollakiuria	2 (0.4%)	0	3 (0.2%)
Urinary incontinence	0	0	2 (0.1%)
Nephrolithiasis	0	0	1 (0.1%)
Urinary hesitation	1 (0.2%)	0	1 (0.1%)
Urinary retention	1 (0.2%)	0	1 (0.1%)
Cardiac disorders	1 (0.2%)	0	4 (0.2%)
Bradycardia	0	0	1 (0.1%)
Cardiac failure acute	0	0	1 (0.1%)
Palpitations	1 (0.2%)	0	1 (0.1%)
Sinus tachycardia	0	0	1 (0.1%)
Skin and subcutaneous tissue disorders	2 (0.4%)	2 (0.4%)	4 (0.2%)
Hyperhidrosis	2 (0.4%)	1 (0.2%)	4 (0.2%)
Night sweats	0	1 (0.2%)	0
Vascular disorders	0	0	3 (0.2%)
Haematoma	0	0	1 (0.1%)
Hot flush	0	0	1 (0.1%)
Hypertensive crisis	0	0	1 (0.1%)
Hepatobiliary disorders	0	0	2 (0.1%)
Cholecystitis acute	0	0	1 (0.1%)
Hepatic steatosis	0	0	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	0	0	2 (0.1%)
Abortion spontaneous	0	0	1 (0.1%)
Ectopic pregnancy	0	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.2%)	0	1 (0.1%)
Ejaculation delayed	1 (0.2%)	0	1 (0.1%)

App 14 - Table 1: Treatment-emergent Adverse Events of Severe Intensity by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Surgical and medical procedures	1 (0.2%)	0	1 (0.1%)
Tooth extraction	1 (0.2%)	0	1 (0.1%)

AD=antidepressant; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Appendix 15: Treatment-emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term

App 15 - Table 1: Treatment-emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Total no. subjects with TEAE	10 (1.8%)	5 (1.0%)	89 (5.2%)
Psychiatric disorders	5 (0.9%)	2 (0.4%)	40 (2.3%)
Depression	3 (0.5%)	1 (0.2%)	15 (0.9%)
Suicidal ideation	0	0	7 (0.4%)
Suicide attempt	0	0	6 (0.4%)
Anxiety	0	0	4 (0.2%)
Major depression	1 (0.2%)	0	2 (0.1%)
Alcohol abuse	0	0	1 (0.1%)
Anxiety disorder	1 (0.2%)	0	1 (0.1%)
Completed suicide	0	0	1 (0.1%)
Delirium	0	0	1 (0.1%)
Delusion	0	0	1 (0.1%)
Depression suicidal	0	0	1 (0.1%)
Disorientation	0	0	1 (0.1%)
Intentional self-injury	0	0	1 (0.1%)
Panic attack	0	0	1 (0.1%)
Feeling of despair	0	1 (0.2%)	0
Infections and infestations	0	0	10 (0.6%)
Gastroenteritis	0	0	2 (0.1%)
Bronchitis	0	0	1 (0.1%)
Dengue fever	0	0	1 (0.1%)
Hepatitis B	0	0	1 (0.1%)
Pneumonia	0	0	1 (0.1%)
Pyelonephritis	0	0	1 (0.1%)
Pyelonephritis acute	0	0	1 (0.1%)
Sepsis	0	0	1 (0.1%)
Urinary tract infection	0	0	1 (0.1%)
Injury, poisoning and procedural complications	2 (0.4%)	0	9 (0.5%)
Costochondral separation	0	0	1 (0.1%)
Fibula fracture	0	0	1 (0.1%)
Foot fracture	0	0	1 (0.1%)
Hip fracture	1 (0.2%)	0	1 (0.1%)
Multiple injuries	1 (0.2%)	0	1 (0.1%)
Overdose	0	0	1 (0.1%)
Poisoning	0	0	1 (0.1%)
Procedural pain	0	0	1 (0.1%)
Road traffic accident	1 (0.2%)	0	1 (0.1%)
Toxicity to various agents	0	0	1 (0.1%)
Nervous system disorders	1 (0.2%)	1 (0.2%)	9 (0.5%)
Headache	1 (0.2%)	0	3 (0.2%)
Autonomic nervous system imbalance	0	0	1 (0.1%)
Lacunar stroke	0	0	1 (0.1%)
Migraine	0	0	1 (0.1%)
Paraesthesia	0	0	1 (0.1%)
Psychomotor hyperactivity	0	0	1 (0.1%)
Sedation	0	0	1 (0.1%)

App 15 - Table 1: Treatment-emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Simple partial seizures	0	0	1 (0.1%)
Dizziness	0	1 (0.2%)	0
Gastrointestinal disorders	0	1 (0.2%)	7 (0.4%)
Anal fissure	0	0	1 (0.1%)
Anal incontinence	0	0	1 (0.1%)
Colitis microscopic	0	0	1 (0.1%)
Haemorrhoids	0	0	1 (0.1%)
Large intestinal obstruction	0	0	1 (0.1%)
Oesophageal ulcer	0	0	1 (0.1%)
Pancreatitis	0	0	1 (0.1%)
Oesophagitis	0	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	0	0	5 (0.3%)
Arthralgia	0	0	1 (0.1%)
Back pain	0	0	1 (0.1%)
Osteoarthritis	0	0	1 (0.1%)
Pain in extremity	0	0	1 (0.1%)
Synovial cyst	0	0	1 (0.1%)
General disorders and administration site conditions	0	1 (0.2%)	3 (0.2%)
Chest pain	0	0	1 (0.1%)
Hypothermia	0	0	1 (0.1%)
Pyrexia	0	0	1 (0.1%)
Gait disturbance	0	1 (0.2%)	0
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	3 (0.2%)
Ectopic pregnancy	1 (0.2%)	0	2 (0.1%)
Abortion spontaneous	0	0	1 (0.1%)
Renal and urinary disorders	0	0	3 (0.2%)
Nephrolithiasis	0	0	1 (0.1%)
Stress urinary incontinence	0	0	1 (0.1%)
Tubulointerstitial nephritis	0	0	1 (0.1%)
Vesical fistula	0	0	1 (0.1%)
Cardiac disorders	0	0	2 (0.1%)
Cardiac failure acute	0	0	1 (0.1%)
Sinus tachycardia	0	0	1 (0.1%)
Investigations	1 (0.2%)	0	2 (0.1%)
Blood pressure increased	1 (0.2%)	0	1 (0.1%)
Transaminases increased	0	0	1 (0.1%)
Vascular disorders	0	0	2 (0.1%)
Hypertensive crisis	0	0	1 (0.1%)
Orthostatic hypotension	0	0	1 (0.1%)
Hepatobiliary disorders	0	0	1 (0.1%)
Cholecystitis acute	0	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.1%)
Ovarian cancer	0	0	1 (0.1%)

App 15 - Table 1: Treatment-emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term; (Safety Analysis Set)

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esketamine+Oral AD (N=571)	Oral AD+Placebo (N=486)	Esketamine+Oral AD (N=1708)
Reproductive system and breast disorders	0	0	1 (0.1%)
Menorrhagia	0	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.1%)
Acute respiratory failure	0	0	1 (0.1%)
Ear and labyrinth disorders	0	1 (0.2%)	0
Vertigo positional	0	1 (0.2%)	0

AD=antidepressant; TEAE=treatment-emergent adverse event
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Adverse events are coded using MedDRA version 20.0.

Appendix 16: Patient Preference Survey

A preference survey was conducted with patients with treatment-resistant depression (TRD) to assess their tradeoff preferences for key benefit and harm outcomes associated with TRD treatments, with a focus on the unique features of ketamine-based treatments. The main goal of the preference survey was to provide information on how patients with TRD would regard the tradeoff between potential benefits of esketamine versus short-term issues associated with dosing and potential long-term safety issues observed with ketamine abuse (cystitis and memory/cognitive difficulties).

Methods and Analysis

The 5 attributes and their levels in the surveys were:

- improved mood (Montgomery-Asberg Depression Rating Scale [MADRS]: 60, 40, 20, 10)
- how quickly the medication works (6 weeks, 24 hours)
- the compound attribute of unusual sensations, wait time, and help getting home (yes, none)
- likelihood of permanent bladder problems in 1 year (none, 1%, 3%, 5%)
- likelihood of permanent memory and thinking problems in 1 year (none, 1%, 3%, 5%, 10%)

The definitions for the levels of improved mood were based on a subset of MADRS dimensions (mood, initiative, anxiety, and pessimism).

Short-term issues associated with dosing were characterized by:

- unusual sensations of dissociation and dizziness persisting for up to 2 hours and attenuating with continued dosing
- the need to take medication at doctor's office/clinic and remain there for 2 hours after dosing
- need to be driven home and being unable to drive for the rest of the day

These three issues are combined and referred to as the compound attribute of unusual sensation and logistical issues with dosing in the results below.

Bladder problems were described as permanent and untreatable pain upon urination with increased need to urinate during the day and about five times per night. Memory and thinking problems were described as permanent trouble learning and remembering new information but still being able to live independently and not needing help from others to do daily activities. These definitions of bladder and memory/thinking problems are more severe than noted from ketamine abuse; however, they were used in the survey since pretest respondents were not at all concerned about these problems when they were described as temporary.

The preference survey was administered to 2 patient samples:

- a clinical trial sample of subjects participating in SUSTAIN-2 and SUSTAIN-3 at sites in the US, UK, Canada and Australia who had direct experience with esketamine nasal spray treatment
- a sample of patients from an online panel selected via a detailed screening survey to identify those with a medical history consistent with TRD. The panel sample was mostly (>87%) ketamine-naive

Results

Both the clinical trial (n=159) and panel (n=297) respondents valued mood improvement from MADRS 40 to 10 and reduced chance of cognitive and memory problems (5% to 0%) more than the other attributes included in the survey. In both groups of respondents, any improvement in mood between MADRS total scores of 40, 20, or 10 was of greater importance than how quickly the medication works and the compound attribute of unusual sensation and logistical issues with dosing. Clinically superior outcomes were significantly preferred to clinically inferior outcomes ($p<0.05$) with 2 exceptions: In the clinical trial sample, the difference between 24 hours versus 6 weeks until the medication works was not significant ($p=0.092$) and the difference between "Unusual sensation and logistical issues with dosing" and "None" was not significant ($p=0.147$). Both of these differences were significant in the panel sample.

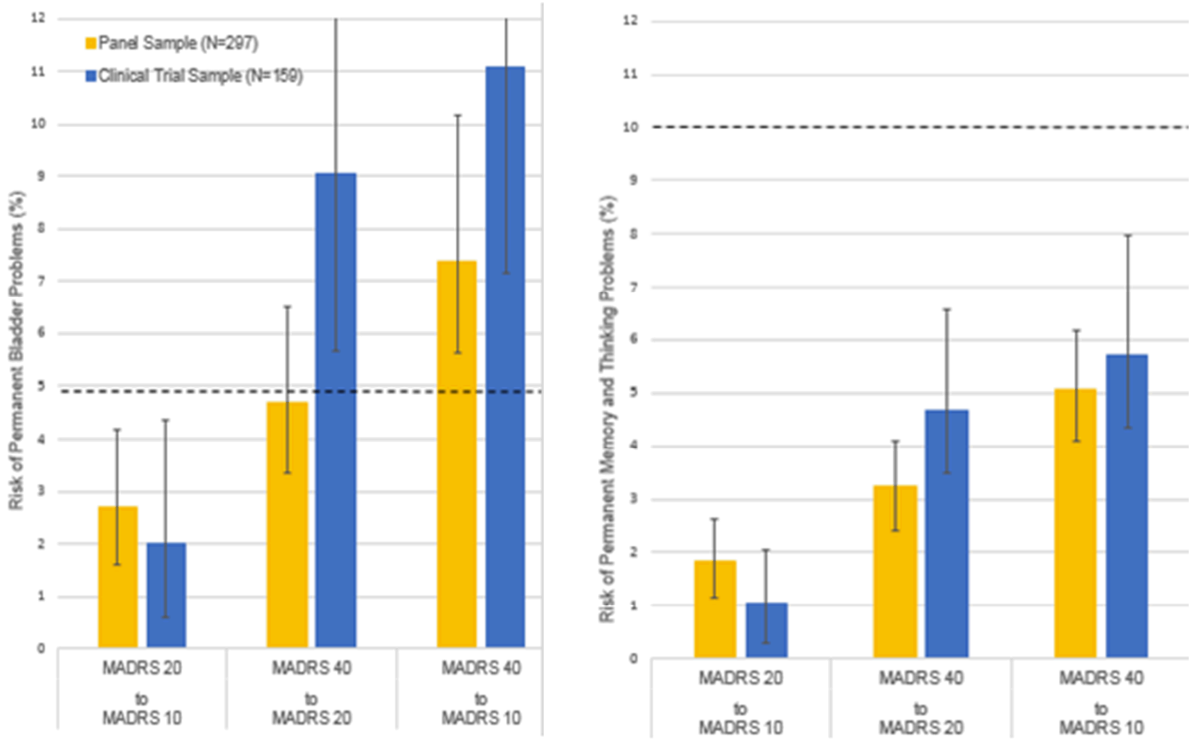
Mood improvement (from MADRS 40 to 10) was valued as 3.6 times more important in the panel sample, and 11 times more important in the clinical trial sample, than elimination of unusual sensations and logistical issues associated with dosing. While the preference survey did not assess the rationale behind patient's preferences, this observation suggests that direct experience with esketamine decreased patients' concern regarding unusual sensations and logistical issues associated with esketamine dosing.

Preference weights were used to estimate the maximum acceptable risk of potential long-term risks associated with ketamine abuse that respondents would be willing to accept. In exchange for an improvement in depression symptoms from a MADRS total score of 40 to 20 (similar to the mean MADRS change observed within the esketamine clinical trials), patients with TRD were willing to accept a risk of:

- permanent and severe bladder/cystitis problems >5% (95% CI: >5%->5%) (clinical trial sample) and 4.7% (95% CI: 3.4->5.0) (panel sample) (App 16 - Figure 1) (Note, the maximum acceptable risk that can be assessed with confidence is 5% as the maximum chance of severe bladder/cystitis problems shown in the survey was 5%.)
- permanent cognitive impairment of 4.7% (95% CI: 3.5->5.0) (clinical trial sample) and 3.2% (95% CI: 2.4->4.1) (panel sample)

Larger gains in efficacy (MADRS 40 to 10) were associated with the maximum acceptable risk, and for gains in efficacy from MADRS 20 to MADRS 10, respondents would accept >2% risk of permanent bladder problems or >1% risk of cognitive and memory problems.

App 16 - Figure 1: Mean Maximum Acceptable Risk (±95% Confidence Interval) of Permanent Bladder Problems and Memory and Thinking Impairment for Improvement in Depression Symptoms in Tradeoff Set of Patients with TRD



MADRS: Montgomery-Asberg Depression Rating Scale; TRD=treatment-resistant depression
Note: Dashed lines indicate the largest chance of harms shown in the survey. A 5% risk of permanent bladder problems was the highest risk level shown to clinical trial and panel sample respondents. A 10% risk of permanent memory and thinking problems was the highest risk level shown to half of panel respondents. For all other respondents (half of panel respondents and all clinical trial respondents), a 5% risk of permanent memory and thinking problems was the highest level shown. Estimates higher than the dashed line are extrapolations outside of the survey data. Bar height is mean maximum acceptable risk, whiskers show 95% confidence interval. Dashed lines indicate largest chance of harms shown in the survey.