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APPLICATION NUMBER:

211243Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 Jean Kim MD, MA; Qi Chen MD, MPH
 NDA 211243
 Spravato (Esketamine)

CLINICAL REVIEW

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Reviewer Name(s)	Jean Kim MD, MA; Qi Chen MD, MPH
Review Completion Date	2/18/19
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Applicant	Janssen
Dosage Form(s)	Intranasal
Applicant Proposed Dosing Regimen(s)	56 mg or 84 mg twice a week for the first 4 weeks, then weekly for the next 4 weeks, then weekly or every other week for ongoing maintenance [REDACTED] (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment Resistant Depression (TRD) in Adults [REDACTED] (b) (4)
Recommendation on Regulatory Action	Approval
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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
BPRS	Brief Psychiatric Rating Scale
BRF	Benefit Risk Framework
CADSS	Clinician Administered Dissociative States Scale
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFB	change from baseline
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450 enzyme
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DRISK	Division of Risk Management
ECG	electrocardiogram
ECT	electroconvulsive therapy
eCTD	electronic common technical document
EQ-5D-5L	European Quality of Life-5 Dimension-5 Level
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GAD	generalized anxiety disorder
GCP	good clinical practice

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GRMP	good review management practice
HVLT-R	Hopkins Verbal Learning Test-Revised
IA	interim analysis
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IM	intramuscular
IN	intranasal
IV	intravenous
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
mITT	modified intent to treat
MOAA-S	Modified Observer's Assessment of Alertness/Sedation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NMDA	N-methyl-D-aspartate glutamate
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWC-20	Physician Withdrawal Checklist-20-Item
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event

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SAP	statistical analysis plan
SGE	special government employee
SIQA	Site Independent Qualification Assessment
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	standard of care
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TEAE	treatment emergent adverse event
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression
UPSIT	University of Pennsylvania Smell Identification Test (UPSIT)
VNS	vagus nerve stimulator

1. Executive Summary

1.1. Product Introduction

The product under review (proposed trade name Spravato) is a drug-device combination of esketamine for intranasal administration. The esketamine drug product is a clear and colorless solution of esketamine HCl in water at a concentration of 161.4 mg/mL and an esketamine base equivalent concentration of 140 mg/mL. The pharmaceutical form proposed for marketing is a nasal spray solution with one presentation: a 28-mg unit-dose nasal spray device.

Esketamine is the S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist that enhances glutamine release in the brain. The FDA previously approved ketamine (under NDA 16812 as Ketalar) for use as a rapid-acting general anesthetic in February 1970, administered in solution form for use either intravenously (IV) or intramuscularly (IM). Esketamine has not been FDA-approved for any other indication, although it has been approved for use as an anesthetic in Europe and South America, administered via IV or IM. Esketamine has greater affinity for the NMDA receptor and greater dopamine transporter inhibition than the R-enantiomer or racemic mixture versions of ketamine. Esketamine is a more potent anesthetic than racemic ketamine but has a more rapid metabolism.

No regulatory agencies have approved ketamine or esketamine for any psychiatric indications worldwide. Researchers have studied ketamine in recent years for use in major depressive disorder (MDD) and several other psychiatric indications; ketamine is being prescribed and administered off-label for those indications.

Under this NDA, the Applicant proposes esketamine nasal spray for intranasal use for the treatment of treatment-resistant depression (TRD). After mutual agreement between FDA and the Applicant, TRD has been defined (from a regulatory standpoint) as a lack of clinically meaningful improvement in depressive symptoms after treatment with at least two different oral antidepressant medications as monotherapy, taken at adequate doses for adequate duration (at least 6 weeks) for their current episode of depression. The previous oral antidepressants could be from the same or different drug classes, which could include selective serotonin-reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or any other oral antidepressants.

The Applicant proposes esketamine be administered intranasally twice a week for an initial 4-week induction period in addition to a newly initiated oral antidepressant. They propose an initial adult esketamine dose of 28 to 56 mg at each administration; the dose can be titrated up to 84 mg at Week 2. The Applicant proposes continuation of treatment on a weekly basis for an

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additional 4-week (b) (4), and then weekly or every other week during an ongoing maintenance phase.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Overall, the studies submitted in support of intranasal esketamine use in the treatment of TRD met the evidentiary standard. The evidence of efficacy for esketamine for TRD includes two positive adequate and well-controlled phase 3 studies: one adequate and well-controlled short-term parallel-group phase 3 study (Study 3002) and one phase 3 study randomized withdrawal trial examining time to relapse in stable remitters on esketamine (Study 3003).

There is also additional supportive but not fully conclusive evidence in the phase 2 and 3 esketamine program such as nominally significant results in the esketamine 56-mg treatment group in Study 3001 and nominally significant differentiation of effect (per MADRS total score) from placebo by Day 2 in Studies 3001 and 3002. In all studies, the primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS), a scale frequently used to measure symptoms of depression in clinical trials and listed in the FDA Clinical Outcome Assessment Compendium.

Of note, Study 3005, a short-term parallel-group phase 3 study in patients with TRD age 65 years and older, did not provide substantial evidence of efficacy for that population. The primary endpoint was not statistically significant, and the response curve was dissimilar to Studies 3001 and 3002. Given that the safety profile was comparable to (and in some respects, milder for) the non-geriatric population, and the potential for individual geriatric subjects to respond to esketamine, we did not recommend a limitation of use for this population in labeling.

TRD is a life-threatening, severely impairing and, by definition, difficult-to-treat condition; in this instance, we must strongly consider the public health benefit to providing this medication without further delay to the population of patients who may improve. Therefore, we considered Study 3003, conducted in an enriched population of patients who are stable remitters and responders, to provide important information about esketamine's efficacy. Study 3003 provided statistically significant evidence of esketamine's maintenance-of-effect over placebo for this clinically pertinent study population. Despite not having two short-term studies (the conventional standard for approval), Study 3003 provided independent confirmation of the effects seen in Study 3002.

Accordingly, there is substantial evidence of effectiveness for intranasal esketamine, in combination with a newly initiated oral antidepressant, for the treatment indication of TRD in a clinically meaningful group of patients with TRD. I recommend approval of intranasal esketamine for this indication in adults.

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Benefit-Risk Integrated Assessment

Overall, the studies submitted for the approval of intranasal esketamine met the evidentiary standard by providing substantial evidence of effectiveness in at least two adequate and well-controlled phase 3 studies for esketamine, but with some caveats. There is evidence of effectiveness in one adequate and well-controlled short-term parallel-group phase 3 study (Study 3002). The second adequate and well-controlled phase 3 study is a randomized withdrawal study examining time to relapse in stable remitters on esketamine; this design uses an enriched population and is not typically used as a study for initial approval of a drug intended to treat major depressive disorder. Study 3003 provides crucial evidence of esketamine's longer-term effectiveness for TRD with maintenance dosing.

There is also supportive but not fully conclusive evidence in the phase 2 and 3 esketamine program: a nominally significant effect of esketamine in the 56-mg treatment group in Study 3001; a nominally significant improvement on MADRS total scores versus placebo as early as Day 2 in Studies 3001 and 3002; a subgroup of esketamine remitters and responders based on changes in MADRS total score consistently greater than placebo across all phase 3 studies and Study SUI2001 (but not statistically compared); MADRS mean total score distribution of response favoring esketamine over placebo in all phase 3 short-term studies (not statistically compared); nominally significant endpoints in phase 2 Study 2003 and statistical significance on the primary endpoint in Study SUI2001; numerical improvement over placebo in nearly all primary and secondary efficacy measures across all phase 3 studies; mean numerical MADRS score reductions in the esketamine arms consistent with literature-based definitions of MDD clinical response ($\leq 50\%$ reduction from baseline to endpoint) in Studies 3001 and 3002; and a numerical difference in MADRS total score change from baseline endpoint improvement comparable to those seen in other FDA-approved antidepressants and in a more seriously ill population (with a higher mean baseline MADRS total score). In all studies, the primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS), a scale frequently used to measure symptoms of depression in clinical trials and listed in the FDA Clinical Outcome Assessment Compendium. The application also includes some limited supportive evidence from additional secondary endpoints (e.g., Patient Health Questionnaire-9 Item (PHQ-9), a self-reported measure of depressive symptoms).

Esketamine also appears generally well-tolerated and comparable to the known profile of ketamine, with manageable acute risks (such as dissociation, sedation, increased blood pressure, and potential for abuse and diversion) mediated by our REMS plan. Other chronic (long-term) dosing concerns (which differentiate the use of this product from the prior approved anesthesia indication for ketamine) brought up by previous ketamine-related data (such as bladder and liver toxicity, cognitive changes and neurotoxicity) have not shown unexpected, severe, or irreversible safety signals thus far in the long-term esketamine safety studies. Ongoing open-label and postmarketing safety studies and pharmacovigilance and surveillance (including REMS reporting) will provide data and continuing attention to these safety concerns. Labeling

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will also address these and other risk factors.

TRD is a life-threatening, severely impairing and, by definition, difficult-to-treat condition; in this instance, we must strongly consider the public health benefit to providing this medication without further delay to the population of patients who may improve. Therefore, we considered Study 3003, conducted in an enriched population of patients who are stable remitters and responders, to provide important information about esketamine's efficacy. Study 3003 provided statistically significant evidence of esketamine's maintenance-of-effect over placebo for this clinically pertinent study population. Despite not having two short-term studies (the conventional standard for approval), Study 3003 provided independent confirmation of the effects seen in Study 3002.

Additional practical considerations of a different time of onset and mechanism of action and side effect profile from previously approved oral antidepressants, fewer drug-drug interactions than other oral antidepressants, standardized intranasal dosing (less invasive than IV or IM) at less frequent intervals than treatments like TMS render esketamine distinctive from existing therapies for TRD, including the off-label use of ketamine.

Accordingly, there is substantial evidence of effectiveness for intranasal esketamine, in combination with a newly initiated oral antidepressant, for the treatment of TRD. I recommend approval of intranasal esketamine for this indication in adults.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Treatment-Resistant Depression (TRD) is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. Patients with TRD can be unable to work, maintain relationships, and in the most severe cases may become hospitalized or even commit suicide. 	TRD is a high-risk condition in serious need of additional approved treatments.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> • Treatment options remain limited for TRD. By definition these patients have not responded adequately to at least 2 existing oral antidepressant medications. Oral antidepressants are all noted to have similar levels of efficacy around 60%; none have demonstrated clear superiority in treating TRD. • The only FDA-approved oral medication for TRD is a fixed-dose combination of fluoxetine and olanzapine. The only other FDA-approved treatments under the Center for Devices and Radiological Health (CDRH) for TRD are electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulator (VNS) implantation. All have significant adverse reactions to consider, including weight gain and extrapyramidal adverse reactions (for combination olanzapine and fluoxetine), risks of general anesthesia and memory loss (ECT), and surgical intervention and infection (VNS). TMS has a more benign side effect profile relative to these other interventions, but some reports indicate decreased efficacy relative to the other approved TRD treatments. 	Existing treatments for TRD are limited and either have serious adverse reactions, slower onset, access/practicality issues, or equivocal efficacy.
<u>Benefit</u>	<ul style="list-style-type: none"> • Evidence: Study 3002 and 3003 were statistically significant on their primary endpoints (change from baseline on MADRS total score at Week 4, and time to relapse based on MADRS total score respectively). Additional support is noted from secondary endpoints in Study 3002; the 56-mg arm in Study 3001, which was nominally significant on its primary endpoint with an overall magnitude of effect size on the MADRS (-4.2) and early nominally significant differentiation from placebo at Day 2 in Studies 3001 and 3002 on MADRS total score; from exploratory secondary endpoints (response 	Taken as a whole, these studies provide substantial evidence of effectiveness for esketamine IN for treatment of TRD. The TRD population is, by definition, extremely difficult to treat. Studies in general for antidepressants have had issues with statistically significant findings in part due to marked placebo effects in trial populations. Given these issues, the overall trends of all studies and the objective

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	<p>and remission rates) in the phase 3 studies which were consistently numerically better for esketamine versus placebo (although not statistically compared); from Study 2003, a proof-of-concept phase 2 study which esketamine was superior to placebo on improvement in depressive symptoms for Panel A; and from Study SUI2001, a proof-of-concept phase 2 study for the related but separate indication of treatment for MDD with imminent suicidal risk, which was statistically significant on its primary endpoint at Day 1 and also at Day 2, with numerical improvement over placebo at Day 25.</p> <ul style="list-style-type: none"> • Uncertainties: Study 3001 was not statistically significant, mainly due to the 84-mg arm which was the higher dose. Study 3005 (in the geriatric population) also was not statistically significant on its primary endpoint. Secondary endpoints were not statistically significant in the phase 3 studies (except the stable responders group for 3003). There is unclear evidence for increased dose response with 84 mg. IN esketamine may or may not only work in combination with a newly initiated oral AD. Study 3003's design might not be considered well-controlled due to functional unblinding (which may have contributed to early placebo relapses) and only examined an enriched population of esketamine remitters and responders. Functional unblinding (perception of treatment assignment due to esketamine's acute effects) also may or may not have affected results due to potential expectation bias in the other phase 3 studies. 	<p>effect sizes and score changes, even in the ones not statistically compared or significant, still show a noticeable and consistent difference from placebo. Study 3002, a short-term parallel group study, was statistically significant for its primary endpoint, and also showed a difference between treatment groups as early as Day 2. Study 3003, conducted in an enriched population of esketamine remitters and responders, provided statistically significant evidence of effectiveness for longer-term use of esketamine in a clinically relevant population. These trends will likely translate into clinically meaningful effects in many patients, which can make a life-saving difference and improve the quality of life for people who would otherwise continue to suffer with TRD.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk and Risk Management</u></p>	<ul style="list-style-type: none"> • Post-Dose Safety (Acute): The major effects of concern were sedation, dissociation, and elevated blood pressure. 49 to 61% of patients experienced sedation and 60 to 79% of patients experienced dissociation compared to 23% or less on placebo. The majority required about 1.5 hours to resolve but there were some outliers. The acute effects follow the PK profile of drug (so will need to monitor longer in hepatic impairment). • Subacute/Chronic-Use Safety: The major effects of concern were nausea/vomiting, hepatotoxicity, bladder toxicity, cognitive impairment, and unknown long-term neurotoxicity (nonclinical concerns with ketamine). A higher rate of urinary tract and bladder AEs was seen in the short-term studies on esketamine compared to placebo, although no cases of interstitial or ulcerative cystitis were reported, including the long-term safety studies. Although sedation and vomiting were common effects, no aspiration cases were noted in the studies. No cases of acute hepatotoxicity or clinically meaningful liver function test trends were noted. Some short-term cognitive function changes were noted on (b) (4) in one phase 1 study, but no long-term findings were noted thus far in open-label studies. • Abuse Potential: Esketamine has similar drug-liking characteristics (i.e., euphoria and dissociation) to ketamine, a known drug of abuse. This effect was confirmed in a phase 1 abuse potential study (Study 1015); subjects on esketamine endorsed similar drug-liking scores to IV ketamine and higher than placebo. 	<ul style="list-style-type: none"> • This application will be approved with a Risk Evaluation Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). The plan is intended to mitigate the risks of sedation, dissociation, and abuse potential. • Acute Effects (REMS safety goals): Because of the risks of sedation and dissociation, patients will require at least 2 hours of observation in clinically supervised settings and advised against driving or working with heavy equipment (b) (4). Blood pressure elevation will need to be monitored closely (and patients should be prescreened to avoid risk factors). (We have recommended >140/90 as a general guideline for not administering the drug, although benefit-risk for individual cases should be clinically assessed.) • Subacute/Long-Term Effects: Labeling will address most of these concerns and inform clinicians and patients of potential safety issues. REMS-mandated data collection,

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		<p>pharmacovigilance and surveillance (i.e., FAERS reporting), and postmarketing safety studies will continue to assess these issues.</p> <ul style="list-style-type: none"> • Abuse potential is clinically significant given ketamine's history of abuse; esketamine will be Schedule III. Prevention of abuse and diversion is another REMS goal: esketamine will only be administered and dispensed per dose administration in clinically supervised, registered settings. Diversion will need to be avoided and monitored.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input checked="" type="checkbox"/> Clinical outcome assessment (COA) data, such as	6.1 (Study Endpoints), 6.2, 6.3, 6.4
	<input checked="" type="checkbox"/> Patient reported outcome (PRO)	
	<input checked="" type="checkbox"/> Observer reported outcome (ObsRO)	
	<input checked="" type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input checked="" type="checkbox"/> Performance outcome (PerFO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input checked="" type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	7.2 Other Efficacy Considerations
	<input type="checkbox"/> Other: (Please specify)	
<input checked="" type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input checked="" type="checkbox"/> Input informed from participation in meetings with patient stakeholders (Patient Focused Medical Product Development Meeting (Depression and Bipolar Support Alliance), November 16, 2018)	2.1 Analysis of Condition
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

MDD is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. More than 16 million people in the United States¹ and more than 300 million people worldwide² have depression. Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates (at a median rate of 10 years of life lost)³. About 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), etc.) and psychotherapy⁴. In addition, the onset to treatment response for these modalities, even when effective, often takes at least four weeks, leading to greater suffering, expense, and risk.

Patients who have failed at least two trials of antidepressant treatment generally comprise the population with treatment-resistant depression (TRD). During an externally-led Patient-Focused Drug Development Meeting held on November 16, 2018, feedback from patient representatives noted concerns such as inadequate or incomplete treatment responses, multiple drug trials, and side effect burden from existing MDD treatments⁵. Relative to other patients with MDD, patients with TRD can incur even more severe morbidity, with higher rates of hospitalizations, suicidal ideation and behavior, and medical complications. The urgent need for a rapid-acting, safe, and effective way to interrupt a severe major depressive episode, and to prevent future episodes afterwards remains of utmost concern; TRD treatments remain an unmet medical need.

2.2. Analysis of Current Treatment Options

¹ <https://www.nimh.nih.gov/health/statistics/major-depression.shtml> Accessed December 11, 2018.

² World Health Organization. Depression and other common mental disorders. Global health estimates. (Geneva: World Health Organization; 2017.)

³ Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72:334-341.

⁴ 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.

⁵ https://secure2.convio.net/dabsa/site/SPageServer/?jsessionid=00000000.app268b?NONCE_TOKEN=68B6AC0BF8CA6ED6EA73E7D0B6B258A9&NONCE_TOKEN=8E5900F85A7E46F4D8095EE821724DA1&pagename=FDA_videos Accessed January 9, 2019.

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Standard of care measures for TRD include switching to a different antidepressant (either the same or a different class), adding adjunctive treatment to an ongoing antidepressant (typically a drug with a different mechanism of action), adding or switching psychotherapy, or referral for a procedure such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)⁶.

The available treatments for TRD are limited. Only one medication is currently FDA-approved for TRD. The only other FDA-approved interventions for TRD are device-related and reviewed by the Center for Devices and Radiological Health (CDRH). Some of these treatments are associated with significant adverse reactions and interventional concerns (such as use of general anesthesia, seizure induction, and memory loss with ECT; or surgical intervention and infection risk with VNS implantation). Other issues include inconvenient daily office visits (such as with TMS).

Table 1 Summary of FDA-Approved Treatments for Treatment-Resistant Depression

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Body
FDA Approved Treatments						
Fluoxetine plus Olanzapine fixed-dose combination	TRD	Dec 2003	Oral daily	MADRS Total Score Change from Baseline of -16 vs. olanzapine -12 and placebo -10 for Study 1, -18 vs. -14 and -9 for Study 2	Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and EPS/akathisia	CDER
ECT	TRD (associated with either MDD or Bipolar Disorder)	1976 (updated Dec 2015)	Bitemporal or unilateral temporal; up to 3 times a week for 6 to 10 treatments initially	Not available; approval based on various studies from research literature.	Memory concerns, use of general anesthesia	CDRH
TMS	TRD (only failed 1 antidepressant)	2008	Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)	MADRS Total Score Change from Baseline of -6 at Week 4 and Week 6 active TMS vs. -4 at	No major safety issues, limited long-term safety data	CDRH

⁶ <https://www.uptodate.com/contents/unipolar-depression-in-adults-treatment-of-resistant-depression> Accessed December 11, 2018.

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Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Body
				Week 4 and Week 6 sham TMS. Approval based on post-hoc analysis and responder/remission rates.		
VNS	TRD	July 2005	Once (surgical implant)	12-week sham placebo-controlled study not statistically significant. Approval was based on long-term open-label HAM-D responder data (30% response in 1 year versus 13% treatment as usual). 12-week open-label pilot study showed 34% MADRS responders.	Surgical intervention risks (allergies, infection, etc.)	CDRH

Quetiapine XR, aripiprazole, and brexpiprazole are approved for the related indication of adjunctive treatment for MDD in combination with an oral antidepressant. Patients enrolling in trials to support an adjunctive treatment indication are typically less severely ill than patient with TRD; they have usually experienced some symptom improvement with antidepressant monotherapy but remain ill enough to enter a trial. Additional off-label pharmacological interventions for TRD include ketamine, and augmentation with other antidepressants or antipsychotics, lithium, thyroid hormone, buspirone, and other drugs.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Esketamine has not yet been FDA-approved in the United States for any indications.

3.2. Summary of Presubmission/Submission Regulatory Activity

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- May 8, 2012, Pre-IND Meeting: FDA and the Applicant discussed nonclinical and clinical pharmacology study requirements, including carcinogenicity studies, repeat Olney lesion studies, and comparison studies to ketamine. The clinical reviewer discussed the regulatory definition of TRD (failure of treatment of at least two different antidepressant classes; this requirement later was modified in March 2014 to any two antidepressants), and the acceptability of the proposed phase 2 dose frequency and phase 3 study designs. The Applicant agreed to modify the proposed parallel-group phase 3 studies to incorporate a longer acute treatment period of at least four weeks to assess for persistence of effect; FDA and the Applicant agreed on the use of the Montgomery-Asberg Depression Rating Scale (MADRS) as the assessment scale during the studies to be measured at each timepoint. They also agreed upon other scales for adverse event (AE) assessment (Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) (later switched to (b) (4) in April 2014)). FDA required abuse potential assessment studies and PDAC review.
- November 7, 2013: FDA granted the Applicant's Breakthrough Therapy Designation (BTD) request for the esketamine for TRD development program. TRD is a serious condition with only one approved treatment. The phase 2 esketamine studies suggested that symptomatic improvement could be observed within 24 hours following esketamine treatment, thus providing preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapy.
- March 13, 2014, and May 6, 2014, BTD Advice Meetings: The Applicant and FDA agreed upon the regulatory definition of TRD for this program (failure of treatment of at least two different antidepressants of the same or different classes, given at an adequate dose and duration); determination that TRD criteria were met was to include retrospective determination of prior treatment failures if validated via scales such as the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and prior records (e.g., pharmacy, medical). (b) (4)

FDA also requested a maintenance-of-effect study; the Applicant then proposed a (b) (4). FDA emphasized the use of centralized, blinded, remote raters in all phase 3 studies. FDA requested the use of "active" intranasal placebo to enhance blinding but later agreed not to require it (accepting inactive intranasal placebo instead) if the Applicant instituted additional blinding precautions for on-site staff. FDA also recommended a severe renal impairment study. The Applicant inquired whether they could

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file their application with [REDACTED] (b) (4)
[REDACTED]; the Agency did not agree, noting that we viewed this product very differently from previously approved oral antidepressants and would require maintenance data at the time of filing. FDA agreed that including at least 30% US subjects in phase 3 pivotal studies would allow for adequate representation relevant to our treatment population.

- June 5, 2014, BTDA Advice Meeting: The Applicant and FDA discussed Chemistry, Manufacturing, and Controls (CMC) and abuse liability study requirements. FDA requested a phase 1 abuse liability study.
- June 18, 2014, Nonclinical Meeting: FDA and the Applicant discussed Olney lesion study (neurotoxicity) specifications for nonclinical requirements. FDA required a 14-day repeat-dose neurotoxicity rat study with post-dosing histological assessment to rule out vacuolization prior to phase 3 initiation.
- September 12, 2014, BTDA Advice Meeting: FDA and the Applicant agreed to the proposed phase 3 short-term and maintenance study designs, with one short-term study being a flexible-dose study. FDA agreed that the maintenance study could be used as one of two positive studies to support a marketing application, along with a short-term fixed-dose study with statistically very persuasive results (later switched to any short-term study in March 2018, see below).
- December 8, 2014, End-of-Phase 2 Meeting: FDA and the Applicant agreed upon doses of 56 mg and 84 mg esketamine for the phase 3 studies. Patients with cardiovascular and cerebrovascular risk factors were to be excluded because of the risk for hypertension (HTN) with esketamine, and blood pressure (BP) was to be monitored pre- and post-dose. FDA agreed that the Applicant's nonclinical study program proposal for esketamine in combination with specific bridging studies to ketamine would be sufficient for NDA submission.
- June 24, 2015, Guidance Meeting: FDA's nonclinical team requested an additional acute neurotoxicity rat study due to concerns about NMDA antagonist class-related issues. The nonclinical team agreed the study could be conducted in parallel with phase 3 human studies.
- March 1, 2016, BTDA Advice Meeting: FDA and the Applicant agreed on defining the important secondary endpoint of Onset of Clinical Response as the point at which a $\geq 50\%$ improvement (instead of score ≤ 19) in MADRS total score was achieved, with sustained response at each subsequent timepoint (with one permitted excursion) for the phase 3

short-term studies. FDA also agreed to the proposed additional secondary endpoint of Sheehan Disability Scale (SDS) total score for potential inclusion in the label.

- March 14, 2018, Pre-NDA Meeting: FDA agreed that the completed (to-date) phase 3 studies (3001, 3002, 3003, 3004, and 3005) were adequate to support filing of an NDA for review, and that phase 2 studies and studies conducted under a separate IND for a related indication would also be taken into consideration during our review. The Applicant was to provide demographic-based exploratory efficacy analyses for the pooled phase 3 short-term studies, 3001 and 3002. FDA requested a list of safety preferred terms in advance for review and agreement (which was provided April 18, 2018).
- June 28, 2018, Second Pre-NDA Meeting: FDA encouraged the Applicant to submit a proposed REMS with the NDA. FDA agreed to inclusion of bridging nonclinical studies with ketamine from Javelin in the submitted NDA.

3.3. Foreign Regulatory Actions and Marketing History

Starting in 1997 in Germany, esketamine has been approved and marketed overseas as a general anesthetic in 17 countries, including much of Europe (including the United Kingdom and Scandinavia) and Brazil. It is marketed under trade names including Esketamine, Ketamin, Ketanest, Ketanest-S, S-Ketamin, and Vesierra. Approval was voluntarily withdrawn from France in December 2016, and the license was suspended in Latvia in June 2017 with distribution ending in December 2017. The Applicant did not note any safety concerns related to those market withdrawals.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the OSI consultation review for more details. Sites were selected for inspection if their effect sizes were noted to be large. For Study 3003, one site in Poland was noted to have driven the primary endpoint efficacy results, with 100% relapse rate in subjects randomized to placebo, but no significant conduct issues were noted at that site on inspection. Please see the efficacy results section in 3003 for more details. Another issue that OSI noted was unblinding concerns at some study sites, with a few subjects conjecturing whether or not they were on active study drug (and at least one subject voluntarily discontinuing the study because they believed they were on placebo). Finally, some issues with device malfunctioning and cases of underdosing of nasal spray medication were noted. Overall, there were no major findings from site inspections affecting interpretation of the phase 3 esketamine study results.

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4.2. Product Quality

No major concerns have been noted. See the CMC/OPQ review for more details.

4.3. Clinical Microbiology

No concerns are noted.

4.4. Nonclinical Pharmacology/Toxicology

Previous 1980s ketamine studies showing Olney lesions developing after exposure in rats were of particular concern. The Applicant agreed to nonclinical exposure studies with esketamine to address this concern. Results of these esketamine studies to date did not replicate the Olney lesion findings.

Ketamine was also noted to cause neurotoxic fetal changes in animal studies. A potential teratogenicity risk warning will be included in labeling.

Another concern is bladder toxicity reported with prior ketamine use in humans, as well as animals.

Per discussion with the nonclinical reviewer Dr. Shiny Mathew: “With racemic ketamine (Javelin’s data), both rats (3-months) and dogs (28-day study) some of the following are seen: hemorrhage/hyperplasia of the transitional epithelium, inflammation of the mucosa of the bladder, kidney/bladder calculi, etc. In rats, this is happening at about 1.5 times maximum recommended human dose (MRHD); and in dogs, it is happening at exposures about 10-fold lower than MRHD in humans. Exposures here are estimated based on 50% of the racemate being esketamine. The bladder effects in dogs were not fully reversed after 2 weeks of recovery.

With IN esketamine administration two male rats showed bladder histopathology changes (“lesions of the submucosa of the urinary bladder”) after daily dosing in a 2-year carcinogenicity study (0.6 times MRHD). Looking at individual animal data in the chronic dog study (9 months), there is a low incidence of inflammation/congestion to the bladder mucosa (1 high dose male, 1 medium dose female, high dose female; N=4/Sex/dose), but these findings are considered within background by the pathologist and not mentioned in the report.”

Please reference the nonclinical review for more details.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review for more details. Some highlights include the following:

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- Esketamine is an NMDA receptor antagonist.
- The mean terminal half-life of esketamine is 7 to 12 hours.
- C_{max} and AUC_{last} are dose-proportional between 56 mg and 84 mg.
- There is a rapid concentration drop-off after C_{max} for the first few hours, then a more gradual decrease.
- The pharmacokinetics appear consistent between single-dose and multiple-dose administration with no plasma accumulation.
- The mean absolute bioavailability of 84 mg esketamine is around 48%, via local absorption from nasal mucosa (within 7 minutes) and the gastrointestinal tract via swallowing (as compared to IV with near 100% bioavailability, and around 14% for oral administration).
- Overall esketamine blood level dosing curves showed no major differences with equivalent dosing (i.e., 28 mg IN dosing was comparable to 0.4 mg/kg IV) between IV and IN esketamine in phase 1 and 2 studies (1002 and 2001).
- The T_{max} for esketamine is around 20 to 40 minutes after the last nasal spray during a treatment session.
- Esketamine metabolism is around 45% protein-bound, and not dependent on hepatic or renal function; there is extensive tissue distribution.
- Esketamine is primarily liver metabolized via N-demethylation to noresketamine, via CYP2B6 and CYP3A4, and to a much lesser extent CYP2C19 and CYP2C9.
- The main route of excretion is urine (78 to 86%) and then feces (2%), as metabolites.
- Esketamine's PK does not appear to be influenced by body weight or gender.
- The C_{max} is greater depending on age, and in some Asians (Chinese and Japanese), and with hepatic or renal impairment, and mildly increased with allergic rhinitis.
- The AUC was markedly affected in subjects with hepatic impairment in the phase 1 PK study, which may lead to next-day residual effects.
- Concomitant CYP substrate testing reveals no major interactions, with mild increases in substrates with 2B6 and 3A4 inhibitors (maximum 1.3 times baseline) and mild decreases in midazolam (3A5 substrate, around 0.8 times decreased dose) with concomitant administration.
- Esketamine was administered without food during the clinical trials, only due to concerns about nausea/vomiting and sedation. Food does not significantly affect its metabolism.
- Cognitive function was impaired for up to 2 hours post-dose, and sleepiness persisted for up to 4 hours post-dose.
- A driving test at 8 hours post-dose and next-day post-dose showed no statistically significant difference from placebo. Two subjects were unable to drive due to esketamine-related adverse events. Post-dose caution remains recommended. Labeling language is recommended to address concerns about not driving home after treatment visits.

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- Abuse potential study showed a drug preference signal for esketamine.
- A QT study showed no clinically significant prolongation.
- Exposure was increased somewhat in patients older than 65 years of age relative to non-elderly adults, particularly in the 75 to 85-year-old subgroup.
- Mean blood pressure was consistently elevated 40 minutes post-dose (about 15 mm Hg SBP and 9 mm Hg DBP) to around twice that seen on placebo (7 mm Hg SBP and 5 mm Hg DBP), with slightly higher BP increases in 84-mg versus 56-mg esketamine doses.
- A phase 2 study showed no clinically significant advantage on the MADRS to dosing 3 times a week versus 2 times a week.
- Interaction with CYP2D6 inhibitors (the majority of antidepressants) initially needed to be clarified. OCP subsequently found published literature that noted esketamine was not a substrate for CYP2D6 (it was stable in CYP2D6 enzyme with an incubation time of up to 120 minutes). An inhibition study of esketamine by quinine (a 2D6 inhibitor) in human liver microsomes only decreased esketamine metabolism by 12%. OCP therefore concluded that esketamine had no potential interaction with CYP2D6 inhibitors.
- Overall there do not appear to be as many drug-drug interactions with esketamine as with most oral antidepressants.

4.6. Devices and Companion Diagnostic Issues

Spravato is dispensed using a unit-dose nasal spray device, issuing a 28-mg total dose divided in two sprays. There is a Type (b) (4) glass vial with a rubber stopper, holding 0.2 mL of drug product solution (equivalent to 32.3 mg of esketamine HCl or 28 mg of esketamine base). The vial is contained within the nasal spray device (b) (4)

The spray is manually activated and dispenses two individual sprays (one for each nostril) for a total volume of 0.2 mL of drug product. A separate device is to be used for each 28-mg dose, so two devices are used for 56 mg, and three devices for 84 mg. An indicator will note if the device has one spray remaining or is empty after use.

4.7. Consumer Study Reviews

Please see the Division of Medication Error Prevention and Analysis (DMEPA) human factors review for more details.

Human factors testing was conducted using the nasal spray device in one study. The study consisted of two trials each for 17 pairs of health care providers and patient participants. As per Nicole Garrison, PharmD, the safety evaluator:

In Trial 1, participants were given the labeled product presentation (2 devices per carton) with no specific guidance or instructions and asked to perform the administration. In Trial 2, the same participants were asked to read the IFU and follow the IFU step-by-step as they supervised the patient to perform the administration. We note that in Trial 1, six participants were unable

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to select the correct number of devices (2 devices) needed to administer the dose. The Applicant has traced the root cause of the use errors to the information presented on the carton. Based on the root cause analysis, those participants were unable to determine the total drug content per spray and total drug content per device. In addition, some participants did not know many devices were required to make a complete dose.

The Applicant has proposed a revision to the carton labeling to increase the prominence of the information about the total dose for each carton pack. However, since the Applicant has not validated the new carton labeling, we do not have any data to support whether the intended users will understand the revised labeling.

A supplemental human factors study conducted in patients with MDD subsequently submitted by the Applicant continued to show issues with label comprehension and package selection problems for appropriate dosing.

The review team initially recommended single-device carton packaging (with one 28-mg device per package) due to concerns over unused device diversion and labeling improvements to increase clarity and minimize the risk for medication dosing errors. However, given that there will be only two approved esketamine doses of 56 mg and 84 mg (and not 28 mg), the team decided that the Applicant's new proposal of single packages containing multiple devices to add up to a given dose was acceptable for now. (There remains the concern of potential diversion of unused devices from a multiple-device kit if a clinician wished to administer a lower dose (e.g., 28 mg) to a patient due to individual side effects or other clinical concerns.) The Applicant then requested at least an initial implementation of the 28 mg packaged dose. Due to the lack of supportive data for this request and potential for introduction of new errors, we declined the proposal and will continue to recommend multiple devices packaged within 56-mg and 84-mg dose kits and no separate 28-mg dose.

The labeling of each dosing package kit also remains a concern, as due to OPQ and FDA Compendium standards, the individual device dose is what must be registered and labeled for a given manufactured product. Although from a human use perspective, labeling the package with the total dose administered may reduce confusion, additional problems and errors may ensue from conflicts with pharmacy product registration codes which must remain at 28 mg.

Additional confusion has also arisen due to each device administering two sprays to add up to a total of 28 mg; testing has indicated users are not always aware one spray contains about 14 mg and may administer the wrong amount of product. We considered a recommendation that package labeling should somehow also note the amount of drug per individual spray for clarity. However, CMC testing notes that only the combination of two sprays per device has been confirmed to reach 28 mg; there is insufficient data to confirm that each spray always contains 14 mg. Therefore, we recommend that package labeling will note that the combination of two sprays delivers a total of 28 mg esketamine.

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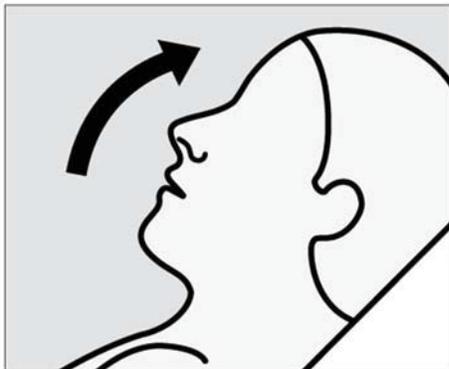
The team considered recommending a post-marketing commitment for the Applicant to study the feasibility of future development of single-unit devices with recommended doses per unit (i.e., one device that delivers 56 mg, and one that delivers 84 mg) to reduce confusion and diversion. However, the team subsequently learned that devices containing new dosages would likely require additional clinical trials and a separate NDA application. Accordingly, we did not feel this recommendation was practical at this time.

There were also additional concerns about several medication use errors noted in the study:

- Patient did not blow nose before using the first device
- Patient did not recline or tilt their head during preparation
- Patient did not close the opposite nostril during administration.
- Patient did not breathe in through nose during administration.
- Patient did not sniff gently after spraying.
- Patient did not rest for 5 minutes after each device.
- Patient administers 2 sprays in one nostril from the same device.

The main concern noted by Kathleen Fitzgerald RN, the CDRH reviewer, is patients not tilting back their heads when administering medication; they may not receive a sufficient dose without this step. It was advised that instructions for use in labeling and medication guides should make this step clear to the patient.

An excerpt from the draft Instructions for Use document which incorporated this advice follows (and appears sufficient):



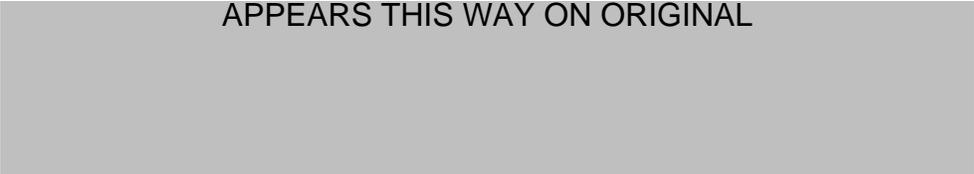
(b) (4) :

- Recline head at about **45 degrees** during administration to keep medication inside the nose.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

APPEARS THIS WAY ON ORIGINAL



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Table 2 Listing of Clinical Trials Relevant to NDA 211243

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
TRD3001 (TRANSFORM -1)	NCT02782104	Randomized, double-blind, multicenter, parallel-group, controlled study	Esketamine (ESK) 56 mg or 84 mg (fixed) or placebo, twice weekly intranasal, plus newly- initiated oral antidepressan t (AD)	Primary: Change from Baseline (CFB) in MADRS Total Score at Week 4	4-week treatment phase, 24- week follow- up or TRD3003	344 total (115 on ESK 56 mg + oral AD; 116 on ESK 84 mg + oral AD; 113 on placebo + oral AD)	Adults (18 to 64 years) with TRD	92 sites in US, Belgium, Brazil, Canada, Estonia, France, Hungary, Mexico, Slovakia
TRD3002 (TRANSFORM -2)	NCT02418585	Randomized, double-blind, multicenter, parallel-group, controlled study	Esketamine (ESK) 56 mg or 84 mg (flexible) or placebo, twice weekly intranasal, plus newly- initiated oral antidepressan t (AD)	Primary: CFB in MADRS Total Score at Week 4	4-week treatment phase, 24- week follow- up or TRD3003	224 total (114 on ESK + oral AD; 110 on placebo + oral AD)	Adults (18 to 64 years) with TRD	47 sites in US, Germany, Poland, Czech Republic, Spain (1 Polish site later excluded)
TRD3005 (TRANSFORM -3)	NCT02422186	Randomized, double-blind, multicenter,	Esketamine (ESK) 28 mg, 56 mg or 84	Primary: CFB in MADRS	4-week treatment phase, 24-	137 total (72 on ESK + oral AD; 65 on placebo +	Elderly adults (65 years and	57 sites in US, Brazil, Belgium,

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		parallel-group, controlled study	mg (flexible) or placebo, twice weekly intranasal, plus newly- initiated oral antidepressan t (AD)	Total Score at Week 4	week follow- up or TRD3004	oral AD)	over) with TRD	Spain, France, Bulgaria, Finland, Lithuania, UK, Italy, Poland, Sweden, South Africa (1 US site later excluded)
TRD3003 (SUSTAIN-1)	NCT02493868	Randomized, double-blind, multicenter, controlled withdrawal study	Esketamine (ESK) 56 mg or 84 mg or placebo, twice weekly intranasal, plus newly- initiated oral antidepressan t (AD) during induction phase, then ESK continued (weekly for 4	Primary: Time to relapse (hazard ratio)	4-week treatment initiated during 3001 or 3002 with response or open-label induction phase with response, then 12-week optimization phase (ESK weekly for 4	705 total (437 new entry + 268 from 3001 or 3002); 437 during induction phase; 445 during optimization phase; 176 during maintenance phase (90 on ESK +oral AD;	Adults (18 to 64 years) with TRD	164 sites in US, Canada, Brazil, Mexico, Turkey, Belgium, Czech Republic, Germany, Estonia, Poland, Slovakia, Sweden,

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			weeks then weekly or every other week) + oral AD during optimization phase, then randomized withdrawal (ESK continued (weekly or every other week) or switched to placebo + oral AD) during maintenance phase		weeks then weekly or every other week, same dose as induction, oral AD ongoing), then ongoing maintenance phase (ESK same dose as induction, or switched to placebo, weekly or every other week, oral AD ongoing); 2-week follow-up	86 on placebo +oral AD). Placebo subjects from 3001 + 3002 continued for safety observation (optimization: 86, maintenance: 54).		France, Spain, Italy, Hungary
TRD2003 (SYNAPSE)	NCT01998958	Randomized, double-blind, multicenter, parallel-group, controlled study	IN ESK 14, 28, 56, or 84 mg (fixed dose), or IN placebo, twice weekly during 2	Primary: MADRS Total Score Change from Day	Two double-blind treatment periods (1 and 2) with IN ESK or placebo	<u>Panel A/Period 1:</u> Total: 67 Esk 28 mg: 11 Esk 56 mg: 11 Esk 84 mg: 12	Adults (Ages 20 to 64) with TRD	24 sites total; Panel A: US and Belgium; Panel B:

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			weeks tx phase (each week being one period), then optional open-label continuation (flexible dose)	1 to Day 9 for Period 1, then Day 8 to Day 15 for Period 2, then Combined Periods Secondary : MADRS ≤ 10 , MADRS $\geq 50\%$ reduction, QIDS-SR16, CGI-S, PGI-S, GAD-7	administered Day 1 and 4 (Period 1), then on Day 8 and 11 (Period 2). Subjects on ESK stayed on same tx throughout; those on placebo in Period 1 switched to ESK during Period 2 if QIDS-SR16 ≥ 11 . Then optional open-label tx phase (either up to 60 days for Panel A or 10 days for Panel B); 8-week follow-up	Placebo: 33 <u>Panel A/Period 2:</u> Total: 28 Esk 28 mg: 8 Esk 56 mg: 9 Esk 84 mg: 5 Placebo: 6 <u>Panel B/Period 1:</u> Total: 41 Esk 14 mg: 11 Esk 56 mg: 9 Placebo: 21 <u>Panel B/Period 2:</u> Total: 13 Esk 14 mg: 5 Esk 56 mg: 3 Placebo: 5 <u>Optional OL Phase:</u> Panel A Total Esk: 57 Panel B Total Esk: 39		Japan

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Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
TRD3006 (Planned)	NCT03434041	Randomized, double-blind, multicenter, parallel-group, controlled study (ONGOING, not yet initiated)	Esketamine (ESK) 56 mg or 84 mg (flexible) or placebo, twice weekly intranasal, plus newly-initiated oral antidepressant (AD)	Primary: CFB in MADRS Total Score at Week 4	4-week treatment phase plus follow-up	N/A (currently recruiting, 234 target)	Adults with TRD (18 to 64 years)	Pending (US and China currently)
TRD2001	NCT01640080	Double-blind, double-randomization, placebo-controlled, multiple dose study	Esketamine (ESK) IV 0.20 mg/kg or 0.40 mg/kg or placebo, doses on Day 1 and Day 4. Optional open-label ESK IV 0.40 mg/kg twice a week for 2 more weeks during follow-up phase.	CFB in MADRS Total Score at 24 hours post-dose	7-Day treatment phase (Day 1 and Day 4 dosing) and 4 week post-treatment phase (including 2-week optional open-label phase, dosed twice per week)	30 total, with 11 on IV ESK 0.40 mg/kg, 9 on IV ESK 0.20 mg/kg, and 10 on placebo on Day 1. Then re-randomized with 21 on IV ESK 0.40 mg/kg and 9 on IV ESK 0.20 mg/kg on Day 4. 26 then received optional open-label treatment.	TRD (18 to 64 years)	8 sites (Belgium, Germany, Poland)

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
SUI2001	NCT02133001	Randomized, double-blind, multicenter, parallel-group, controlled study	Initial hospitalization plus oral AD; Screening within 24 hours of study drug dose, then 25-day double-blind treatment phase on ESK or placebo, twice weekly	Primary: CFB in MADRS Total Score at Hour 4/Day 1	Initial hospitalization plus oral AD; Screening within 24 hours of study drug dose, then 25-day double-blind treatment phase; 56-day follow-up phase	66 total; 31 on ESK 56 mg + standard of care and 35 on placebo + standard of care	Adults with Suicidal Ideation in MDD (ages 19 to 64 years, initially hospitalized)	US
		Studies to Support Safety						
TRD3004 (SUSTAIN-2)	NCT02497287	Open-label, multicenter, long-term safety study	Esketamine (ESK) 28 mg (elderly only), 56 mg or 84 mg (flexible), or placebo (3005 only), twice weekly intranasal, plus newly-initiated oral antidepressant (AD) during	N/A	4-week induction phase (either direct-entry open-label or from 3005); then maintenance phase (open-label ESK weekly for 4 weeks, then weekly or	802 total (692 direct-entry, 111 from 3005); 779 during induction phase (691 new-entry, 23 3005 responders and 88 3005 nonresponders) ; 603 during maintenance phase (580	Adults with TRD (18 and over, including elderly)	114 sites at 21 countries worldwide including US

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			induction phase (either direct-entry open-label or from 3005); then maintenance phase (open-label ESK weekly for 4 weeks, then weekly or every other week + oral AD ongoing)		every other week + oral AD ongoing) for up to 48 weeks; 4-week follow-up phase for all subjects	from induction, 23 3005 responders)		
TRD3008 (SUSTAIN-3)	NCT02782104	Open-label, multicenter, long-term safety study (ONGOING, Not complete)	Esketamine (ESK) open-label, 28 (elderly only), 56, or 84 mg (flexible) IN; twice weekly during 4-week open-label induction phase for direct entry	N/A	4-week induction phase then maintenance phase ongoing long-term (up to 3 years estimated)	1092 total	Adults with TRD (18 and over including elderly)	222 sites at 27 countries worldwide including US

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			(others also transferred after induction phase from all other Phase 3 studies, responders only), then weekly for 1 st 4 weeks then weekly or every other week during maintenance phase					

*Unless otherwise noted, phase 2 and 3 studies opened with a 4-week screening phase before the treatment phase.

Additional Safety Studies Under Consideration:

- TRD1006: Phase 1 Driving Study (IN esketamine 84 mg vs. 30 mg mirtazapine; healthy volunteers)
- TRD1019: Phase 1 Driving Study (IN esketamine 84 mg vs. placebo; subjects with MDD)
- TRD1005: Phase 1 Cognition Study (IN esketamine 84 mg vs. placebo; healthy volunteers; (b) (4) as assessment tool)
- TRD1013: Phase 1 QT/QTc Study (IV esketamine vs. placebo or moxifloxacin; healthy volunteers)
- TRD1015: Phase 1 Abuse Potential Study (IN esketamine vs. IV ketamine or placebo; healthy volunteers who were polydrug users)

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- TRD1011: Phase 1 Hepatic Impairment Study (IN esketamine vs. placebo; healthy volunteers and medically stable volunteers with hepatic impairment)
- TRD1014: Phase 1 Renal Impairment Study (IN esketamine vs. placebo; healthy volunteers and medically stable volunteers with renal impairment)
- TRD1007: Phase 1 Allergic Rhinitis Study (IN esketamine vs. placebo with mometasone and oxymetazoline; healthy volunteers and volunteers with allergic rhinitis)
- Human Factors Study (subjects with MDD)
- Drug Interaction, Elderly, and Asian PK Studies (healthy volunteers)

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5.2. Review Strategy

Jean Kim, MD, MA completed the efficacy review. Qi Chen, MD, MPH completed the safety review.

The efficacy review will focus mainly on the four controlled phase 3 trials with double-blind phases, 3001 (TRANSFORM-1, fixed-dose, adult, parallel-group study), 3002 (TRANSFORM-2, flexible-dose, adult, parallel-group study), 3003 (SUSTAIN-1, adult randomized withdrawal maintenance study), and 3005 (TRANSFORM-3, flexible-dose, geriatric, parallel-group study). In addition to these adequate and well-controlled trials, we will review two phase 2 studies (Study TRD2001: fixed-dose, adult, parallel group study; and SUI2001: fixed-dose, adult, parallel group study in patients with imminent risk for suicide). The evidence from these phase 2 studies is considered supportive. Andrew Potter, PhD, our statistical reviewer replicated the Applicant's analyses; Dr. Potter also conducted additional analyses described below and in greater detail in his own review.

The safety review will examine the aforementioned studies, as well as 3004 (SUSTAIN-2, open-label, long-term 1-year safety study) and interim data from 3008 (open-label, long-term, multi-year safety study), as well as supplemental consideration of pertinent phase 1 and 2 trials, and preliminary trial data from the separate indication of treatment of suicidal ideation in MDD (including the completed phase 2 study SUI2001). The Applicant's Integrated Summary of Safety includes pooled data from 3001 and 3002. The safety review will also examine the 120-Day Safety Update Report submitted December 20, 2018.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 3001 (TRANSFORM-1)

6.1.1. Study Design

Overview and Objective

A Randomized, Double-blind, Multicenter, Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression: Trial of Rapid-acting Intranasal Esketamine for Treatment-resistant Major Depressive Disorder (TRANSFORM-1)

Trial Design

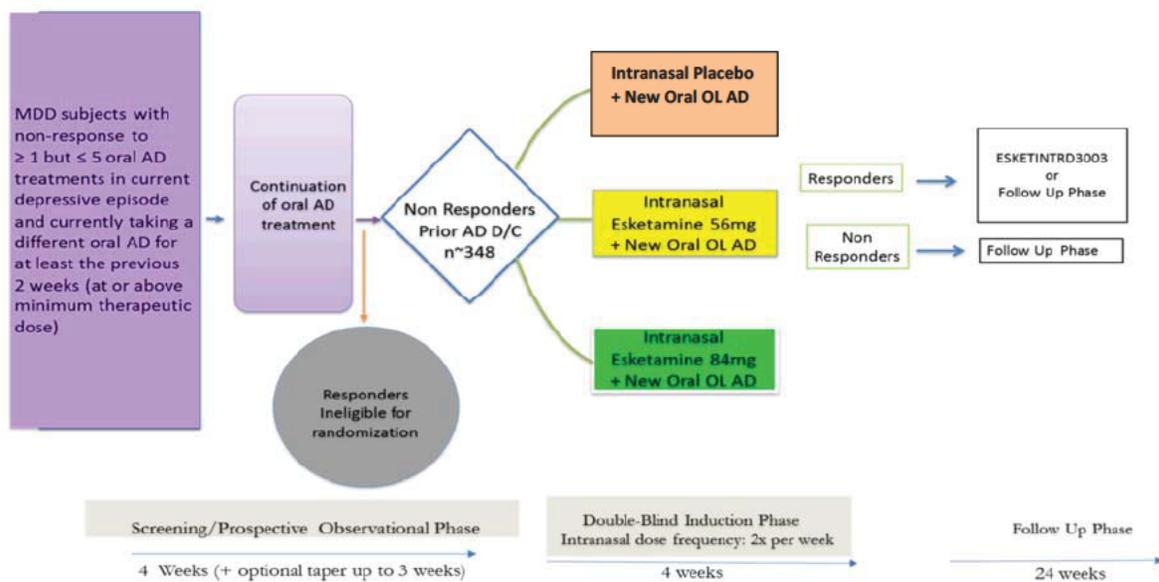
- *Basic study design:*

Study 3001 is a randomized, double-blind, controlled, multicenter study in adult subjects with TRD (ages 18 to 64 years).

This study had 3 phases:

- Screening Phase: Up to 4 weeks duration to prospectively observe and assess treatment response to subject’s current oral antidepressant treatment. Non-responders were deemed eligible to move on to the next phase. (See the next section on Diagnostic Criteria for the definition of non-response used.)
- Treatment Phase (Double-Blind Induction): Subjects were randomized 1:1:1 to receive twice-weekly intranasal doses of esketamine 56 mg, esketamine 84 mg, or placebo. At the time of randomization, all subjects discontinued their previous oral antidepressant and initiated daily open-label dosing with a new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended-release capsules). Subjects who were deemed “stable responders” (see definition below) were eligible to enter Study 3003 (maintenance of effect), or to enter the Follow-Up Phase. Non-responders entered the Follow-Up Phase.
- Follow-Up Phase: 24 weeks total duration to assess safety and tolerability of the study medication, including any withdrawal concerns. (The oral antidepressant was also continued for at least 2 weeks into follow-up, unless not deemed clinically appropriate by the investigator.)

Figure 1 Study 3001 Study Design Schematic



Source: Adapted from Study 3001 CSR Figure 1, page 29

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This study design allows one to examine both the more rapid effect of esketamine within Week 1 relative to placebo, as well as the effect relative to an oral AD with its slower onset of action by Week 4 (although the oral AD is ongoing in all treatment arms).

- *Choice of Controls:*

The study design incorporates currently accepted treatment algorithms for TRD involving a complete switch in treatment after lack of response. Intranasal placebo is the control group compared to intranasal ketamine, given in 2 fixed-dose comparator arms. Of note, several different oral antidepressants (two SSRIs and two SNRIs) were permitted as the background oral antidepressant. (The justification for doing so may be that all oral antidepressants have shown comparable effect sizes for treatment response in clinical trials.)

- *Trial location:*

Study 3001 was conducted at 92 sites in 9 countries; 42 sites in the US, 9 sites each in France, Belgium, and Mexico, 8 sites in Brazil, 5 sites each in Canada and Slovakia, 3 sites in Hungary, and 2 sites in Estonia.

- *Diagnostic (Key Inclusion) criteria:*

The diagnostic criteria for this trial and the others in the TRD program are based on criteria derived from both regulatory definitions (from FDA and EMA) and established research criteria (including those derived from the STAR*D trials). The following criteria are quoted from pages 24 to 25 of the Applicant's Clinical Overview:

Subjects were required to meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD or single-episode MDD (duration ≥ 2 years) without psychotic features, which was verified by the structured Mini International Neuropsychiatric Interview (MINI). Subjects must have been experiencing moderate to severe depressive symptomatology, as defined by a minimum total score on the investigator-rated Inventory of Depressive Symptomatology-Clinician rated, 30-item (ICD-C₃₀) (≥ 34 for TRD3001 and TRD3002; ≥ 31 for TRD3005), and have a MADRS total score of ≥ 28 for TRD3001 and TRD3002 and ≥ 24 for TRD3005 based on assessment by a remote, independent rater at Weeks 1, 2, and 4 of the screening/observational phase. In addition to assessing severity of depression, the qualitative and quantitative interview conducted by a remote rater, independent from the site, during screening assessed the diagnosis of depression and nonresponse to prior ADs to ensure appropriate subject selection for the studies.

In all controlled phase 3 studies, **treatment resistance** was defined in accordance with the regulatory definition, i.e., a lack of clinically meaningful improvement (defined for

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phase 3 studies as $\leq 25\%$) in the current episode of depression after treatment with at least 2 different AD agents prescribed in adequate dosages for an adequate duration (defined for phase 3 studies as at least 6 weeks). Subjects in the phase 3 short-term DB studies were required to have demonstrated nonresponse to at least 2 different oral ADs, with nonresponse to 1 AD demonstrated prospectively prior to randomization. The Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ), a reliable, and validated scale to determine treatment resistance in MDD, was used to document oral AD use and response (medication, dose, duration of treatment) in the current depression episode. Finally, written documentation of the MDD diagnosis and prior AD use from medical/pharmacy records was obtained.

1. Retrospective assessment of prior AD nonresponse in current episode of depression: all subjects in the phase 3 short-term studies were required to have had documented nonresponse ($\leq 25\%$ improvement per clinical judgment) to at least 1 oral AD treatment taken for the current episode of depression prior to the initial screening visit, at adequate dosage and for an adequate duration, as assessed on the MGH-ATRQ and confirmed by structured interview and documented records.
2. Prospective assessment of AD nonresponse: at the initial screening visit, subjects must have been receiving treatment for the current depression episode with a different oral AD for at least 2 weeks at or above the minimum therapeutic dose (per MGH-ATRQ). This drug was continued prospectively for 4 weeks during the screening/prospective observational phase. Only subjects who demonstrated (prospectively) nonresponse to the current oral AD after at least 6 weeks ($\leq 25\%$ 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 elderly subjects in TRD3005]), were eligible for randomization. Medication adherence was documented on the Patient Adherence Questionnaire during the screening/prospective observational phase to ensure that subjects took at least a minimum therapeutic dose of the current oral AD.

Of note, the Applicant submitted a protocol amendment (Amendment 2: May 31, 2016) in which the screening criteria for non-response in the current episode were clarified; subjects who had started their second antidepressant just before the screening phase had to have been taking it for at least 2 weeks at or above the therapeutic dose (for those on TCAs, verified by blood level) and continuously adherent (could not miss more than 4 days) before they could be designated as non-responders. They would have to continue this second antidepressant at or above the minimum therapeutic dose during the screening phase.

- *Key exclusion criteria:*

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- Previous history of non-response to ketamine or esketamine, or to all of the oral AD options for the induction phase, or to ECT (at least 7 treatments)
- History of VNS or deep brain stimulation in current episode of depression
- History of psychotic disorder (including MDD with psychotic symptoms), bipolar disorder, obsessive-compulsive disorder, intellectual disability, autism, cluster B personality disorder
- History of moderate or severe substance or alcohol use disorder within last 6 months before screening (and/or positive drug screen, unless due to prescribed medication that can be discontinued at least 1 week or 5 half-lives before treatment phase, or cannabis use that is negative as of Day 1 of treatment phase)
- History of homicidal ideation/intent
- History of suicidal ideation/intent within last 6 months prior to screening as noted via positive answers to Items 4 or 5 on C-SSRS, or during screening
- History of suicidal behavior in the past year before screening, or during screening
- QT prolongation ≥ 450 msec during screening ECG or other clinically significant arrhythmias
- Other major medical conditions including coronary artery disease

- *Dose selection:*

Doses of 56 mg and 84 mg IN esketamine and administration interval (2 treatment sessions per week over 4 weeks) were selected based on prior phase 1 PK and phase 2 dose response studies (with both IN and IV esketamine), particularly Panel A of Study 2003 which utilized these doses and this timing regimen.

- *Assignment to treatment:*

Subjects were randomized via a computer-generated randomization schedule. The randomization was balanced by using randomly permuted blocks (block size = 6) and was stratified by country and class of oral antidepressant (SNRI or SSRI) initiated during the double-blind induction phase. An interactive web response system (IWRS) assigned a unique treatment code providing the treatment assignment and matching medication kits for each subject. The investigator would add into IWRS which oral antidepressant each subject was taking.

- *Blinding:*

Randomization codes were maintained within IWRS to blind the investigators. (The blind could be broken for individual subjects as needed for emergency reasons after sponsor consultation.) Data that could unblind the treatment assignment (such as PK concentrations, treatment allocation) were handled with special care to maintain blinding. For unbiased efficacy evaluations, independent, remote (by phone), blinded MADRS raters were used to assess

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antidepressant treatment response. Any unblinding events (intentional or otherwise) were fully documented and dated, with subjects entering early withdrawal and follow-up phases. Investigators and site personnel remained blinded until study participation for each subject completed through the follow-up phase.

The placebo IN solution was designed to appear identical to esketamine IN; a bittering agent (denatonium benzoate) was added to placebo to simulate the taste of active drug. However, there were some gaps in blinding if common drug-related effects like marked increases in blood pressure or dissociative effects (both of which were stringently monitored) were detected. (For blood pressure, site personnel were instructed not to tell subjects about abnormal readings unless acute clinical intervention was required; however, those personnel may have become unblinded.)

- *Dose modification, dose discontinuation:*

In order to improve tolerability, subjects assigned to the 84-mg dose were started at 56 mg on Day 1, and then increased to 84 mg on Day 4 in a blinded fashion. No other esketamine dose adjustments were permitted in this study.

For the newly initiated oral antidepressant, a mandatory titration schedule (see Attachment 3 under Protocol Amendment 2) was outlined for each of the four drugs to be used. (The protocol amendment noted sometimes there were adjustments required in certain countries to conform to local prescribing information, but these instances were not specified.)

Table 3 Study 3001 Oral Antidepressant Dosing Schedule

Global titration schedule:

Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (Starting Day 1)	Week 2 (Starting Day 8)	Week 3 (Starting Day 15)	Week 4 (Starting Day 22)
Duloxetine	60 mg ^a	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

^aSubjects should be initiated with 60 mg/day. Subjects that have in the past shown increased sensitivity towards serotonin reuptake inhibitors (SSRI) /norepinephrine reuptake inhibitors (SNRI) can, at the discretion of the treating physician, be started on a 30 mg dose and up-titrated into the therapeutic range of 60 mg by the start of Week 2.

Source: CSR Study 3001

- *Administrative structure:*

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An Independent Data Monitoring Committee (IDMC) monitored the data to ensure ongoing safety. An interim IDMC meeting was conducted on May 18, 2017; no major concerns were identified. A higher AE incidence and dropout rate was noted in the 84-mg arm versus the 56-mg arm. Preliminary efficacy results appeared stronger in the 56-mg arm as well. No adjustments in sample size were recommended.

Contract research organizations (CRO) were involved with the randomization system and site rater training and qualifications (b) (4), data monitoring (b) (4), independent MADRS rating (b) (4), (b) (4), the interim analysis (b) (4), and medical monitoring (b) (4).

- *Procedures and schedule:*

Please see Section 13.1.1 in the Appendices.

- *Dietary restrictions/instructions:*

Subjects were not allowed to eat at least 2 hours before and during intranasal dosing sessions. This precaution was reasonable to prevent nausea or vomiting or aspiration issues.

- *Concurrent medications:*

QT-prolonging medications were prohibited. Other prohibited medications include: anticonvulsants, non-assigned antidepressants (even if used for non-depression indications), antipsychotics, chloral hydrate, clonidine, melatonin, ketanserin, metyrosine, CYP3A4 potent inducers, dextromethorphan, lithium, memantine, methyl dopa, oral anticoagulation agents, scopolamine, reserpine, thyroid hormone derivatives for depression, St. John's Wort, opioids.

Antihypertensive medications had to be taken in the morning before IN dosing.

Psychostimulants for non-MDD indications or other non-stimulant ADHD medications could be continued but not within 12 hours prior to IN dosing or 2 hours after. Benzodiazepines were permitted at doses less than the equivalent of 6 mg/day of lorazepam, but not within 12 hours of IN dosing or cognitive testing. Benzotropine and diphenhydramine could only be used on a PRN basis and not within 12 hours of cognitive testing. Systemic corticosteroids could only be used on a PRN basis.

Cognitive-behavior psychotherapy (CBT) could be continued but only if it had been ongoing for at least 3 months prior to entering screening. CBT could not be initiated during the study until after the double-blind induction phase. All other forms of psychotherapy could be continued or newly initiated during the study and were to be recorded as concomitant therapy.

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ECT, DBS, TMS, and VNS were prohibited from study entry until the end of the double-blind induction phase.

- *Treatment compliance:*

Antidepressant treatment adherence was assessed during screening using the Patient Acceptability Questionnaire (PAQ), a brief 2-item subject-report outcome measure scored from 0 to 2. Missing 4 days or more of antidepressant medication in the prior 2-week period during screening was considered inadequate adherence.

During the double-blind induction phase, investigators or designated personnel maintained logs of all IN and oral medication dose administrations. After being educated on oral antidepressant treatment compliance, subjects were also asked to maintain diaries of oral antidepressant use from the double-blind phase into the follow-up phase. Drug supplies for each subject were counted and monitored throughout the study. All IN doses were self-administered and directly observed by study site investigators or their designees and then recorded in the eCRF.

Plasma PK concentrations were also monitored during the study.

- *Rescue medication:*

- For agitation or anxiety: as required, midazolam (maximum dose 2.5 mg orally or IM) or short-acting benzodiazepine.
- For nausea: as required, ondansetron (8 mg sublingually), metoclopramide (10 mg orally or IV or IM) or dimenhydrinate (25 to 50 mg, IV or IM).
- Unless clinically indicated, it was recommended that transient increases in BP following administration of intranasal study medication not be treated, as the BP typically returns to pre-dose values within 2 hours. The effect of any treatment could potentially result in hypotension.

- *Subject completion, discontinuation, or withdrawal:*

Subjects were defined as study completers if they finished the MADRS assessment at the end of the 4-week double-blind induction phase (i.e., Day 28 MADRS score). Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind induction phase were not considered completers. Follow-up phase completers had to complete the Week 24 MADRS assessment.

Subjects were to be withdrawn from the study if: lost to follow-up, withdrew consent, severe protocol violation (case-by-case basis), broken blind during double-blind induction phase, lack of efficacy, investigator-designated safety concern, QTcF change from baseline ≥ 60 msec AND QTcF > 480 msec, or QTcF > 500 msec, pregnancy, futility, or death. If subject withdrew before

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end of double-blind induction phase, an early withdrawal visit was to be conducted if possible. All reasons for withdrawal were to be documented in the eCRF.

Subjects could withdraw from the follow-up phase to enter one of the long-term safety or maintenance studies with investigator approval.

Every reasonable effort was to be made by study personnel to contact subjects lost to follow-up and determine reason for withdrawal, including at least 3 forms of contact.

Study Endpoints

Primary Endpoint:

- Montgomery-Asberg Depression Scale (MADRS) Total Score Change from Baseline at End of Week 4

Key Secondary Endpoints:

- MADRS Total Score Change from Baseline at Day 2 ($\geq 50\%$ response, maintained through Day 28 with no worse than 25% response and one excursion)
- Sheehan Disability Scale (SDS) total score change from baseline at Day 28
- Patient Health Questionnaire-9-Item Depression Module (PHQ-9) total score change from baseline at Day 28

Other Secondary Endpoints:

- MADRS Total Score Change from Baseline Responders ($\geq 50\%$ response, no worse than 25% response) and Remitters (MADRS ≤ 12) (with one excursion)
- MADRS Total Score CFB Onset of Response at Day 8 ($\geq 50\%$ response, maintained through Day 28 with no worse than 25% response and one excursion)
- Clinical Global Impression-Severity (CGI-S)
- Generalized Anxiety Disorder 7-Item Scale (GAD-7)
- European Quality of Life (EuroQol)-5 Dimensions-5 Level (EQ-5D-5L)

Safety Endpoints:

- Adverse event (AE) monitoring
- Clinical laboratory tests
- Vital signs/pulse oximetry
- Physical examination (including nasal)
- Electrocardiogram (ECG)
- Nasal Symptom Questionnaire (NSQ)

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- Columbia Suicide Severity Rating Scale (C-SSRS)
- Clinician Administered Dissociative States Scale (CADSS)
- Brief Psychiatric Rating Scale (4-item Positive Symptom Subscale): BPRS+
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S)
- Clinical Global Assessment of Discharge Readiness (CGADR)
- Physician Withdrawal Checklist 20-item (PWC-20)
- Bladder Pain-Interstitial Cystitis Symptom Score (BPIC-SS)
- Cognition testing: computerized cognitive test battery and Hopkins Verbal Learning Test-Revised (HVLTR)
- University of Pennsylvania Smell Identification Test (UPSIT)
- Smell Threshold Test (STT)

Other Analyses/Endpoints:

- PK levels (40 minutes and 2 hours post-dose on Day 4 and 22) of esketamine and noresketamine
- Pharmacogenomic biomarkers (Screening, Day 1, 8, and 25)

Statistical Analysis Plan

The initial statistical plan was based on a drop-out rate of 25% and recommended a sample size of 116 subjects per arm for 90% power.

The Full Analysis (FA) population was defined as all randomized subjects receiving at least one dose of IN study medication AND at least one dose of oral antidepressant during the double-blind induction phase. The Safety population was defined as all randomized subjects receiving at least one dose of IN study medication OR at least one dose of oral antidepressant during the double-blind induction phase.

To control for multiplicity, a truncated fixed sequence parallel gatekeeping approach was applied to control type I error across the primary and three key secondary endpoints (onset of clinical response by Day 2, change in SDS total score, change in PHQ-9 total score) and across each dose treatment comparison arm. The four endpoints were to be tested in order as just listed for each treatment arm. The 56-mg arm was only to be tested at the 1-sided 0.02125 level if the 84-mg arm reached significance at the 1-sided 0.025 level for a given endpoint, in order.

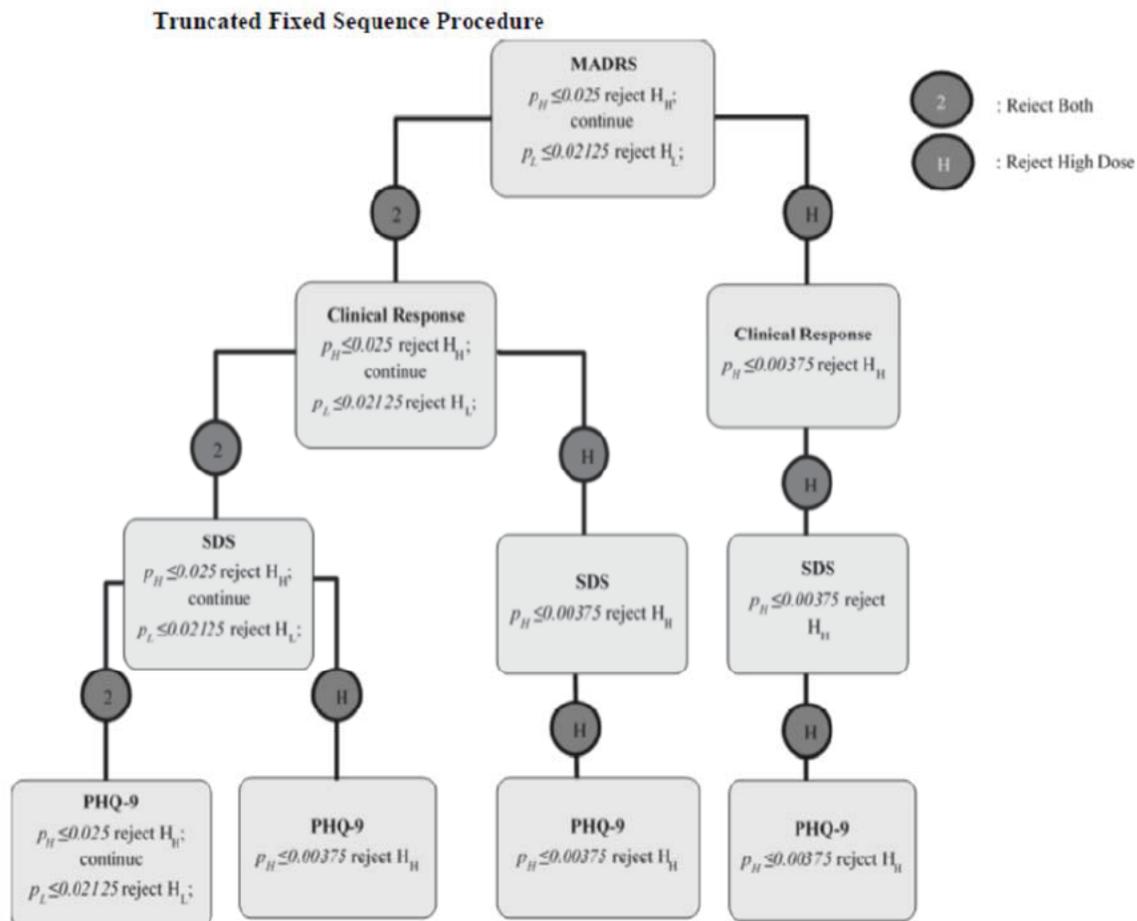
Except for the European Union (EU) sites, the primary endpoint (change from baseline in MADRS total score at Day 28) was to be analyzed using mixed-effects model with repeated measures (MMRM) based on observed case data. The EU used the analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data. These analyses were performed for each stage separately (before and after interim analysis) to account for sample

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size re-estimation. Other analyses included weighted combination test between Stage 1 and 2, Fisher's Exact Test between Day 2 responders on esketamine versus placebo, and independent MMRM/ANCOVA analyses of the key secondary endpoints.

An interim analysis was to be conducted to re-evaluate the sample size and preliminary efficacy (and stop the study for futility), 4 weeks after 120 subjects were enrolled.

Figure 2 Study 3001 Statistical Analysis Plan



Abbreviations: H_H : Null hypothesis for the higher dose (esketamine 84 mg); H_L : Null hypothesis for the lower dose (esketamine 56 mg); MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: patient health questionnaire – 9 item; SDS: sheehan disability scale. Adapted from Statistical Analysis Plan (SAP).

Source: Study 3001 CSR

Protocol Amendments

See discussion of Amendment 2 under the inclusion/diagnostic criteria section above.

6.1.2. Study Results

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Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with good clinical practice (GCP) as per CFR requirements.

Financial Disclosure

There are no major concerns. See Appendix 13.2 for more details.

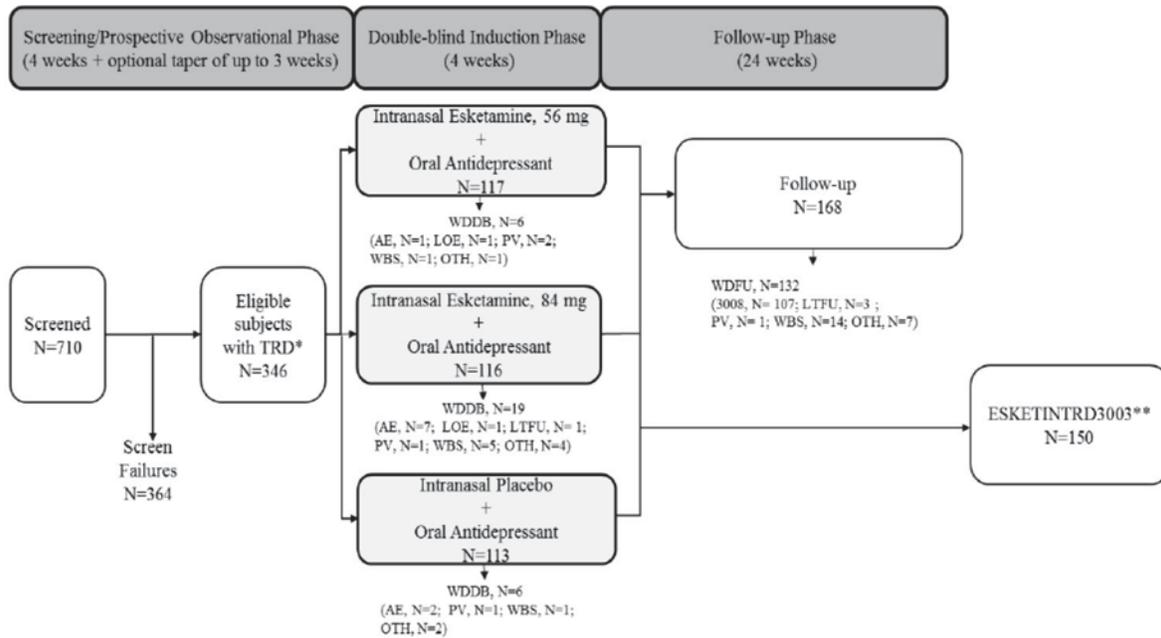
Patient Disposition

Table 4 Study 3001 Patient Disposition

	Intranasal Esk 56 mg + Oral AD (N=117)	Intranasal Esk 84 mg + Oral AD (N=116)	Oral AD + Intranasal Placebo (N=113)	Total (N=346)
All randomized	117 (100.0%)	116 (100.0%)	113 (100.0%)	346 (100.0%)
Full	115 (98.3%)	114 (98.3%)	113 (100.0%)	342 (98.8%)
Safety	115 (98.3%)	116 (100.0%)	113 (100.0%)	344 (99.4%)
Follow-up	47 (40.2%)	52 (44.8%)	69 (61.1%)	168 (48.6%)

Out of 346 subjects randomized to Study 3001, there were 315 (91%) who completed the double-blind induction treatment phase, and 31 subjects (9%) who withdrew. The withdrawal rate was higher in the 84-mg esketamine arm (16%) compared to 5% each in the 56-mg and placebo arms. Out of the 19 subjects who withdrew from the 84-mg arm, 11 withdrew after only the first intranasal dose (which was 56 mg before scheduled titration to 84 mg on Day 4). (This dropout timing indicates that the higher dropout rate in the 84-mg arm was not necessarily related to poorer tolerability on the higher 84-mg dose relative to 56 mg.)

Figure 3 Study 3001 Patient Disposition



Protocol Violations/Deviations

Table 5 Study 3001 Protocol Violations and Withdrawn Subjects

(Study ESKETINTRD3001: All Randomized Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=117)	Intranasal Esk 84 mg + Oral AD (N=116)	Oral AD + Intranasal Placebo (N=113)	Total (N=346)
Completed	111 (94.9%)	97 (83.6%)	107 (94.7%)	315 (91.0%)
Withdrawn	6 (5.1%)	19 (16.4%)	6 (5.3%)	31 (9.0%)
Adverse event	1 (0.9%)	7 (6.0%)	2 (1.8%)	10 (2.9%)
Lack of efficacy	1 (0.9%)	1 (0.9%)	0	2 (0.6%)
Lost to follow-up	0	1 (0.9%)	0	1 (0.3%)
Protocol violation	2 (1.7%)	1 (0.9%)	1 (0.9%)	4 (1.2%)
Withdrawal by subject	1 (0.9%)	5 (4.3%)	1 (0.9%)	7 (2.0%)
Other	1 (0.9%)	4 (3.4%)	2 (1.8%)	7 (2.0%)

[TSIDS01A.RTF] [JNJ-54135419\TRD3001\DBR_FINAL2\RE_CSR\PROD\TSIDS01A.SAS] 21MAR2018, 17:41
 Abbreviations: AD: antidepressant; Esk: esketamine.

There were four subjects who withdrew from Study 3001 due to protocol violations, across all three treatment arms; accordingly, there are no major concerns about imbalance in violations affecting study results.

- Esketamine 56 mg: abnormal thyroid function tests which should have met exclusion criteria, initially enrolled due to site error but withdrawn before receiving study drug

- Esketamine 56 mg: positive urine drug screen which should have met exclusion criteria, initially enrolled due to site error but withdrawn before receiving study drug
- Esketamine 84 mg: did not meet some consent criteria (changed desvenlafaxine dose against instructions during screening phase before randomization); withdrawn on Day 43.
- Placebo: did not meet non-response criteria but enrolled due to site error; withdrawn on Day 8.

Table 6 Study 3001 Major Protocol Deviations

(Study ESKETINTRD3001: All Randomized Analysis Set)

	Intranasal Esk 56 mg + Oral AD (N=117)	Intranasal Esk 84 mg + Oral AD (N=116)	Oral AD + Intranasal Placebo (N=113)	Total (N=346)
No. of subjects with protocol deviations	27 (23.1%)	29 (25.0%)	24 (21.2%)	80 (23.1%)
Developed withdrawal criteria but not withdrawn	2 (1.7%)	0	0	2 (0.6%)
Entered but did not satisfy criteria	19 (16.2%)	17 (14.7%)	16 (14.2%)	52 (15.0%)
Received a disallowed concomitant treatment	1 (0.9%)	4 (3.4%)	4 (3.5%)	9 (2.6%)
Received wrong treatment or incorrect dose	0	1 (0.9%)	0	1 (0.3%)
Other	7 (6.0%)	8 (6.9%)	9 (8.0%)	24 (6.9%)

[TSIDEM05.RTF] [JNJ-54135419\TRD3001\DBR_FINAL2\RE_CSR\PROD\TSIDEM05.SAS] 29MAY2018, 10:41

Major protocol deviations were reported for 80 of 346 subjects (23%), with 97 total deviations. The percentage and types of deviations was noted to be similar across treatment groups. Only one subject on esketamine 84 mg received one incorrect dose (56 mg) on Day 8 only.

Of the 346 randomized subjects, two subjects did not receive any study medication and were not included in the Safety or FA populations. Two additional subjects did not receive oral antidepressant medication (but did receive IN medication) and were included in the Safety population but not FA.

The reason for the higher number of withdrawals in the 84-mg arm remains unclear, although a higher percentage reported AEs (6%) as the reason compared to the other arms (1% on 56 mg and 2% on placebo).

Table of Demographic Characteristics

Table 7 Study 3001 Demographic Characteristics of the Primary Efficacy Analysis

Demographic Parameters	Control Group Placebo + Oral AD (N=113) n (%)	Treatment Group		Total (N=342) n (%)
		Treatment arm #1 IN Esketamine 56 mg +Oral AD (N=115) n (%)	Treatment arm #2 IN Esketamine 84 mg +Oral AD (N=114) n (%)	
Sex				
Male	32 (28%)	34 (30%)	35 (31%)	101 (30%)
Female	81 (72%)	81 (70%)	79 (69%)	241 (71%)
Age				
Mean years (SD)	46.8 (11.36)	46.4 (11.18)	45.7 (11.10)	46.3 (11.19)
Median (years)	47.0	48.0	47.0	47.0
Min, max (years)	(18; 64)	(22; 64)	(18; 64)	(18; 64)
Age Group				
18 to 44 years	45 (40%)	45 (39%)	48 (42%)	45 (40%)
45 to 64 years	68 (60%)	70 (61%)	66 (58%)	68 (60%)
Race				
White	86 (76%)	91 (79%)	85 (75%)	262 (77%)
Black or African American	5 (4.4%)	7 (6.1%)	7 (6.1%)	19 (5.6%)
Asian	2 (1.8%)	2 (1.7%)	1 (0.9%)	5 (1.5%)
American Indian or Alaska Native	0	0	1 (0.9%)	1 (0.3%)
Multiple	1 (0.9%)	0	0	1 (0.3%)
Other	10 (8.8%)	8 (7.0%)	11 (9.6%)	29 (8.5%)
Unreported	9 (8.0%)	7 (6.1%)	9 (7.9%)	25 (7.3%)
Ethnicity				
Hispanic or Latino	31 (27%)	33 (29%)	27 (24%)	91 (27%)
Not Hispanic or Latino	71 (63%)	74 (64%)	78 (68%)	223 (65%)
Unreported/Unknown	11 (9.7%)	8 (7.0%)	9 (7.8%)	28 (8.2%)
Region				
United States	45 (40%)	45 (39%)	45 (40%)	135 (40%)
Rest of the World				
Canada	6 (5.3%)	7 (6.1%)	6 (5.3%)	20 (5.8%)
Mexico	15 (13%)	14 (12%)	16 (14%)	45 (13%)
Brazil	18 (16%)	20 (17%)	19 (17%)	57 (17%)
Europe**	29 (26%)	29 (25%)	27 (24%)	85 (25%)
BMI (kg/m²)				
Underweight (<18.5)	0	2 (1.7%)	1 (0.9%)	3 (0.9%)
Normal (18.5 to < 25)	31 (27%)	32 (28%)	34 (30%)	97 (28%)
Overweight (25 to <30)	39 (35%)	39 (34%)	41 (36%)	119 (35%)
Obese (30 to <40)	35 (31%)	37 (32%)	32 (28%)	104 (30%)

Demographic Parameters	Control Group Placebo + Oral AD (N=113) n (%)	Treatment Group		
		Treatment arm #1 IN Esketamine 56 mg +Oral AD (N=115) n (%)	Treatment arm #2 IN Esketamine 84 mg +Oral AD (N=114) n (%)	Total (N=342) n (%)
Morbidly Obese (40+)	8 (7.1%)	5 (4.3%)	6 (5.3%)	19 (5.6%)
Hypertension Status				
Yes	24 (21%)	28 (24%)	20 (18%)	72 (21%)
No	89 (79%)	87 (76%)	94 (83%)	270 (79%)
Oral AD Class/Type				
SNRI	64 (57%)	65 (57%)	67 (59%)	196 (57%)
SSRI	49 (43%)	50 (44%)	47 (41%)	146 (43%)
Duloxetine	44 (49%)	49 (43%)	43 (38%)	136 (40%)
Venlafaxine XR	20 (18%)	16 (14%)	24 (21%)	60 (18%)
Sertraline	73 (21%)	24 (21%)	24 (21%)	73 (21%)
Escitalopram	73 (21%)	26 (23%)	23 (20%)	73 (21%)

**Europe included Belgium, Estonia, France, Hungary, Slovakia

There were no major discrepancies in demographic characteristics across treatment arms in this study. The majority of subjects in this study were white, female, mean age in the late 40s, employed (57% although this included dependent wife or husband) with elevated BMI scores (71% had overweight and above BMI). About 2/3rds were assigned to SNRIs versus SSRIs as the newly initiated oral antidepressant in this study, most commonly duloxetine (40%). A slightly higher number of subjects in the control group (49%) were assigned to duloxetine versus the drug treatment arms (43% on 56 mg and 38% on 84 mg).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The mean baseline total MADRS score in this study was 37.6 (± 5.51 SD), ranging from 18 to 53. (There were eight subjects whose baseline MADRS total score was less than 28, which was the inclusion criteria cutoff value: five on placebo (including one with the outlier score of 18), two on esketamine 84 mg, and one on esketamine 56 mg. Some of those subjects' scores had improved between screening and before their first intranasal dose, which technically was not a protocol violation. Despite their inclusion, the overall mean baseline score is higher than that seen in most previously approved antidepressant trials, which range from 28 to 36. Also, the overall mean baseline MADRS scores were still even across treatment arms.)

At least 57% met criteria for severe depression based on CGI-S scores (5). The mean duration of the current depressive episode was 202.9 weeks (± 290.24 SD). About 63% reported a family history of depression, 18% reported family history of alcohol abuse, and 12% family history of anxiety disorder. About 40% had a lifetime history of suicidal ideation per the C-SSRS, and 24% had a lifetime history of suicidal behavior. Distribution of these values across treatment arms

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was generally even and unremarkable.

Per the Applicant, about 9% of subjects had failed only one antidepressant and had recently initiated a second one before screening. The distribution across treatment arms was slightly uneven between drug versus placebo, with each drug arm having about 10.5% subjects each who had failed one previous antidepressant, versus 6.2% on placebo (which might indicate less treatment resistance in the drug arms versus placebo). However, there was still a notable placebo response in this study, so it is difficult to know if this distribution was really a factor. Also, the overall number of subjects failing three or more antidepressants (30% on 56 mg, 48% on 84 mg, 41% on placebo) was somewhat unevenly distributed and may be a stronger indication of treatment resistance in a given arm, particularly with the 84-mg arm. Also mean duration of the current depressive episode was longer in the 84-mg arm (212.7 weeks \pm 327.62) although the SD range is large. Previous lifetime history of suicidal ideation and behavior was similar across treatment groups (59 to 69%, 64% total).

In terms of number of major depressive episodes (including current episode), about 20% total in the study had only one episode. The distribution of these subjects was somewhat uneven, with only 13% in the 56-mg arm versus 22% in the 84-mg arm and 25% on placebo. It is hard to interpret if this would be a factor indicating less illness severity in the 56-mg arm versus the others, as it is still possible to have clinically significant treatment resistance within one severe depressive episode and multiple medication trials within that one episode.

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Table 8 Study 3001 Baseline Psychiatric Characteristics

Baseline Psychiatric History (Study ESKETINTRD3001: 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)	Total (N=342)
Age when diagnosed with MDD (years)				
N	115	114	113	342
Mean (SD)	30.3 (12.34)	32.1 (12.86)	31.8 (12.44)	31.4 (12.54)
Median	28.0	30.0	32.0	30.0
Range	(11; 61)	(9; 59)	(10; 63)	(9; 63)
Baseline MADRS total score				
N	115	114	113	342
Mean (SD)	37.4 (4.76)	37.8 (5.58)	37.5 (6.16)	37.6 (5.51)
Median	37.0	37.5	37.0	37.0
Range	(27; 50)	(25; 51)	(18; 53)	(18; 53)
Screening IDS-C30 total score				
N	115	113	113	341
Mean (SD)	47.4 (6.98)	46.9 (7.84)	47.6 (7.52)	47.3 (7.44)
Median	47.0	46.0	47.0	47.0
Range	(34; 71)	(34; 67)	(34; 68)	(34; 71)
Baseline CGI-S				
N	115	114	113	342
Mean (SD)	5.1 (0.66)	5.1 (0.73)	5.1 (0.69)	5.1 (0.69)
Median	5.0	5.0	5.0	5.0
Range	(4; 7)	(4; 7)	(3; 7)	(3; 7)
Baseline CGI-S category, n (%)				
N	115	114	113	342
Normal, not at all ill	0	0	0	0
Borderline mentally ill	0	0	0	0
Mildly ill	0	0	1 (0.9%)	1 (0.3%)
Moderately ill	18 (15.7%)	24 (21.1%)	14 (12.4%)	56 (16.4%)
Markedly ill	67 (58.3%)	59 (51.8%)	70 (61.9%)	196 (57.3%)
Severely ill	29 (25.2%)	29 (25.4%)	25 (22.1%)	83 (24.3%)
Among the most extremely ill patients	1 (0.9%)	2 (1.8%)	3 (2.7%)	6 (1.8%)
Baseline PHQ-9 total score				
N	115	114	113	342
Mean (SD)	20.3 (4.11)	20.7 (3.58)	20.8 (3.69)	20.6 (3.80)
Median	21.0	21.0	21.0	21.0
Range	(7; 27)	(7; 27)	(12; 27)	(7; 27)
Screening C-SSRS lifetime (a), n (%)				
N	115	113	113	341
No event	47 (40.9%)	41 (36.3%)	35 (31.0%)	123 (36.1%)
Suicidal ideation	40 (34.8%)	46 (40.7%)	49 (43.4%)	135 (39.6%)
Suicidal behavior	28 (24.3%)	26 (23.0%)	29 (25.7%)	83 (24.3%)
Screening C-SSRS past 6 or 12 months (a), n (%)				
N	115	113	113	341
No event	62 (53.9%)	60 (53.1%)	57 (50.4%)	179 (52.5%)
Suicidal ideation (past 6 months)	53 (46.1%)	53 (46.9%)	56 (49.6%)	162 (47.5%)
Suicidal behavior (past 12 months)	0	0	0	0
Duration of current episode (wks)				
N	115	114	113	342
Mean (SD)	202.8 (277.25)	212.7 (327.62)	193.1 (264.10)	202.9 (290.24)
Median	99.0	115.5	104.0	104.0

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	Intranasal Esk 56 mg + Oral AD (N=115)	Intranasal Esk 84 mg + Oral AD (N=114)	Intranasal Placebo (N=113)	Total (N=342)
Range	(12; 1525)	(12; 2288)	(6; 1720)	(6; 2288)
No. of previous antidepressant medications (b), n (%)				
N	113	114	113	340
1	12 (10.6%)	12 (10.5%)	7 (6.2%)	31 (9.1%)
2	67 (59.3%)	47 (41.2%)	60 (53.1%)	174 (51.2%)
3	29 (25.7%)	33 (28.9%)	32 (28.3%)	94 (27.6%)
4	2 (1.8%)	20 (17.5%)	12 (10.6%)	34 (10.0%)
5	2 (1.8%)	2 (1.8%)	2 (1.8%)	6 (1.8%)
6	1 (0.9%)	0	0	1 (0.3%)
No. of major depressive episodes including current episode, n (%)				
N	114	114	113	341
1	15 (13.2%)	25 (21.9%)	28 (24.8%)	68 (19.9%)
2-5	75 (65.8%)	69 (60.5%)	56 (49.6%)	200 (58.7%)
6-10	12 (10.5%)	12 (10.5%)	25 (22.1%)	49 (14.4%)
>10	12 (10.5%)	8 (7.0%)	4 (3.5%)	24 (7.0%)
Family history of depression, n (%)				
N	115	114	113	342
Yes	70 (60.9%)	71 (62.3%)	74 (65.5%)	215 (62.9%)
No	45 (39.1%)	43 (37.7%)	39 (34.5%)	127 (37.1%)
Family history of anxiety disorder, n (%)				
N	115	114	113	342
Yes	13 (11.3%)	16 (14.0%)	13 (11.5%)	42 (12.3%)
No	102 (88.7%)	98 (86.0%)	100 (88.5%)	300 (87.7%)
Family history of bipolar disorder, n (%)				
N	115	114	113	342
Yes	12 (10.4%)	9 (7.9%)	9 (8.0%)	30 (8.8%)
No	103 (89.6%)	105 (92.1%)	104 (92.0%)	312 (91.2%)
Family history of schizophrenia, n (%)				
N	115	114	113	342
Yes	7 (6.1%)	6 (5.3%)	5 (4.4%)	18 (5.3%)
No	108 (93.9%)	108 (94.7%)	108 (95.6%)	324 (94.7%)
Family history of alcohol abuse, n (%)				
N	115	114	113	342
Yes	23 (20.0%)	16 (14.0%)	21 (18.6%)	60 (17.5%)
No	92 (80.0%)	98 (86.0%)	92 (81.4%)	282 (82.5%)
Family history of substance abuse, n (%)				
N	115	114	113	342
Yes	12 (10.4%)	6 (5.3%)	9 (8.0%)	27 (7.9%)
No	103 (89.6%)	108 (94.7%)	104 (92.0%)	315 (92.1%)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

Doses of intranasal study medication were self-administered by subjects at each study site under direct supervision of the investigator or designee.

Oral antidepressant treatment was assessed by performing pill counts and drug accountability.

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The mean treatment compliance for each of the four oral antidepressants during the induction phase was greater than 92% in each treatment group.

The overall dosing exposure for IN study medication was as follows:

Table 9 Study 3001 Dosing Exposure

(Study ESKETINTRD3001: 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)
Number of days dosed			
1	0	9 (7.9%)	1 (0.9%)
2	1 (0.9%)	2 (1.8%)	2 (1.8%)
3	1 (0.9%)	0	0
4	3 (2.6%)	1 (0.9%)	1 (0.9%)
5	0	4 (3.5%)	1 (0.9%)
6	2 (1.7%)	2 (1.8%)	3 (2.7%)
7	7 (6.1%)	7 (6.1%)	6 (5.3%)
8	101 (87.8%)	89 (78.1%)	99 (87.6%)

It appears that the esketamine 84-mg arm did not reach as consistent levels of dosing exposure as the other two arms, likely due to the higher number of dropouts in that arm. It is unclear if this decreased average exposure affected that arm's results.

Plasma esketamine and noresketamine concentrations also verified consistent levels of study drug with regard to each dose arm, from Day 4 to Day 22.

Table 10 Study 3001 Plasma Esketamine and Noresketamine Concentrations

Plasma Esketamine Concentrations (ng/mL) Following Intranasal Administration of 56 mg Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	103	76.2	23.8	144	28.2	36.9
4	2 h	104	39.8	14.1	142	18.1	45.4
22	40 min	105	77.7	18.6	174	31.0	39.9
22	2 h	104	41.2	8.94	136	18.4	44.6

Adapted: Attachment TablePK01_ESKETINTRD3001

Plasma Esketamine Concentrations (ng/mL) Following Intranasal Administration of 84 mg Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	95	109	28.8	243	40.9	37.5
4	2 h	96	63.0	22.6	131	25.8	40.9
22	40 min	94	109	30.6	262	43.1	39.5
22	2 h	94	63.9	21.9	176	28.7	44.9

Adapted: Attachment TablePK02_ESKETINTRD3001

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Plasma Noreскетamine Concentrations (ng/mL) Following Intranasal Administration of 56 mg Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	103	91.2	10.2	303	70.4	77.1
4	2 h	104	118	13.3	302	52.1	44.2
22	40 min	105	105	5.47	316	70.6	67.6
22	2 h	104	119	5.54	239	49.5	41.6

Adapted: Attachment TablePK03_ESKETINTRD3001

Plasma Noreскетamine Concentrations (ng/mL) Following Intranasal Administration of 84 mg Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	95	114	8.30	494	111	97.0
4	2 h	96	174	12.8	409	78.7	45.3
22	40 min	94	123	7.88	476	97.3	78.8
22	2 h	94	185	42.1	416	86.9	47.0

Adapted: Attachment TablePK04_ESKETINTRD3001

Source: Tables 17 to 20, CSR Study 3001

Oral antidepressant exposure during the double-blind induction phase was as follows:

Table 11 Study 3001 Oral Antidepressant Exposure

Extent of Exposure to Oral Antidepressant; Double-blind Induction Phase (Study ESKETINTRD3001: Full Analysis Set)						
	Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)			Selective Serotonin Reuptake Inhibitors (SSRI)		
	Duloxetine	Venlafaxine XR	Total	Escitalopram	Sertraline	Total
Intranasal Esk 56 mg + Oral AD	(N=49)	(N=16)	(N=65)	(N=26)	(N=24)	(N=50)
Total duration, days						
Category, n (%)						
≤ 7	0	0	0	0	0	0
8 - 14	1 (2.0%)	0	1 (1.5%)	0	0	0
15 - 21	1 (2.0%)	0	1 (1.5%)	1 (3.8%)	1 (4.2%)	2 (4.0%)
22 - 28	26 (53.1%)	9 (56.3%)	35 (53.8%)	14 (53.8%)	15 (62.5%)	29 (58.0%)
>28	21 (42.9%)	7 (43.8%)	28 (43.1%)	11 (42.3%)	8 (33.3%)	19 (38.0%)
Mean (SD)	27.9 (3.35)	28.3 (0.70)	28.0 (2.93)	28.7 (3.33)	28.0 (3.29)	28.4 (3.29)
Median	28.0	28.0	28.0	28.0	28.0	28.0
Range	(11; 34)	(27; 29)	(11; 34)	(20; 42)	(15; 36)	(15; 42)
Intranasal Esk 84 mg + Oral AD	(N=43)	(N=24)	(N=67)	(N=23)	(N=24)	(N=47)
Total duration, days						
Category, n (%)						
≤ 7	3 (7.0%)	2 (8.3%)	5 (7.5%)	1 (4.3%)	4 (16.7%)	5 (10.6%)
8 - 14	1 (2.3%)	0	1 (1.5%)	1 (4.3%)	0	1 (2.1%)
15 - 21	1 (2.3%)	0	1 (1.5%)	1 (4.3%)	0	1 (2.1%)
22 - 28	23 (53.5%)	10 (41.7%)	33 (49.3%)	12 (52.2%)	8 (33.3%)	20 (42.6%)
>28	15 (34.9%)	12 (50.0%)	27 (40.3%)	8 (34.8%)	12 (50.0%)	20 (42.6%)
Mean (SD)	25.7 (7.00)	26.5 (7.50)	26.0 (7.13)	25.8 (7.18)	25.4 (10.50)	25.6 (8.97)
Median	28.0	28.5	28.0	28.0	28.5	28.0
Range	(2; 32)	(1; 33)	(1; 33)	(2; 33)	(1; 40)	(1; 40)
Oral AD + Intranasal Placebo	(N=44)	(N=20)	(N=64)	(N=24)	(N=25)	(N=49)
Total duration, days						
Category, n (%)						
≤ 7	0	1 (5.0%)	1 (1.6%)	0	0	0
8 - 14	0	0	0	2 (8.3%)	0	2 (4.1%)
15 - 21	2 (4.5%)	0	2 (3.1%)	0	0	0
22 - 28	24 (54.5%)	10 (50.0%)	34 (53.1%)	9 (37.5%)	14 (56.0%)	23 (46.9%)
>28	18 (40.9%)	9 (45.0%)	27 (42.2%)	13 (54.2%)	11 (44.0%)	24 (49.0%)
Mean (SD)	28.6 (3.49)	27.4 (5.17)	28.2 (4.08)	27.4 (6.21)	28.7 (1.99)	28.0 (4.57)
Median	28.0	28.0	28.0	29.0	28.0	28.0
Range	(17; 42)	(6; 31)	(6; 42)	(8; 34)	(26; 36)	(8; 36)

Note: Percentages are calculated with the number of subjects in each treatment group as the denominator.

Note: The duration of exposure is defined as the duration between the date of the first antidepressant exposure and the date of the last antidepressant exposure. It includes days on which subjects did not actually take medication.

Generally, subjects in each treatment arm had comparable rates of oral antidepressant exposure across all four options, with the majority at least 22 days or greater. As with

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esketamine exposure, the esketamine 84-mg arm had slightly lower mean exposure time on all oral antidepressants (25 to 26-day range) than the other two arms (27 to 28-day range). (This is likely due to the higher number of dropouts in that arm.) More subjects received duloxetine in all three arms as compared to the other three oral antidepressants.

Plasma concentrations and recorded dosing times confirmed consistent dosing exposures. The mean duration of exposure to esketamine and oral antidepressants was shorter in the 84-mg esketamine treatment arm than in the other two arms, and is consistent with the higher number of dropouts in that arm. Whether this decreased overall exposure explains the statistically insignificant efficacy in that arm is unclear and improbable aside from perhaps affecting overall sample population effects; esketamine should still induce some effect at each dose administration in a rapid-acting fashion in the remaining subjects, at immediate plasma levels higher than the 56-mg or placebo arms per the plasma concentration tables. Any additive contribution from the oral antidepressant would also probably remain consistent in the subjects who remained in the 84-mg arm relative to the other arms (and the median exposure values are the same across treatment arms).

Concomitant Medications:

Given the inclusion criteria in this study, all subjects had a history of being on prior antidepressants and had to be switched to a new one at the start of the double-blind induction phase. Venlafaxine was the most common prior oral antidepressant in the safety population (35%), followed by bupropion (32%), escitalopram (31%), fluoxetine (30%), and sertraline (29%).

During the induction phase, 89% of subjects used concomitant medications (89% on esketamine 56 mg, 91% on 84 mg, and 86% on placebo) with the most common ones being clonazepam (19%), acetaminophen (12%), lorazepam (12%), ibuprofen (12%), and alprazolam (11%). More subjects used clonazepam in the 56-mg arm (28%) than in the other arms (18% on 84 mg, 12% on placebo), but more used lorazepam in the opposite arms (8% on 56 mg versus 15% on 84 mg and 14% on placebo), and a similar number used alprazolam across all groups, so there was likely no dose- or drug-dependent pattern to the use of benzodiazepines in this study, or anything that confounded overall study results.

During the follow-up phase, 94% received concomitant medications, with the most common medications being similar to the induction phase but also including duloxetine.

Rescue Medications:

In terms of rescue medication use for AEs, a total of 30% of subjects on esketamine 56 mg, 36% of subjects on esketamine 84 mg, and 30% of subjects on placebo, with oral antidepressant ongoing in all arms required concomitant medications administered in response to an AE.

Table 12 Study 3001 Percentage of Subjects Who Used Medication for AEs of Interest

AE	Esketamine 56 mg+Oral AD (N=115)	Esketamine 84 mg+ Oral AD (N=116)	Placebo+Oral AD (N=113)
Nausea/Vomiting	6.1%	14%	2.7%
Anxiety/Panic Attack	4.3%*	5.2%	6.2%
Dissociation	2.6%	1.8%	0
BP Increased/HTN	0.9%	2.6%	1.8%
Agitation	0	1.8%	0
Depression	2.6%	0	0

*One additional subject on 56 mg with “anticipatory anxiety” not included, as AE was presumably pre-esketamine dose.

Source: Applicant Response to IR, November 12, 2018

Overall, there appeared to be increased use of rescue medications for certain AEs of interest in the esketamine arms versus the placebo arm, although use for anxiety was about the same between drug and placebo and not likely to have affected overall study efficacy results. There was a dose-dependent increase in rescue medication use for nausea/vomiting in particular.

Efficacy Results – Primary Endpoint

For the primary endpoint, investigators utilized the MADRS. The MADRS is a clinician-rated scale measuring depression severity and changes after antidepressant treatment. The scale contains 10 items scored from 0 (not present) to 6 (most severe) for a total possible score of 60. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, anhedonia, pessimistic thoughts, and suicidal thoughts. The recall period is 7 days.

The primary endpoint of change from baseline on the MADRS mean total score at Day 28 was not statistically significant for the study via MMRM analysis. The 84-mg esketamine arm was not significant at a one-sided <0.025 p-value; and due to the SAP prespecification to control for multiplicity, the 56-mg esketamine arm could not be analyzed afterwards with validated p-values. On an exploratory basis only, via one-sided p-value <0.02125, the 56-mg arm was nominally significant at 0.013. (The same trends were found using ANCOVA/LOCF analysis for the primary endpoint.)

At all earlier timepoints (Day 2, 8, 14, 22), the MADRS mean total score was decreased in both esketamine arms relative to the placebo arm; these differences were nominally significant at all time points except for Day 14. (Notably, there were nominally significant differences as early as Day 2, indicating a potential rapid effect in at least a subgroup of patients on esketamine.)

MADRS mean total scores in all arms decreased during the course of the 4-week study (with the

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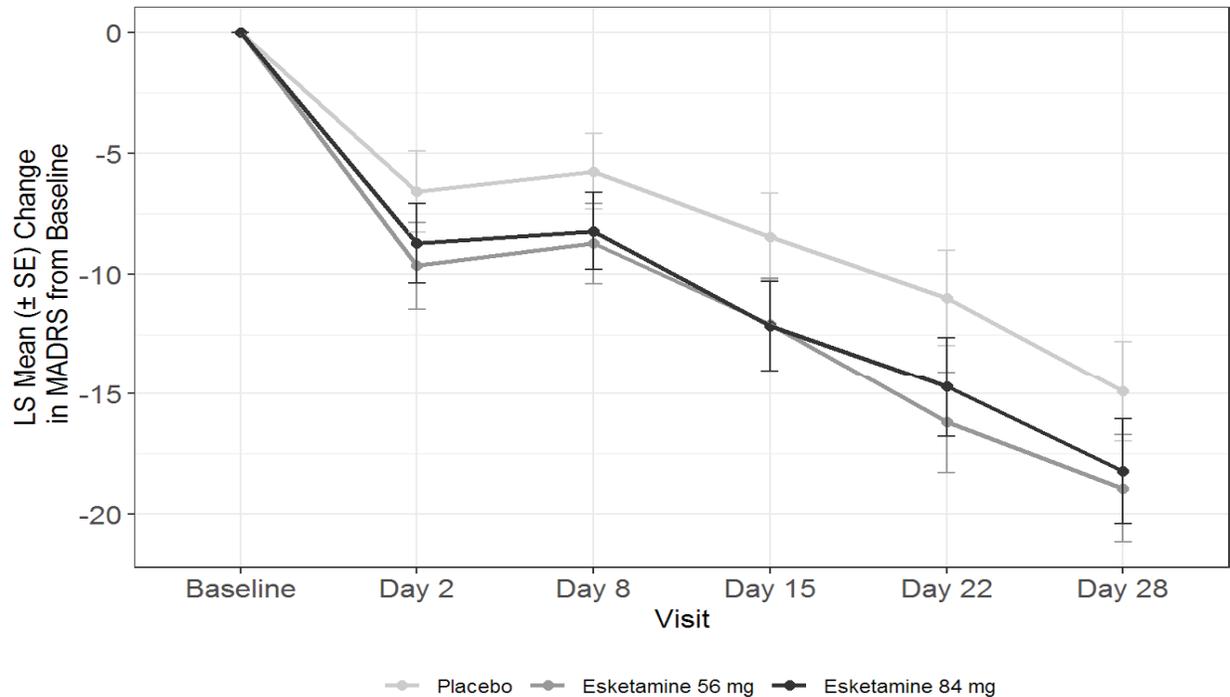
exception of a slight increase on Day 8, in all arms, relative to Day 2). The trend in all arms seemed to be continuing a steady downward trajectory at Day 28, so it is possible that more improvement on the MADRS could have occurred if the study had continued past Day 28. (The results of the 2-week follow-up phase endpoint seem to corroborate this hypothesis; it is unclear if increasing effect from the newly initiated oral antidepressant is also a factor. See the Persistence of Effect section below for more details.)

Table 13 Study 3001 MADRS Total Score Change from Baseline to Day 28

Treatment Arm	N	Baseline MADRS Total Score (SD)	Mean Change from Baseline (SD) at Week 4	LS Mean Change from Placebo (95% CI) at Week 4	1-Sided P-Value <0.025
Placebo+Oral AD	113	37.5 (6.2)	-14.8 (15.1)	--	--
Esketamine 56 mg+Oral AD	115	37.4 (4.8)	-19.0 (13.9)	-4.1 (-7.7 to -0.5)	0.013*
Esketamine 84 mg+Oral AD	114	37.8 (5.6)	-18.8 (14.1)	-3.2 (-6.9 to +0.5)	0.044

Source: Table 22, CSR Study 3001

Figure 4 Study 3001 Primary Efficacy Endpoint (MADRS Total Score LS Mean Change from Baseline)



TRD 3001 - Combined Estimates

Source: Andrew Potter, PhD, Statistical Reviewer

In terms of magnitude of effect, the overall MADRS total score decrease of -4.1 in the 56-mg arm, and even -3.2 in the 84-mg arm, at Day 28 is comparable to that seen in trial of most approved antidepressant, including adjunctive and TRD indications. Also, the decrease is relative to a higher average MADRS baseline total score (around 37.5) than the other trials, indicating a more severely ill study population. (Average MADRS baseline scores in the other antidepressant trials ranged from 28 to 36. See Table 62 in the Integrated Efficacy Summary section.)

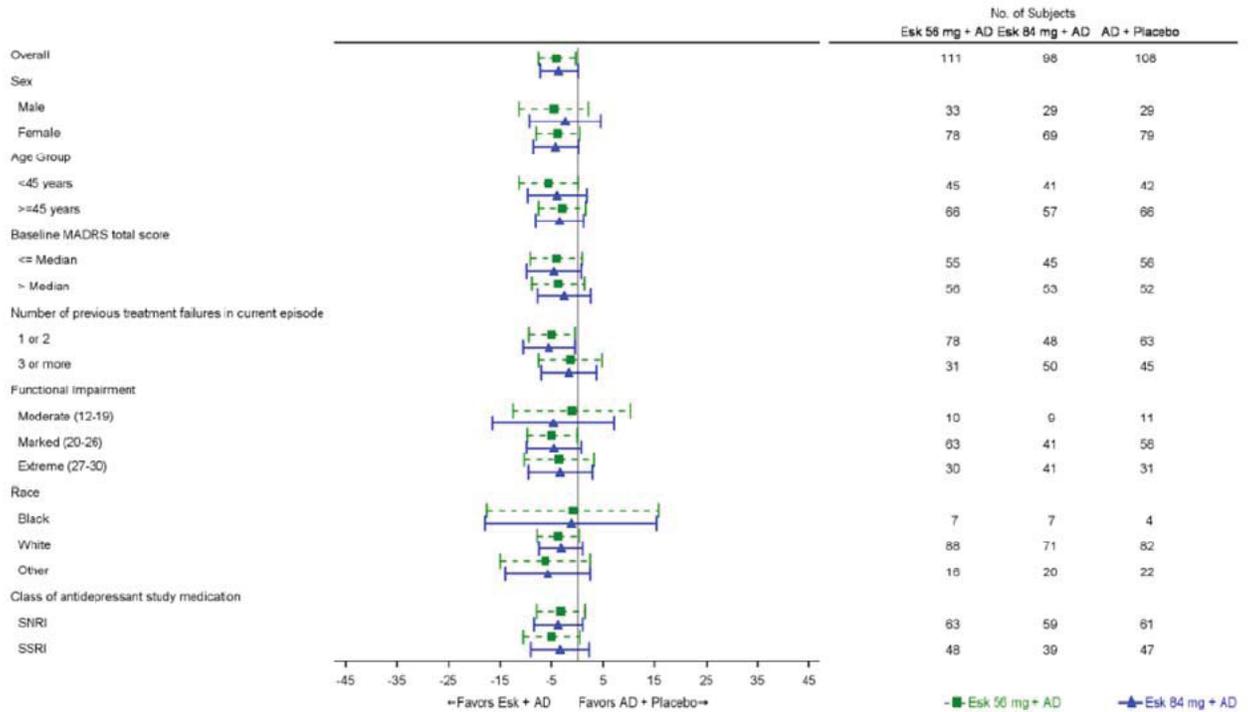
Subgroup Analyses of Primary Efficacy Endpoint

Subgroup stratifications to account for illness severity (such as prior antidepressant use and baseline MADRS scores) and demographics were reviewed as exploratory analyses.

The Applicant provided this Forest Plot of MADRS Total Score LS Mean Change from Baseline (CFB) at Day 28 based on various subgroup characteristics:

Figure 5 Study 3001 Subgroup Forest Plot

Forest Plot for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Least Squares Mean Treatment Difference of Change From Baseline (95% Confidence Interval) to Day 28 MMRM by Subgroup; Double-blind Induction Phase
 (Study ESKETINTRD3001: Full Analysis Set)



Source: Figure 5, CSR Study 3001

None of the above subgroup factors showed major differences in treatment response compared to the overall study population for each dose arm. All subgroup LS mean CFB values showed some improvement, though in some cases this change was small and in others the confidence interval overlapped worsening.

Males on esketamine 84 mg did not respond as well as on 56 mg, whereas females showed the opposite trend. Younger subjects less than 45 years seemed to respond better in both treatment arms (particularly 56 mg) than older ones. Subjects with higher baseline severity (greater than median MADRS baseline total score) in the 84-mg arm showed less response, where the opposite was true (slightly) in the 56-mg arm. Subjects who had failed 3 or more antidepressants showed less treatment response in both arms than those who had failed less. Subjects with moderate impairment on CGI-S did not respond much in the 56-mg arm versus placebo, compared to the other functional impairment levels and the 84-mg arm. Black subjects did not respond as well as white subjects, where “other” subjects responded better than either.

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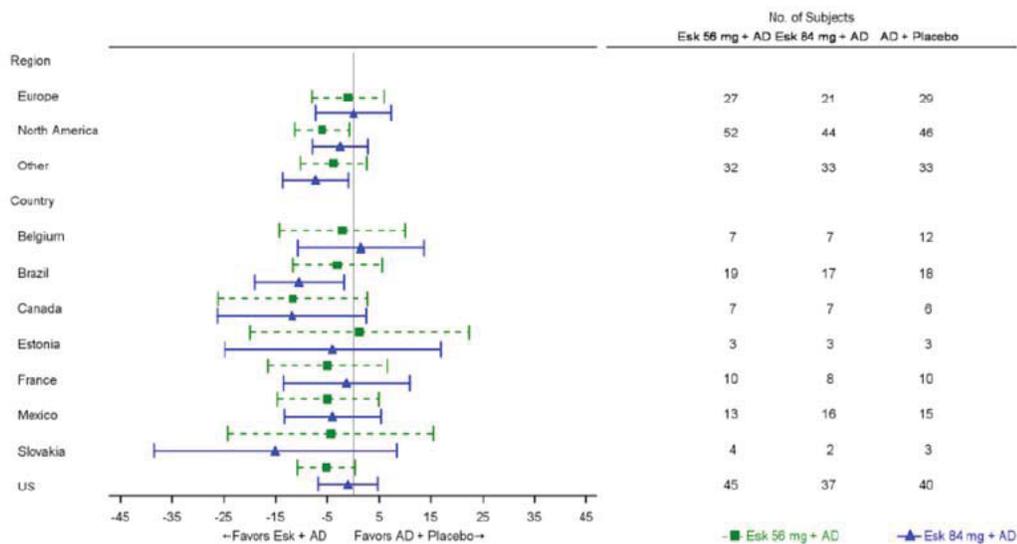
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Subjects on SSRIs responded slightly better in both esketamine arms than those on SNRIs.

Overall it seemed that subjects with more severe treatment-resistant characteristics, particularly in the 84-mg group, showed less treatment response on the primary outcome measure in Study 3001. Given the higher percentage of these baseline characteristics in the 84-mg group, this may have been a factor in its negative efficacy result; but it is not conclusive (especially as a similar trend was not evident in the 56-mg arm).

Figure 6 Study 3001 Geographical Region Subgroup Forest Plot

Forest Plot for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Least Squares Mean Treatment Difference of Change From Baseline (95% Confidence Interval) to Day 28 MMRM by Subgroup; Double-blind Induction Phase
(Study ESKETINTRD3001: Full Analysis Set)



Note: Subgroups with 5 or less number of subjects are not included.

Source: Figure 5, CSR Study 3001

When looking at the Forest Plot by region, the European subgroup overall showed almost no treatment effect in both arms versus placebo, as compared to the other regions. (However, the results varied widely by individual European countries.) The 84-mg arm showed less effect than the 56-mg arm in North America, but more effect in Latin America. Canada showed very robust effects in both arms, where the US showed good response in the 56-mg arm but minimal response in the 84-mg arm. There are no clear conclusions to be made based on this regional subgroup analysis, although at least the US subgroup did not favor placebo.

The Applicant also provided subgroup analyses by stages before and after the interim analysis

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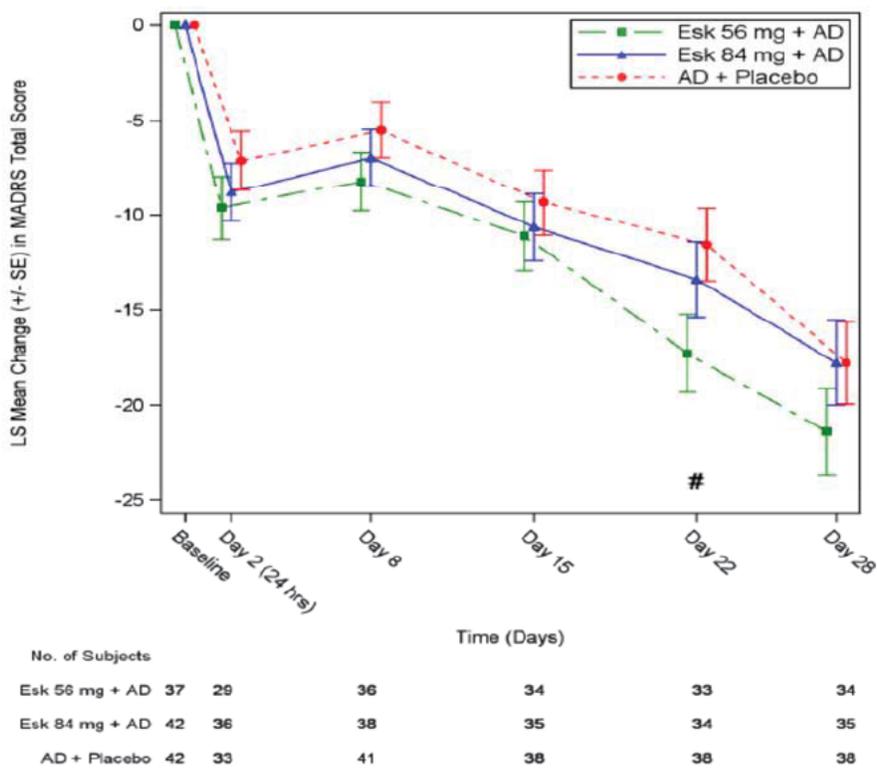
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(IA). Before the IA (Stage 1), the 84-mg arm showed 0 difference from placebo on the primary endpoint, and the 56-mg arm showed -3.6. After the IA (Stage 2), the 84-mg arm difference was -5.6, and the 56-mg arm difference was -4.5. The rationale for this difference is unclear, aside from there being fewer dropouts for the Stage 2 subgroup (possibly in part due to training procedures instituted to improve subject adherence taking effect for that phase). The Applicant also mentioned an even weighting scheme applied to each stage statistically for the primary endpoint analysis, even though the second stage had more subjects enrolled, which may have undervalued the result of that stage. It is still difficult to interpret this type of post-hoc analysis, although on face it appears a more robust treatment effect was evident in the 84-mg arm for Stage 2 without the early dropout issues from Stage 1.

Figure 7 Study 3001 Pre-Interim Analysis Stage 1 MADRS Total Score LS Mean CFB

Least Squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM for Stage 1; Double-blind Induction Phase

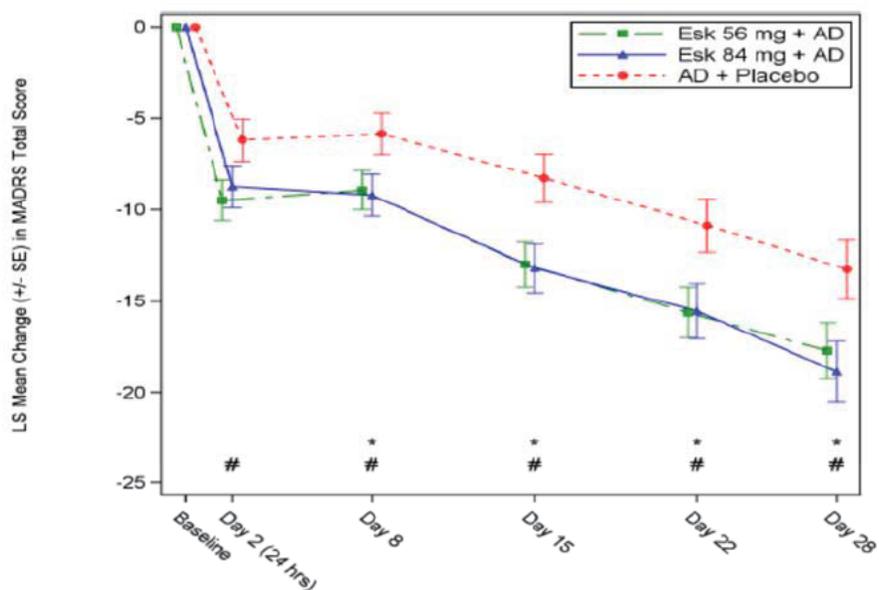
(Study ESKETINTRD3001: Full Analysis Set)



Source: Figure 6, CSR Study 3001

Figure 8 Study 3001 Post-Interim Analysis Stage 2 MADRS Total Score LS Mean CFB

Least Squares Mean Changes (+/- SE) in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time Observed Case MMRM for Stage 2; Double-blind Induction Phase
 (Study ESKETINTRD3001: Full Analysis Set)



	Time (Days)					
	Baseline	Day 2 (24 hrs)	Day 8	Day 15	Day 22	Day 28
No. of Subjects						
Esk 56 mg + AD	78	76	78	76	74	77
Esk 84 mg + AD	72	68	69	64	62	63
AD + Placebo	71	68	70	68	67	70

Source: Figure 7, CSR Study 3001

Data Quality and Integrity

OSI did not plan to conduct inspections for the sites in this study, due to the efficacy result on the primary endpoint not meeting significance.

It remains unclear why the 84-mg esketamine arm demonstrated poorer efficacy than the nominal result from the 56-mg arm, although the higher number of dropouts in the 84-mg arm may have affected its analysis. The higher dropout rate in the 84-mg arm did not necessarily appear dose-dependent, as most of the dropouts occurred very early, after the first dose which was only 56 mg. It may have just been unfortunate that too many subjects withdrew early from the 84-mg arm relative to its sample size and affected its results. Or it may have been that indeed the drug was not sufficiently efficacious versus placebo at that dose. (The PK results from Study 2001 indicated a clear dose-response curve from 56 to 84 mg, which the results of this study did not confirm. See the Clinical Pharmacology review for more details.)

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The interim analysis recommended a final sample size of 234, although this information was kept blinded except to Clinical Supplies staff until around 4 months after the data cutoff for the interim analysis. At that point, there was an ethical obligation to continue already screened and eligible subjects in the study, and accordingly, the total still ended up being near the originally planned sample size of 348, at 346 subjects.

Efficacy Results – Key Secondary Endpoints

Overall the key secondary endpoints provided equivocal support for the efficacy of esketamine at both doses in this study. Significance was not met for either treatment arm for the rapid onset measure of MADRS total score change by Day 2, the functional outcome measure of the SDS, or the validating depression measure of the PHQ-9.

- Onset of Clinical Response by Day 2 (24 Hours)

This was the first of three key secondary endpoints, where the p-values were evaluated in a testing sequence to account for multiplicity. A subject was defined as having a clinical response by Day 2 if there was at least 50% improvement (decrease) from baseline in MADRS total score, then maintained to Day 28. One excursion (non-response) on Days 8, 15, or 22 was allowed if at least 25% improvement occurred. Anyone who discontinued early was considered a non-responder. (The MADRS normally requires a 7-day recall period but was modified to use a 24-hour recall period for this endpoint.)

Both treatment groups were not statistically significant compared to placebo for this endpoint (per prespecifications to control Type I error, the esketamine 56-mg arm could only be tested if the 84-mg arm was significant, as with the primary endpoint; the 56-mg arm’s p-value would have been nominally significant, but interpretability of this result is unclear).

Table 14 Study 3001 Onset of Clinical Response by Day 2

Onset of Clinical Response Based on Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Fisher's Exact Test; Double-blind Induction Phase			
<i>(Study ESKETINTRD3001: Full Analysis Set)</i>			
	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)			
1-sided p-value (esk+AD vs. AD+placebo)	0.010 (e)	0.041 (e)	
Odds ratio (95% CI) (d)	6.47(1.38,60.45)	5.34(1.09,50.91)	

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Source: Table 28, CSR Study 3001

- Sheehan Disability Scale (SDS)

The second key secondary endpoint was used to assess functional impairment and disability, with the total score ranging from 0 to 30, and a decrease in total score indicating improvement. The endpoint was total score change from baseline at Day 28 versus placebo. Both MMRM and ANCOVA analyses were used for this endpoint.

The esketamine 56-mg arm missed nominal one-sided statistical significance on MMRM at 0.036 (0.02125 being the cutoff), where the 84-mg arm also missed one-sided nominal statistical significance at 0.059 (0.025 being the cutoff). Technically according to the prespecified analysis, neither p-value could then be considered valid in any case if the first key secondary endpoint was not statistically significant. The same trends were found on ANCOVA analysis as well.

Table 15 Study 3001 SDS Total Score Change from Baseline at Day 28

Sheehan Disability Scale (SDS) Total Score: Change From Baseline to Day 28 MMRM; Double-blind Induction Phase			
<i>(Study ESKETINTRD3001: Full Analysis Set)</i>			
	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	
1-sided p-value (esk + AD minus AD + placebo) (d)	0.036 (e)	0.059 (e)	

Source: Table 29, CSR Study 3001

- Patient Health Questionnaire-9-Item (PHQ-9) Total Score

The third key secondary endpoint used the PHQ-9, a self-report scale assessing depressive symptoms, with the total score ranging from 0 to 27 and decrease in score indicating

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improvement. Both MMRM and ANCOVA analyses were performed by the Applicant. The endpoint was total score change from baseline at Day 28 compared to placebo.

Both treatment arms were nominally significant on this endpoint versus placebo on MMRM analysis, but because of the prespecified analysis following a testing sequence, and relying on the SDS results which were not statistically significant, these p-values could not be validated. ANCOVA analysis of this endpoint was not even nominally significant in the esketamine 84-mg arm but was on 56 mg.

Table 16 Study 3001 PHQ-9 Total Score Change from Baseline at Day 28

Patient Health Questionnaire (PHQ-9) Total Score: Change From Baseline to Day 28 MMRM; Double-blind Induction Phase			
(Study ESKETINTRD3001: 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	
1-sided p-value (esk + AD minus AD + placebo) (d)	0.012 (e)	0.016 (e)	

Source: Table 31, CSR Study 3001

Efficacy Results – Other Secondary Endpoints

Of note, the following endpoints have not been controlled for multiplicity and/or have not been compared for statistical significance.

- Response Rates Based on MADRS Total Score

Treatment response for this secondary endpoint was defined as ≥50% reduction from baseline in MADRS total score for each induction phase visit timepoint in the study. The percentage of subjects meeting the response definition was tracked for each timepoint. At every timepoint, there was a higher percentage of responders in both drug arms versus placebo, sometimes more than double the percentage. The percentage of responders also continued to increase in

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all arms as the study progressed, reaching around 53 to 54% response in the drug arms by Day 28, versus 39% on placebo. The same trend was seen when using LOCF. This result provides supportive nominal evidence that there is a greater subgroup of treatment responders to esketamine as compared to placebo, when combined with the newly initiated oral antidepressant; some of these responders show differentiation from placebo as early as Day 2 (24 hours) of starting esketamine treatment (which may be expected given esketamine’s possible rapid-acting profile). (Of course, these values have not been compared for statistical significance.)

Table 17 Study 3001 Responder Rates

Response Based on Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time for Observed Case and LOCF; Double-blind Induction

(Study ESKETINTRD3001: 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)
Day 2 (24 hrs)			
N	105	104	101
≥50% improvement	20 (19.0%)	17 (16.3%)	8 (7.9%)
<50% improvement	85 (81.0%)	87 (83.7%)	93 (92.1%)
Day 8			
N	114	107	111
≥50% improvement	21 (18.4%)	16 (15.0%)	5 (4.5%)
<50% improvement	93 (81.6%)	91 (85.0%)	106 (95.5%)
Day 15			
N	110	99	106
≥50% improvement	29 (26.4%)	25 (25.3%)	15 (14.2%)
<50% improvement	81 (73.6%)	74 (74.7%)	91 (85.8%)
Day 22			
N	107	96	105
≥50% improvement	52 (48.6%)	33 (34.4%)	25 (23.8%)
<50% improvement	55 (51.4%)	63 (65.6%)	80 (76.2%)
Day 28			
N	111	98	108
≥50% improvement	60 (54.1%)	52 (53.1%)	42 (38.9%)
<50% improvement	51 (45.9%)	46 (46.9%)	66 (61.1%)

Source: Table 33, CSR Study 3001

- Remission Rates Based on MADRS Total Score

This secondary endpoint examined the percentage of subjects who achieved full remission of their depressive episode, as defined by a MADRS total score of ≤12, during each study visit timepoint during the induction phase. The percentage of subjects achieving remission was higher in both drug arms than placebo at every timepoint in the study; the percentage also continued to increase in all arms as the study progressed to its endpoint. By the study endpoint, the drug arms had reached 36 to 39% in remission versus 31% on placebo. The same trends

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were seen when using LOCF analysis. Again, this endpoint provides supportive nominal evidence that there is a subgroup of patients who are more responsive, to the point of achieving remission, on esketamine versus placebo, plus a newly initiated oral antidepressant. Some of these remitters show this greater response as early as Day 2 (24 hours).

Table 18 Study 3001 Remitter Rates

Remission Based on Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time for Observed Case and LOCF; Double-blind Induction Phase			
(Study ESKETINTRD3001: 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)
Day 2 (24 hrs)			
N	105	104	101
<=12	11 (10.5%)	8 (7.7%)	3 (3.0%)
>12	94 (89.5%)	96 (92.3%)	98 (97.0%)
Day 8			
N	114	107	111
<=12	9 (7.9%)	11 (10.3%)	1 (0.9%)
>12	105 (92.1%)	96 (89.7%)	110 (99.1%)
Day 15			
N	110	99	106
<=12	20 (18.2%)	15 (15.2%)	9 (8.5%)
>12	90 (81.8%)	84 (84.8%)	97 (91.5%)
Day 22			
N	107	96	105
<=12	29 (27.1%)	21 (21.9%)	17 (16.2%)
>12	78 (72.9%)	75 (78.1%)	88 (83.8%)
Day 28			
N	111	98	108
<=12	40 (36.0%)	38 (38.8%)	33 (30.6%)
>12	71 (64.0%)	60 (61.2%)	75 (69.4%)

Source: Table 34, CSR Study 3001

- Response Rates Based on SDS Score

Treatment response based on the SDS was defined as SDS total score ≤12 and individual item scores each ≤4. This secondary endpoint examined the percentage of treatment responders at Day 15 and Day 28 during the induction phase. While at Day 15, there was a higher percentage of responders in both drug arms compared to placebo (28% on 56 mg and 20% on 84 mg versus 7% placebo), by Day 28, the percentage of responders was almost even across treatment arms (40% in both drug arms versus 38% placebo). These results may indicate a subgroup of early functional responders on esketamine versus placebo, but no major difference by Day 28.

- Remission Rates Based on SDS Score

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Remission based on the SDS was defined as SDS total score ≤ 6 and individual item scores each ≤ 2 . This secondary endpoint examined the percentage of remitters at Day 15 and Day 28 during the induction phase. The percentage of remitters was higher in both drug arms than placebo at both timepoints (Day 15: 15% on 56 mg, 12% on 84 mg, 2% on placebo; Day 28: 32% on 56 mg, 30% on 84 mg, 21% on placebo) and showed an increase in all groups by Day 28. These results provide supportive evidence that there is a subgroup of functional remitters more responsive to esketamine versus placebo, plus a newly initiated oral antidepressant. It is unclear why the remission trend at Day 28 is different than the response trend for SDS at that timepoint. But given that remission is a higher standard to achieve, the result should be taken under consideration accordingly.

- Onset of Clinical Response by Day 8

This secondary endpoint examined early treatment response as based on MADRS total score showing at least 50% improvement from baseline at Day 8, that maintained efficacy through Day 28 at each following visit. One excursion (non-response) on Day 15 or 22 was permitted if at least 25% improvement was achieved. A higher percentage of subjects in both drug arms reached this response standard versus placebo (13% on 56 mg, 11% on 84 mg, 3.5% placebo), plus newly initiated oral antidepressant. Odds ratios for the drug arms versus placebo were 3.98 (95% CI: 1.28 to 12.31) for 56 mg and 3.83 (95% CI: 1.18 to 12.44) for 84 mg. An exploratory one-sided p-value was nominally significant for both drug arms versus placebo (0.005 for 56 mg and 0.009 for 84 mg). This result provides nominal support for esketamine providing earlier benefit (Day 8) to a subgroup of TRD patients versus placebo plus oral antidepressant that continued until Day 28.

- Clinical Global Impression-Severity (CGI-S)

The CGI-S provides a clinician-rated measure of the severity of a subject's illness rated on a scale from 0 to 7, with a decrease in score showing improvement. Median CGI-S scores improved in all treatment arms from baseline to endpoint (from 5 to 3 in both drug arms, and from 5 to 4 on placebo). The Applicant provided odds ratios and did an exploratory p-value comparison using ANCOVA and ranks of change from baseline. However, these values do not appear fully interpretable due to the use of LOCF with a categorical variable that has limited granularity and is more prone to skewing. No meaningful difference in illness severity outcome between drug arms versus placebo can be determined.

- Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a 7-item subject-reported assessment used to measure anxiety symptoms, with the total score ranging from 0 to 21, and a decrease indicating improvement. Cutoffs of 5, 10, and 15 correspond with mild, moderate, and severe anxiety respectively.

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Mean GAD-7 total scores improved from baseline to endpoint (Day 28) in all treatment groups, with difference from placebo of -1.5 on 56 mg and -1.4 on 84 mg. An exploratory ANCOVA analysis showed nominally significant one-sided p-values of 0.012 on 56 mg and 0.016 on 84 mg, but these results were not corrected for multiplicity.

Overall, there may be a slight trend towards greater improvement on esketamine versus placebo, plus a newly initiated oral antidepressant, by Day 28 for anxiety, which is worth noting giving the different mechanism of action for esketamine versus SSRIs and SNRIs, and the frequent comorbidity of anxiety and depression; SSRIs and SNRIs are already known to be anxiolytic in addition to being antidepressants due to their effects on serotonin and norepinephrine. (Per the safety review however, the rate of anxiety AEs may have been higher on esketamine versus placebo, possibly secondary to its dissociative effects.) At the very least, based on the GAD-7 results alone, esketamine does not appear to worsen anxiety in these depressed patients relative to SSRIs or SNRIs.

- EuroQol Group 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L assessment is a 2-part, subject-reported instrument consisting of the EQ-5D-5L descriptive system and the European Quality of Life-Visual Analog Scale (EQ-VAS), a health outcome measure. The descriptive system examines five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated from Level 1 to 5, with 5 indicating “extreme problems” versus Level 1 indicating “no problem”, for a given day. The responses are used to generate a health status index (FSI) using crosswalk value sets, rated from 0 (dead) to 1 (full health). (An increase in HSI indicates improvement.) Changes in HSI of 0.03 to 0.07 are considered a threshold of meaningful change for a given subject. The VAS is self-rated from 0 (worst health you can imagine) to 100 (best health you can imagine), with an increase indicating improvement. Changes in VAS from 7 to 10 are considered a threshold of meaningful change for a given subject. There is also a sum score measure derived from the 5 dimension score, scored from 0 to 100, which decreases with improvement.

For Study 3001, the mean HSI change from baseline showed improvement in all treatment arms by Day 28/Endpoint (+0.224 for 56 mg, +0.243 for 84 mg, +0.181 for placebo). The mean VAS score also improved by Day 28/Endpoint (+20.9 for 56 mg, +19.1 for 84 mg, +14.9 for placebo). The mean sum score showed the same trend of improvement (-19.0 for 56 mg, -19.4 for 84 mg, -14.6 for placebo).

Overall, the raw scores indicate greater improvement in the drug arms versus placebo by study endpoint, although no comparative p-value analysis was performed. The degrees of self-reported meaningful change were high relative to the thresholds provided by the assessment. This measure provides some evidence of patient-reported meaningful change in functional outcome and quality of life improvement for the treatment interventions provided in this study, and a possible (if statistically unsubstantiated) greater improvement on esketamine versus

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placebo, plus a newly initiated oral antidepressant.

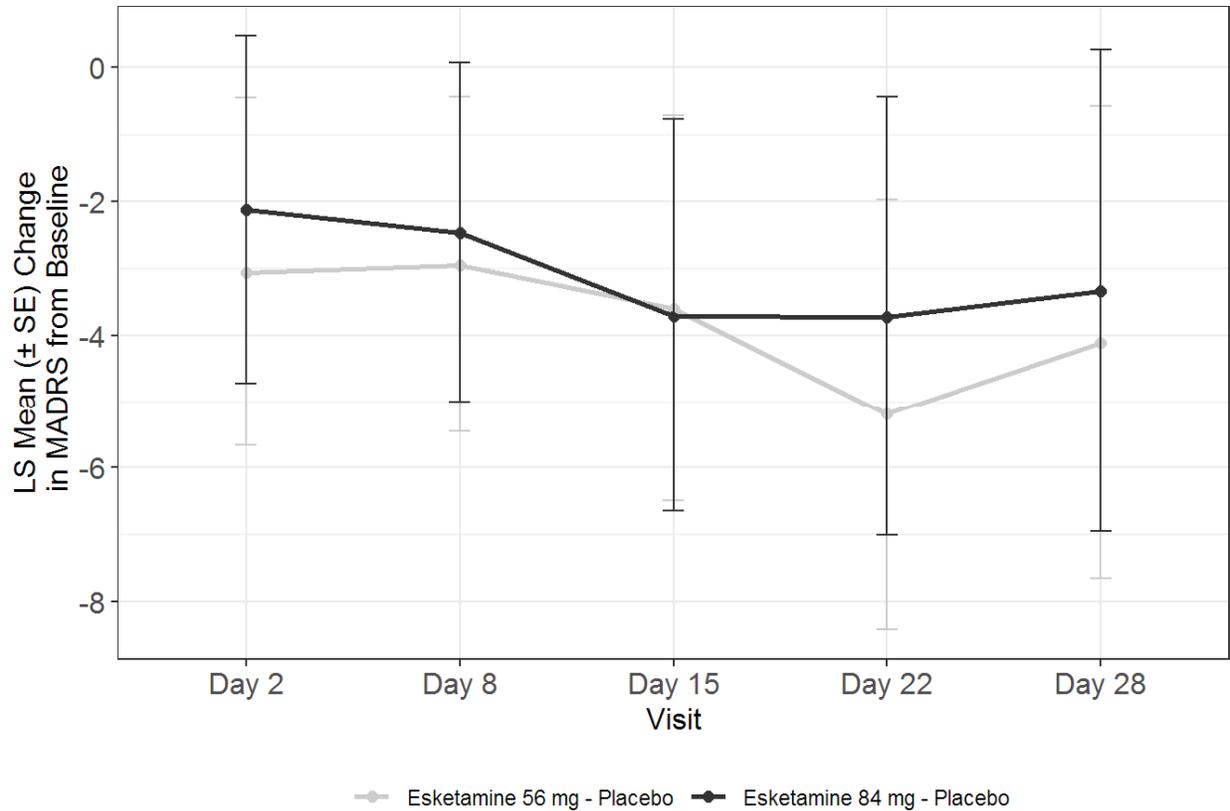
Dose/Dose Response

Despite the fixed-dose design of this study, dose response is difficult to interpret, given the overall weaker efficacy values in the 84-mg arm compared to the 56-mg arm. The higher number of dropouts in the 84-mg arm also affects interpretability of the fixed-dose comparison between these arms. On face, reviewing the totality of outcome measure results, this study does not support the conclusion that the higher dose is more effective than the lower dose of esketamine. (If esketamine is approved, and there is no way to extrapolate sufficient dose response data from the other non-fixed dose studies, a postmarket repeat dose response study may need to be considered to justify the higher dose's efficacy moving forward, as the higher dose is still associated with some increased adverse event (AE) rates compared to the lower dose. However the increased rates and type of AEs do not appear severe enough to warrant a dosing restriction. See the safety review for more AE details.)

Durability of Response

It appeared in this study that esketamine dosed twice weekly demonstrated an ongoing effect over the 4-week induction period, as the treatment response curves (see Figure 4 Study 3001 Primary Efficacy Endpoint (MADRS Total Score LS Mean Change from Baseline)) continued to trend steadily towards improvement at Day 28, without leveling off. The placebo group also showed similar trends though, which may reflect the parallel effects of the newly initiated oral antidepressant. At the very least, esketamine did not show a weakening effect relative to placebo, as the oral antidepressant should have increased in effect throughout the induction phase. Esketamine appeared to have a generally consistent "add-on" effect to the underlying oral antidepressant curve (based on the placebo + oral antidepressant arm) at all timepoints in this study. (An analysis in the statistical review of the baseline oral antidepressant trend appears to confirm this response effect.)

Figure 9 Study 3001 Placebo Subtracted LS Mean Change from Baseline in MADRS Total Score



Source: Andrew Potter PhD, Statistical Reviewer

Persistence of Effect

After Day 28, subjects were eligible to enter the Maintenance-of-Effect study 3003 or one of the open-label safety studies. Some still entered the follow-up phase to completion for up to 24 weeks, where their IN study drug or placebo was discontinued but their oral antidepressant was continued for at least 2 weeks. (Some may have also been subjects who withdrew early and/or had drug discontinued but still enrolled for some period of follow-up.) The study included examination of MADRS total score values and other secondary endpoints in those enrolled through the follow-up phase. (The degree of continuation of the oral antidepressant for each arm was somewhat unclear past 2 weeks.)

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Table 19 Study 3001 Follow-Up Phase MADRS Total Score Results

TEFMAD03B: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Means and Mean Changes From Baseline Over Time; Follow-up Phase (Study ESKE1NTRD3001: Follow-up Analysis Set)														
	N	Mean	SD	Median	Min	Max	Base Mean (SD)	Change From Baseline						
								N	Mean	SE	SD	Median	Min	Max
MADRS total score														
Intranasal Esk 56 mg + Oral AD														
Baseline	47	36.7	4.52	36.0	27	48								
End point(DB)	47	30.4	8.45	30.0	14	47	36.7 (4.52)	47	-6.2	1.06	7.27	-6.0	-20	11
Week 2(F/U)	40	29.1	10.71	30.5	5	49	35.9 (4.01)	40	-6.9	1.55	9.79	-5.5	-32	15
Week 24(F/U)	8	23.6	14.46	33.0	3	35	37.1 (5.19)	8	-13.5	4.20	11.88	-9.0	-33	-4
End point(F/U)	43	29.8	10.32	33.0	3	49	36.3 (4.16)	43	-6.5	1.41	9.25	-5.0	-33	15
Intranasal Esk 84 mg + Oral AD														
Baseline	52	37.9	5.58	37.0	26	51								
End point(DB)	52	31.0	9.31	32.0	1	49	37.9 (5.58)	52	-7.0	1.18	8.48	-5.5	-33	12
Week 2(F/U)	33	28.1	11.17	29.0	1	51	38.0 (5.87)	33	-9.9	1.63	9.36	-7.0	-33	5
Week 24(F/U)	11	29.5	11.81	29.0	11	52	37.2 (5.88)	11	-7.6	3.41	11.31	-11.0	-25	11
End point(F/U)	39	28.6	11.70	29.0	1	52	37.7 (5.78)	39	-9.1	1.63	10.20	-7.0	-33	11
Oral AD + Intranasal Placebo														
Baseline	69	36.3	6.09	36.0	18	49								
End point(DB)	69	31.2	8.87	31.0	2	48	36.3 (6.09)	69	-5.2	1.05	8.71	-5.0	-42	21
Week 2(F/U)	51	31.1	10.42	33.0	4	50	37.4 (5.38)	51	-6.3	1.20	8.58	-5.0	-33	9
Week 24(F/U)	19	28.5	11.70	32.0	3	44	33.5 (6.28)	19	-5.0	2.27	9.88	-2.0	-27	10
End point(F/U)	64	30.8	10.59	32.5	3	50	36.5 (5.97)	64	-5.6	1.06	8.51	-4.0	-33	10

Source: CSR Study 3001

On the MADRS total score, mean CFB values continued to improve (decrease) for all groups by Week 2 of follow-up. The interpretability of this result is somewhat affected by the number of dropouts by that time. The Week 24 and follow-up endpoint results are not interpretable, as the number of dropouts as the follow-up phase continued was even higher, with only 19 subjects on esketamine and 19 on placebo remaining by Week 24, and heavy reliance on LOCF values for the final follow-up endpoint value.

These results possibly indicate at least 2 weeks of persistence of improvement (based on decreasing MADRS total mean scores) after stopping esketamine 2 weeks into the follow-up phase, compared to placebo which stayed about the same (with oral antidepressant ongoing in all arms), although interpretability is limited. At the very least, there does not seem to be an acute worsening rebound or withdrawal effect in the remaining follow-up subjects by Week 2 post-discontinuation in this study. (The ongoing oral antidepressant may have continued to take effect during this period, reaching Weeks 5 and 6 post-initiation. The twice-weekly esketamine dosing regimen during acute treatment may also be a factor, as compared to the more infrequent dosing studied for maintenance effects in 3003.)

Again, due to high dropout rates, low sample size, and LOCF reliance, the total follow-up endpoint result is not interpretable.

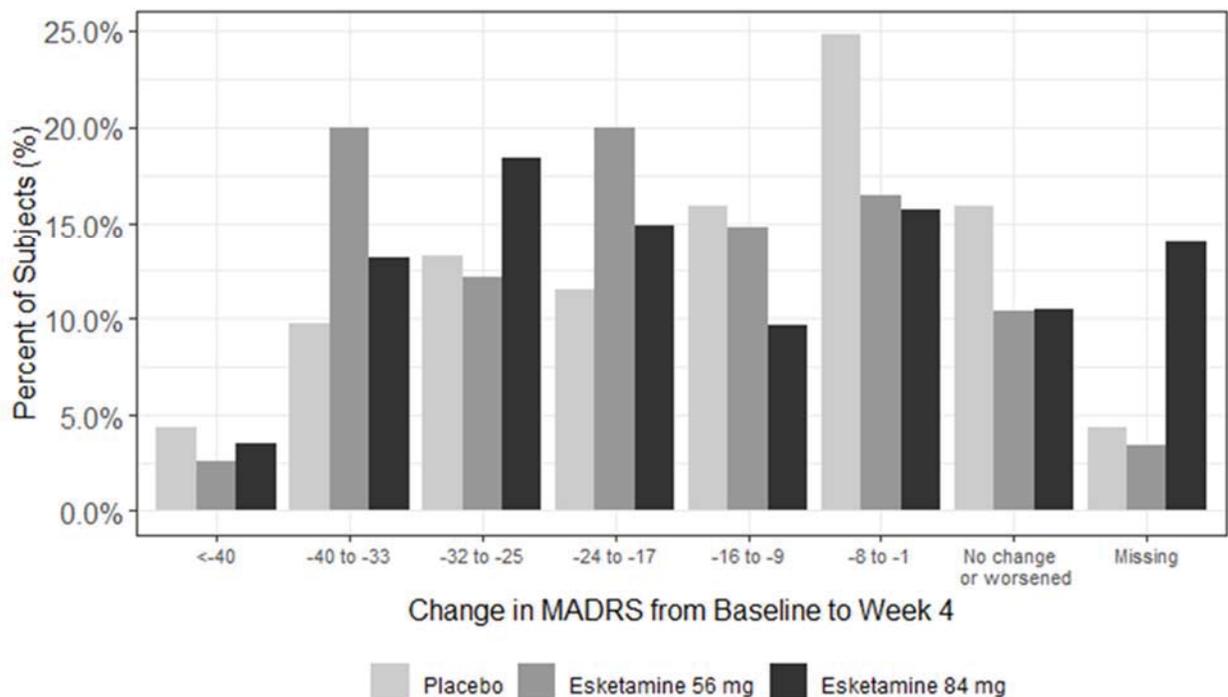
Additional Analyses Conducted on the Individual Trial

- Distribution of Response

Andrew Potter PhD, the statistical reviewer, looked at the distribution of response for the

primary endpoint by treatment arm. The bar graph shows a trend towards smaller MADRS total score reduction by Week 4 in more subjects in the placebo arm (with a higher percentage showing no change or only up to -8 change) as compared to the esketamine arms. Both esketamine doses generally showed a higher percentage of subjects with MADRS total score reduction greater than -16. This distribution seems to confirm the presence of a positive, clinically relevant esketamine effect versus placebo on MADRS total score reduction by Week 4 in at least a subgroup of subjects.

Figure 10 Study 3001 Distribution of Response for MADRS Total Score



Source: Andrew Potter PhD, Statistical Reviewer

6.2. Study 3002 (TRANSFORM-2)

6.2.1. Study Design

Overview and Objective

A Randomized, Double-Blind, Multicenter, Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-Resistant Depression: Trial of Rapid-Acting Intranasal Esketamine for Treatment-Resistant Major Depressive Disorder (TRANSFORM-2)

Trial Design

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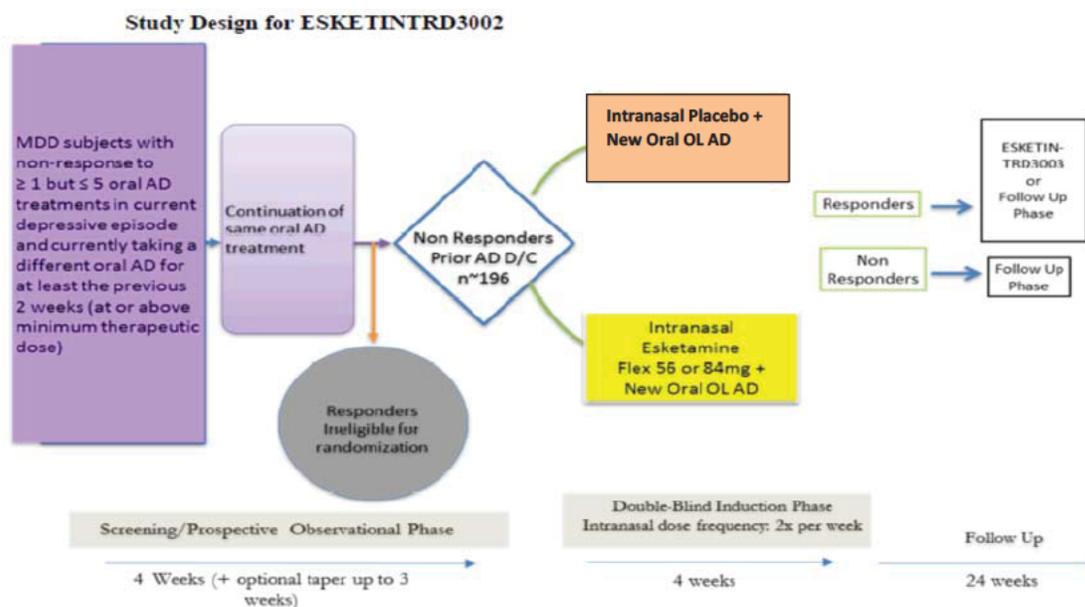
- *Basic study design:*

Study 3002 is a randomized, double-blind, controlled, multicenter study in adult subjects with TRD (ages 18 to 64 years).

This study had 3 phases:

- Screening Phase: Up to 4 weeks duration to prospectively observe and assess treatment response to subject's current oral antidepressant treatment. Non-responders were deemed eligible to move on to the next phase. An optional taper period of up to 3 weeks was offered to these non-responders. (See the next section on Diagnostic Criteria for the definition of non-response used.)
- Treatment Phase (Double-Blind Induction): 4 weeks total duration where subjects were switched to a new oral antidepressant for daily administration, and then also randomized to either receive intranasal esketamine (dosed flexibly from 56 to 84 mg), or placebo, twice a week. (Subjects who were responders were eligible to enter Study 3003 (maintenance of effect), or to enter the follow-up phase. Non-responders entered the follow-up phase.)
- Follow-Up Phase: 24 weeks total duration to assess safety and tolerability of the study medication, including any withdrawal concerns. (The oral antidepressant had to also be continued for at least 2 weeks into follow-up, unless not deemed clinically appropriate by the investigator.)

Figure 11 Study 3002 Study Design Schematic



Source: Adapted from Figure 1, CSR Study 3002

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This study design allows one to examine both the more rapid effect of esketamine within Week 1 relative to placebo, and then also the effect relative to an oral AD with its slower onset of action by Week 4 (although the oral AD is ongoing in all treatment arms). The maximum study duration for a subject in 3002 was 35 total weeks including screening and follow-up (or 11 weeks before entering Study 3003).

- *Choice of Controls:*

The study design incorporates currently accepted treatment algorithms for TRD involving a complete switch in treatment after lack of response, as opposed to an adjunctive add-on treatment modality. The newly initiated oral antidepressant plus intranasal placebo serves as a control relative to the other treatment arm with the new oral antidepressant plus flexibly-dosed intranasal ketamine. Of note, several different oral antidepressants (two SSRIs and two SNRIs) were permitted as the background oral antidepressant. (The justification for doing so may be that all oral antidepressants have shown comparable effect sizes for treatment response in clinical trials.) They are: escitalopram, sertraline, duloxetine, and venlafaxine XR.

- *Trial location:*

Study 3002 was conducted at 46 sites in the Czech Republic, Germany, Poland, Spain, and the United States. There was one site excluded due to Good Clinical Practice (GCP) issues with 9 subjects after an on-site audit.

- *Diagnostic criteria:*

Please see the criteria for TRD discussed under this section corresponding to the previous Study 3001. This definition was used for all phase 3 studies.

- *Key inclusion/exclusion criteria:*

See the criteria for Study 3001.

- *Dose selection:*

Doses of 56 mg to 84 mg IN esketamine and the administration regimen (2 treatment sessions per week over 4 weeks) were selected based on prior phase 1 PK and phase 2 dose response studies (with both IN and IV esketamine), particularly Panel A of Study 2003 which utilized these doses and this timing regimen.

- *Assignment to treatment:*

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Subjects were randomized to one of two treatment groups (IN esketamine plus oral antidepressant, or IN placebo plus oral antidepressant) in a 1:1 ratio via a computer-generated randomization schedule. The randomization was balanced by using randomly permuted blocks (block size = 4) and was stratified by country and class of oral antidepressant (SNRI or SSRI) initiated during the double-blind induction phase. An interactive web response system (IWRS) assigned a unique treatment code providing the treatment assignment and matching medication kits for each subject. The site would add into IWRS which oral antidepressant each subject was taking.

- *Blinding:*

Randomization codes were maintained within IWRS to blind the investigators. (The blind could be broken for individual subjects as needed for emergency reasons after sponsor consultation.) Data that could unblind the treatment assignment (such as PK concentrations, treatment allocation) were handled with special care to maintain blinding. For unbiased efficacy evaluations, independent, remote (by phone), blinded MADRS raters were used to assess antidepressant treatment response. Any unblinding events (intentional or otherwise) were fully documented and dated, with subjects entering early withdrawal and follow-up phases. Investigators and site personnel remained blinded until study participation for each subject completed through the follow-up phase.

The placebo IN solution was designed to appear identical to esketamine IN; a bittering agent (denatonium benzoate) was added to placebo to simulate the taste of active drug.

However, as with Study 3001, there were some limitations with blinding for subjects and site personnel if common effects like marked increases in blood pressure or dissociative effects (both of which were stringently monitored) were detected while on esketamine. At least independent remote raters conducted the outcome measure assessments.

- *Dose modification, dose discontinuation:*

Esketamine doses were to be initiated at 56 mg for Day 1, then could be titrated to 84 mg by Day 4, depending on efficacy and tolerability as judged by the investigator. (The CSR did not contain further details on what those investigator efficacy and tolerability criteria were.) Each subsequent dosing visit followed a similar choice of continuing the previous dose, or reducing or increasing as warranted (except no dose increases were permitted as of Day 15, and no dose changes as of Day 18 unless Day 15 was skipped).

Table 20 Study 3002 Flexible Dose Titration of Intranasal Esketamine

Day	Dose	Dose Titration Guidance
Day 1	56 mg	
Day 4	56 or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8 and 11	56 or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84mg) as determined by the investigator based on efficacy and tolerability.
Day 15	56 or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability; no dose increase was permitted on Day 15.
Days 18, 22 and 25	56 or 84 mg	The dose was to remain unchanged. If there was no intranasal treatment session on Day 15, a dose reduction from 84 mg to 56 mg was permitted on Day 18 if required for tolerability; no dose increase was permitted.

Source: CSR Study 3002

An assigned oral antidepressant was also initiated as of Day 1, either duloxetine, escitalopram, sertraline, or venlafaxine XR. The titration schedule is the same as used in Study 3001 (see that section for more details). By the end of the induction phase, doses could not be lowered below sertraline 50 mg daily, venlafaxine XR 150 mg daily, escitalopram 10 mg daily, or duloxetine 60 mg daily. Subjects received a 4-week supply of oral antidepressant study medication on Day 1 after receiving instruction from site personnel on medication use and storage. On intranasal dosing days, subjects were asked not to take their oral antidepressant until at least 3 hours after an intranasal treatment session.

Subjects received an additional 4-week supply at the start of the follow-up phase. Continuation depended on investigator discretion but was strongly encouraged to continue for at least 2 weeks into follow-up.

- *Administrative structure:*

An IDMC consisting of four clinical specialists (three psychiatrists and one nephrologist) and one statistician monitored data in the study on an ongoing basis to ensure subject safety. The committee met every 6 months to review safety data and make recommendations on study continuation.

Contract research organizations (CRO) were involved with the randomization system, (b) (4) and site rater training and qualifications (b) (4); data monitoring (b) (4); independent MADRS rating (b) (4); the interim analysis (b) (4); and medical monitoring (b) (4).

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- *Procedures and schedule:*

Please see Section 13.1.2 in the appendices.

- *Dietary restrictions/instructions:*

Subjects were not allowed to eat at least 2 hours before and during intranasal dosing sessions. Drinking of fluids was not allowed for at least 30 minutes before the first nasal spray. This precaution was reasonable to prevent nausea or vomiting or aspiration issues.

- *Concurrent medications:*

See Study 3001.

- *Treatment compliance:*

See Study 3001.

- *Rescue medication:*

See Study 3001.

- *Subject completion, discontinuation, or withdrawal:*

See Study 3001.

Study Endpoints

Primary Endpoint:

- Montgomery-Asberg Depression Scale (MADRS) Total Score Change from Baseline at End of Week 4

Key Secondary Endpoints:

- MADRS Total Score Change from Baseline at Day 2 ($\geq 50\%$ response, maintained through Day 28 with no worse than 25% response and one excursion)
- Sheehan Disability Scale (SDS) total score change from baseline at Day 28
- Patient Health Questionnaire-9-Item Depression Module (PHQ-9) total score change from baseline at Day 28

Other Secondary Endpoints:

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- MADRS Total Score Change from Baseline Responders ($\geq 50\%$ response, no worse than 25% response) and Remitters (MADRS ≤ 12) (with one excursion)
- MADRS Total Score CFB Onset of Response at Day 8 ($\geq 50\%$ response, maintained through Day 28 with no worse than 25% response and one excursion)
- Clinical Global Impression-Severity (CGI-S)
- Generalized Anxiety Disorder 7-Item Scale (GAD-7)
- European Quality of Life (EuroQol)-5 Dimensions-5 Level (EQ-5D-5L)

Safety Endpoints:

- Adverse event (AE) monitoring
- Clinical laboratory tests
- Vital signs/pulse oximetry
- Physical examination (including nasal)
- Electrocardiogram (ECG)
- Nasal Symptom Questionnaire (NSQ)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Clinician Administered Dissociative States Scale (CADSS)
- Brief Psychiatric Rating Scale (4-item Positive Symptom Subscale): BPRS+
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S)
- Clinical Global Assessment of Discharge Readiness (CGADR)
- Physician Withdrawal Checklist 20-item (PWC-20)
- Bladder Pain-Interstitial Cystitis Symptom Score (BPIC-SS)
- Cognition testing: computerized cognitive test battery and Hopkins Verbal Learning Test-Revised (HVLTR)
- University of Pennsylvania Smell Identification Test (UPSIT)
- Smell Threshold Test (STT)

Other Analyses/Endpoints:

- Healthcare Resource Use Questionnaire (HRUQ)
- PK levels (40 minutes and 2 hours post-dose on Day 4 and 22) of esketamine and noresketamine
- Pharmacogenomic biomarkers (Screening, Day 1, 8, and 25)
- STOP-Bang Questionnaire for Sleep Apnea
- Site Independent Qualification Assessment ((b) (4) Depression Confirmation
- IDS-C₃₀ (Depression Severity Assessment)
- Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire (MGH-Female RLHQ): Module I and Menstrual Cycle Tracking

Statistical Analysis Plan

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The sample size planned for this study was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between esketamine and the active comparator, a standard deviation (SD) of 12, a 1-sided significance level of 0.025, and a dropout rate of 25%. About 98 subjects needed to be randomized to each treatment group to achieve 90% power using a fixed design. The treatment difference and SD were based on results from Panel A of Study 2003 and clinical judgment.

An interim analysis to re-estimate sample size was originally planned but was removed during Amendment 2, as recruitment dynamics indicated that sample size changes were not recommended.

The Full Analysis (FA) population was defined as all randomized subjects receiving at least one dose of IN study medication AND at least one dose of oral antidepressant during the double-blind induction phase. The efficacy analyses were performed on the FA population.

The Safety population was defined as all randomized subjects receiving at least one dose of IN study medication OR at least one dose of oral antidepressant during the double-blind induction phase. Analyses of change from baseline for the safety population only included subjects with at least one post-baseline assessment. Subjects who received incorrect treatment were analyzed under the planned treatment.

The All Randomized Analysis population included all randomized subjects regardless of whether or not treatment was received. This population was used to summarize overall study completion and withdrawal information.

To control for multiplicity, a serial fixed sequence gatekeeping approach was applied to strongly control type I error across the primary and 3 key secondary endpoints (onset of clinical response by Day 2, change in SDS total score, change in PHQ-9 total score) and across each dose treatment comparison arm. Statistical analysis tests were conducted at a 1-sided 0.025 level of significance unless otherwise specified. The 3 key secondary endpoints were analyzed sequentially and were considered statistically significant only if the endpoint was individually significant AND previous endpoints in the hierarchy were also significant, including the primary endpoint, all at the 1-sided 0.025 level. If the primary endpoint was statistically significant, the selected secondary endpoints were assessed in the following order: onset of clinical response by Day 2 (24 hours); change in SDS total score; change in PHQ-9 total score.

MMRM analysis was used for the primary endpoints for non-EU sites. ANCOVA analyses were to use last observation carried forward (LOCF) data for each endpoint during the double-blind induction phase; ANCOVA was used at EU sites. An imputation method was described for the MADRS total score for missing data. For MMRM, missing data was assumed to be missing at random (MAR); this data underwent a delta adjustment multiple imputation method for

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sensitivity analysis.

The Applicant also conducted subgroup analyses based on demographics and diagnostic characteristics.

Protocol Amendments

There were two global protocol amendments, both instituted after subjects had already started enrollment in this study. Amendment 1 (dated January 15, 2016) occurred after 50 subjects were enrolled (7 from Germany, 9 from Poland, 5 from Spain, and 29 in the US). Amendment 2 (dated June 3, 2016) occurred after 88 subjects were enrolled (2 more from Germany, 16 more from Poland, and 20 more from the US).

Both amendments discussed clarifications to the TRD inclusion criteria definition (see inclusion criteria section above for more details; these were similar to the amendments made to Study 3001's TRD inclusion criteria). There were also additional exclusion criteria (see Study 3001 which had similar criteria) clarifying medical and diagnostic restrictions. Amendment 2 revised the key secondary endpoints to correspond to the planned order of analysis and deleted an interim analysis for sample size re-estimation.

6.2.2. Study Results

Compliance with Good Clinical Practices

As noted earlier, one site in Poland was excluded after not meeting GCP standards per an on-site audit. The Applicant otherwise attested to the other study sites meeting GCP standards in their CSR.

Financial Disclosure

See Financial Disclosure section at the end of this review.

Patient Disposition

A total of 227 subjects were enrolled in this study (after 435 were screened). Three subjects did not receive any study medication and were not included in the FA or Safety populations. One subject only received IN medication and not an oral antidepressant and was excluded from the FA population. The subjects excluded from the FA population were (b) (6). The first two were randomized to esketamine and the other two to placebo.

In addition, there were two subjects ((b) (6)) randomized to esketamine who were included in the FA population who did not have a post-baseline MADRS score recorded in

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the datasets. They only received the first dose of their study medications and then dropped out of the study.

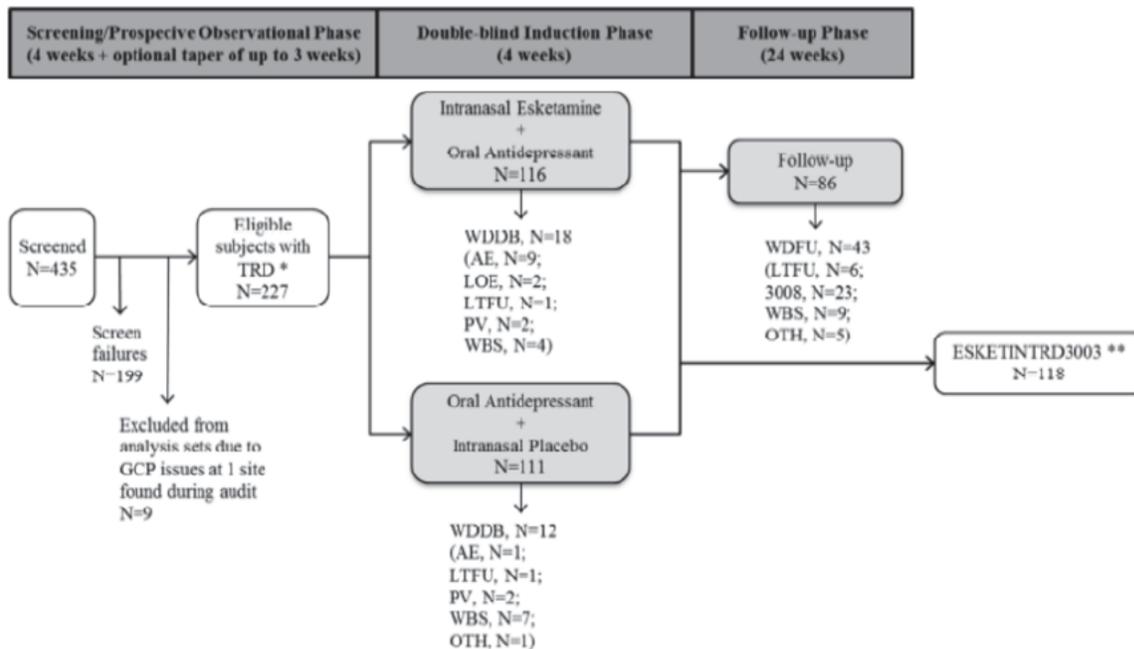
There were 9 subjects from a site in Poland that were also excluded from the FA population due to GCP violations at the site.

Table 21 Study 3002 Patient Disposition

Number of Subjects in Each Analysis Set (Study ESKETINTRD3002: All Randomized Analysis Set)			
	Intranasal Esk + Oral AD (N=116)	Oral AD + Intranasal Placebo (N=111)	Total (N=227)
All randomized	116 (100.0%)	111 (100.0%)	227 (100.0%)
Full	114 (98.3%)	109 (98.2%)	223 (98.2%)
Safety	115 (99.1%)	109 (98.2%)	224 (98.7%)
Follow-up	34 (29.3%)	52 (46.8%)	86 (37.9%)

Source: Table 5, CSR Study 3002

Figure 12 Study 3002 Patient Disposition



Source: CSR Study 3001

Protocol Violations/Deviations

A total of 30 subjects (13%) withdrew early from the double-blind induction phase of Study

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3002. The most common reasons were voluntary subject withdrawal (5%) and AEs (4%). A higher number of withdrawals due to AEs were in the IN esketamine arm (8%) versus placebo (1%). The other withdrawal factors were fairly even across treatment groups, including protocol violations.

Table 22 Study 3002 Subject Withdrawals

Study Completion/Withdrawal Information; Double-blind Induction Phase (Study ESKETINTRD3002: All Randomized Analysis Set)			
	Intranasal Esk + Oral AD (N=116)	Oral AD + Intranasal Placebo (N=111)	Total (N=227)
Completed	98 (84.5%)	99 (89.2%)	197 (86.8%)
Withdrawn	18 (15.5%)	12 (10.8%)	30 (13.2%)
Adverse event	9 (7.8%)	1 (0.9%)	10 (4.4%)
Lack of efficacy	2 (1.7%)	0	2 (0.9%)
Lost to follow-up	1 (0.9%)	1 (0.9%)	2 (0.9%)
Protocol violation	2 (1.7%)	2 (1.8%)	4 (1.8%)
Withdrawal by subject	4 (3.4%)	7 (6.3%)	11 (4.8%)
Other	0	1 (0.9%)	1 (0.4%)

Source: Table 6, CSR Study 3002

There were 118 subjects who completed the double-blind induction phase who decided to enroll in the maintenance-of-effect Study 3003 (to be discussed next): 70 were originally in the esketamine arm, and 48 were on placebo, plus oral antidepressant. There were 86 subjects who continued to the follow-up phase instead: 34 who were originally on esketamine and 52 who were on placebo, plus oral antidepressant.

A total of 161 subjects (71%) completed the study including the follow-up phase. A total of 66 subjects (29%) withdrew from at least one phase of the study.

About 38 subjects (17%) had one or more major protocol deviations reported. There were 18 subjects (8%) who did not meet inclusion and/or exclusion criteria but were still assigned to treatment. The most common deviations were 6 subjects who did not confirm their current depressive episode and response to treatment using (b) (4) and 6 subjects who had clinically significant ECG abnormalities during screening and/or Day 1. Another 9 subjects (4%) did not have the MADRS assessment performed at specified times in the protocol. Only three subjects (1.3%) received the wrong treatment or incorrect dose during the study.

The number of major deviations was somewhat high in this study, but none appear to have had a gross impact on the study results.

Table of Demographic Characteristics

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About 40% of subjects were from the US, with the rest from Europe. As with study 3001, the majority of subjects in this study were in their 40s and 50s and were white females with elevated BMI scores. The distribution of characteristics was generally even between treatment groups. The placebo + oral antidepressant group was slightly heavier (mean weight 82.7 kg±19.5) and older (mean age 46.4 years±11.1) with more HTN (25%) than the esketamine + oral antidepressant group (mean weight 79.3 kg±20.1, mean age 44.9 years±12.6, HTN 16%).

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Table 23 Study 3002 Demographic Characteristics of the Primary Efficacy Analysis

Demographic Parameters	Control Group (Placebo + Oral AD) (N=109) n (%)	Esketamine + Oral AD Group (N=114) n (%)	Total (N=223) n (%)
Sex			
Male	46 (42%)	39 (34%)	85 (38%)
Female	69 (63%)	75 (66%)	138 (62%)
Age			
Mean years (SD)	46.4 (11.14)	44.9 (12.58)	45.7 (11.89)
Median (years)	47.0	45.0	47.0
Min, max (years)	(20; 64)	(19; 64)	(19; 64)
Age Group			
18 to 44 years	40 (37%)	54 (47%)	94 (42%)
45 to 64 years	69 (63%)	60 (53%)	129 (58%)
Race			
White	102 (94%)	106 (93%)	208 (93%)
Black or African American	5 (4.6%)	6 (5.3%)	11 (4.9%)
Asian	1 (0.9%)	1 (0.9%)	2 (0.9%)
Multiple/Other	1 (0.9%)	1 (0.9%)	2 (0.9%)
Ethnicity			
Hispanic or Latino	7 (6.4%)	5 (4.4%)	12 (5.4%)
Not Hispanic or Latino	99 (91%)	108 (95%)	207 (93%)
Region			
United States	44 (40%)	45 (40%)	89 (40%)
Europe	65 (60%)	69 (61%)	134 (60%)
Germany	10 (9.2%)	10 (8.8%)	20 (9.0%)
Czech Republic	28 (26%)	30 (26%)	58 (26%)
Poland	18 (17%)	20 (18%)	38 (17%)
Spain	9 (8.3%)	9 (7.9%)	18 (8.1%)
BMI (kg/m²)			
Underweight (<18.5)	2 (1.8%)	1 (0.9%)	3 (1.3%)
Normal (18.5 to < 25)	28 (26%)	41 (36%)	69 (31%)
Overweight (25 to <30)	36 (33%)	41 (36%)	77 (35%)
Obese (30 to <40)	39 (36%)	28 (25%)	67 (30%)
Morbidly Obese (40+)	4 (3.7%)	3 (2.6%)	7 (3.1%)
Hypertension Status			
Yes	27 (25%)	18 (16%)	45 (20%)
No	82 (75%)	96 (84%)	178 (80%)
Oral AD Class/Type			

Demographic Parameters	Control Group (Placebo + Oral AD) (N=109) n (%)	Esketamine + Oral AD Group (N=114) n (%)	Total (N=223) n (%)
SNRI	75 (69%)	77 (68%)	152 (68%)
SSRI	34 (31%)	37 (33%)	71 (32%)
Duloxetine	61 (56%)	60 (53%)	121 (54%)
Venlafaxine XR	15 (14%)	17 (15%)	32 (14%)
Sertraline	16 (15%)	16 (14%)	32 (14%)
Escitalopram	17 (16%)	21 (18%)	38 (17%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The mean baseline MADRS total score for this study was 37.1, which is higher than is typically seen for most standard antidepressant trials (ranging from 28 to 36) and indicates a more seriously ill population. These scores, and the mean confirmatory depression scale scores (IDS-C₃₀, CGI-S, PHQ-9) were fairly even across treatment groups. As with Study 3001, a few subjects with baseline MADRS total scores less than 28 were still included (as low as 21) who had improved after screening; again, they probably did not significantly affect the overall results, given the high baseline mean score and similar mean score across treatment groups.

Baseline rates of suicidal ideation and behavior per C-SSRS were also fairly even across treatment groups, although lifetime suicidal behavior was slightly higher in the placebo arm (13%) than the esketamine arm (8%). The number of prior antidepressant medication trials was somewhat uneven for the category of those who had taken one or two prior antidepressants, with 8% having tried one in the esketamine arm versus 17% in the placebo arm, and 61% having tried two in the esketamine arm versus 50% in the placebo arm. It is unclear if this would have much significance, as both numbers still indicate a low number of antidepressant trials (and perhaps less overall illness severity) than those who failed three or more. For subjects with prior trials of three or more antidepressants, the rates were similar (32% for esketamine, 34% for placebo). There were also slightly higher rates of family psychiatric histories across several disorders (depression, anxiety, bipolar, alcohol abuse) in the placebo group versus the esketamine group. Overall though, it does not seem there is a major difference in baseline psychiatric severity between the two groups that could affect study results.

Table 24 Study 3002 Baseline Psychiatric History

Baseline Psychiatric History (Study ESKETINTRD3002: Full Analysis Set)			
	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)	Total (N=223)
Age when diagnosed with MDD (years)			
N	114	109	223
Mean (SD)	32.1 (12.53)	35.3 (13.04)	33.7 (12.86)
Median	30.5	36.0	33.0
Range	(8; 60)	(5; 64)	(5; 64)
Baseline MADRS total score			
N	114	109	223
Mean (SD)	37.0 (5.69)	37.3 (5.66)	37.1 (5.67)
Median	37.0	37.0	37.0
Range	(22; 48)	(21; 52)	(21; 52)
Screening IDS-C30 total score			
N	114	109	223
Mean (SD)	46.0 (6.26)	45.7 (5.89)	45.9 (6.07)
Median	46.0	46.0	46.0
Range	(34; 60)	(35; 63)	(34; 63)
Baseline CGI-S			
N	113	109	222
Mean (SD)	5.1 (0.66)	5.1 (0.67)	5.1 (0.67)
Median	5.0	5.0	5.0
Range	(4; 7)	(4; 7)	(4; 7)
Baseline CGI-S category, n (%)			
N	114	109	223
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	0	0
Moderately ill	21 (18.4%)	19 (17.4%)	40 (17.9%)
Markedly ill	64 (56.1%)	63 (57.8%)	127 (57.0%)
Severely ill	27 (23.7%)	26 (23.9%)	53 (23.8%)
Among the most extremely ill patients	1 (0.9%)	1 (0.9%)	2 (0.9%)
Not assessed	1 (0.9%)	0	1 (0.4%)
Baseline PHQ-9 total score			
N	114	109	223
Mean (SD)	20.2 (3.63)	20.4 (3.74)	20.3 (3.68)
Median	20.0	21.0	20.0
Range	(5; 27)	(10; 27)	(5; 27)
Screening C-SSRS lifetime (a), n (%)			
N	114	109	223
No event	65 (57.0%)	61 (56.0%)	126 (56.5%)
Suicidal ideation	40 (35.1%)	34 (31.2%)	74 (33.2%)
Suicidal behavior	9 (7.9%)	14 (12.8%)	23 (10.3%)
Screening C-SSRS past 6 or 12 months (a), n (%)			
N	114	109	223
No event	77 (67.5%)	74 (67.9%)	151 (67.7%)
Suicidal ideation (past 6 months)	37 (32.5%)	34 (31.2%)	71 (31.8%)
Suicidal behavior (past 12 months) (c)	0	1 (0.9%)	1 (0.4%)
Duration of current episode (wks)			
N	114	109	223
Mean (SD)	111.4 (124.28)	118.0 (187.37)	114.6 (157.96)
Median	63.5	52.0	60.0
Range	(9; 649)	(8; 1196)	(8; 1196)

Baseline Psychiatric History (Study ESKETINTRD3002: Full Analysis Set)			
	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)	Total (N=223)
No. of previous antidepressant medications (b), n (%)			
N	114	109	223
1	9 (7.9%)	18 (16.5%)	27 (12.1%)
2	69 (60.5%)	54 (49.5%)	123 (55.2%)
3	24 (21.1%)	22 (20.2%)	46 (20.6%)
4	7 (6.1%)	13 (11.9%)	20 (9.0%)
5	3 (2.6%)	1 (0.9%)	4 (1.8%)
6	1 (0.9%)	1 (0.9%)	2 (0.9%)
9	1 (0.9%)	0	1 (0.4%)
No. of major depressive episodes including current episode, n (%)			
N	114	109	223
1	15 (13.2%)	14 (12.8%)	29 (13.0%)
2-5	81 (71.1%)	78 (71.6%)	159 (71.3%)
6-10	16 (14.0%)	15 (13.8%)	31 (13.9%)
>10	2 (1.8%)	2 (1.8%)	4 (1.8%)
Family history of depression, n (%)			
N	114	109	223
Yes	51 (44.7%)	56 (51.4%)	107 (48.0%)
No	63 (55.3%)	53 (48.6%)	116 (52.0%)
Family history of anxiety disorder, n (%)			
N	114	109	223
Yes	10 (8.8%)	16 (14.7%)	26 (11.7%)
No	104 (91.2%)	93 (85.3%)	197 (88.3%)
Family history of bipolar disorder, n (%)			
N	114	109	223
Yes	8 (7.0%)	11 (10.1%)	19 (8.5%)
No	106 (93.0%)	98 (89.9%)	204 (91.5%)
Family history of schizophrenia, n (%)			
N	114	109	223
Yes	6 (5.3%)	4 (3.7%)	10 (4.5%)
No	108 (94.7%)	105 (96.3%)	213 (95.5%)
Family history of alcohol abuse, n (%)			
N	114	109	223
Yes	18 (15.8%)	20 (18.3%)	38 (17.0%)
No	96 (84.2%)	89 (81.7%)	185 (83.0%)
Family history of substance abuse, n (%)			
N	114	109	223
Yes	8 (7.0%)	4 (3.7%)	12 (5.4%)
No	106 (93.0%)	105 (96.3%)	211 (94.6%)

Source: Table 10, CSR Study 3002

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- Treatment Compliance

The mean percentage of treatment compliance for each of the four oral antidepressants during the double-blind induction phase was $\geq 91.7\%$ in both treatment groups. There were four

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subjects with medication dosing protocol violations, three on placebo (one subject received the wrong IN medication one study day, one received less than the minimum therapeutic oral antidepressant dose once, and one received the wrong oral antidepressant medication from IWRS assignment) and one on esketamine (received the wrong IN medication one study day). These issues were not likely to have affected overall study results.

The IN treatment exposure times between the two treatment arms were comparable, with the mean duration of IN exposure (SD) being 23.0 (5.77) days on esketamine versus 23.9 (4.34) days on placebo, plus oral antidepressant ongoing each day during the double-blind induction phase. A slightly higher number of subjects only received one treatment dose (on esketamine) compared to IN placebo (4.4% versus 0.9%, likely due to dropouts/tolerability issues after the initial dose). Similar rates of subjects in each treatment arm received less than 7 days of IN dosing: 11 subjects (9.6%) on esketamine versus 10 subjects on placebo (9.2%).

Table 25 Study 3002 Esketamine Total Exposure Days

Number of Days Dosed with Intranasal Study Medication; Double-blind Induction Phase (Study ESKETINTRD3002: Full Analysis Set)		
Number of days dosed	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
1	5 (4.4%)	1 (0.9%)
2	0	2 (1.8%)
3	2 (1.8%)	1 (0.9%)
4	2 (1.8%)	2 (1.8%)
5	2 (1.8%)	2 (1.8%)
6	0	2 (1.8%)
7	9 (7.9%)	6 (5.5%)
8	94 (82.5%)	93 (85.3%)

Source: Table 13, CSR Study 3002

In terms of which esketamine dose was administered to subjects in this flexible-dosing study, a frequency distribution table shows each study visit's dosing trend. All but one subject (who received 42 mg due to a device issue) in the esketamine arm received 56 mg IN on Day 1. On Day 4, 54% received 56 mg, and 46% received 84 mg. For the other days, about one-third of subjects remained on 56 mg, and two-thirds received 84 mg. On Day 25, 67% of 99 subjects received 84 mg versus 32% of 99 subjects receiving 56 mg (and one subject receiving 70 mg due to a device issue). There were 11 (9.6%) subjects who decreased their dose during the study. (three on Day 8, two on Day 11, four on Day 15, one on Day 18, and one on Day 25.)

Oral antidepressant exposure was slightly lower for all four antidepressants in the esketamine arm versus the placebo arm, with mean duration of exposure ranging from 23.8 (9.50) to 27.6 (4.73) days for the esketamine arm versus 27.3 (4.99) to 28.6 (1.12) days for the placebo arm. It is unclear what effect this small imbalance might have on study results, or whether this may contribute to a stronger placebo result by Day 28 than would have been expected with a more balanced exposure between groups. (Given that the primary endpoint result was still positive,

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this imbalance was likely not crucial.)

Plasma PK levels confirmed esketamine administration at consistent levels during the study between Day 4 and Day 22 in that treatment arm and increased plasma levels with the higher dose.

Table 26 Study 3002 Plasma PK Esketamine Concentrations

Plasma Esketamine Concentrations (ng/mL) Following Administration of 56 mg Intranasal Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	53	65.7	0.829	153	29.0	44.2
4	2 h	55	39.2	0.932	106	18.8	48.0
22	40 min	32	69.0	10.1	166	37.8	54.7
22	2 h	32	44.6	8.26	101	24.1	54.1

Source: Attachment Table PK01_ESKETINTRD3002

Plasma Esketamine Concentrations (ng/mL) Following Administration of 84 mg Intranasal Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	47	97.9	22.1	207	36.9	37.7
4	2 h	47	63.0	15.4	139	27.0	42.9
22	40 min	67	102	21.2	250	43.7	42.9
22	2 h	68	62.4	1.82	155	27.1	43.5

Source: Attachment Table PK02_ESKETINTRD3002

Plasma Noreketamine Concentrations (ng/mL) Following Administration of 56 mg Intranasal Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	53	62.3	1.33	315	60.7	97.5
4	2 h	55	93.6	1.02	292	64.3	68.6
22	40 min	32	62.4	0.986	274	67.2	108
22	2 h	32	91.8	3.22	216	68.3	74.4

Source: Attachment Table PK03_ESKETINTRD3002

Plasma Noreketamine Concentrations (ng/mL) Following Administration of 84 mg Intranasal Esketamine

Day	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
4	40 min	47	94.1	2.55	325	71.4	75.9
4	2 h	47	180	2.40	436	90.8	50.4
22	40 min	67	115	BQL	361	93.6	81.1
22	2 h	68	169	BQL	413	88.1	52.0

BQL = Below quantification limit

Source: Attachment Table PK04_ESKETINTRD3002

Source: Tables 20 to 23, CSR Study 3002

- Concomitant Medications

For the double-blind phase, 77% of subjects in the esketamine arm and 84% of subjects in the

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placebo arm (81% total) used concomitant medications. The most commonly used medications were ibuprofen (13%), lorazepam (11%), and clonazepam (11%). A slightly higher number of subjects used lorazepam, clonazepam, and alprazolam (30%) on esketamine versus placebo (24%).

Overall, the distribution of concomitant medications across treatment arms was not uneven enough to affect study results.

- Rescue Medications

There were 27% of subjects in the esketamine arm and 20% of subjects in the placebo arm who required medications in response to AEs.

Table 27 Study 3002 Percentage of Subjects Who Required Medications for AEs of Interest

AE	Esketamine+Oral AD (N=115)	Placebo+Oral AD (N=109)
Nausea/Vomiting	5.2%	0.9%
Anxiety/Panic Attack*	6.1%	2.8%
Dissociation	2.6%	0
BP Increased/HTN	0	0
Agitation	0.9%	0
Depression/Crying	4.3%	1.8%

*Includes "Emotional Distress," "Tension," "Restlessness"
Source: Applicant Response to IR, Nov 12, 2018

Overall, for the AEs of interest, the esketamine arm used rescue medications more often than the placebo arm, except for hypertension/BP increases (there were none needed in this study). However, the overall rates of rescue medication use were on the low side and likely did not affect study efficacy results.

Efficacy Results – Primary Endpoint

The primary endpoint of mean MADRS total score change from baseline to Day 28 on IN esketamine versus IN placebo (plus oral antidepressant in both arms) was statistically significant. The mean CFB at Day 28 was -21.4 (12.3) for IN esketamine versus -17.0 (13.9) for IN placebo. Using MMRM analysis, the LS mean difference between groups was -4.0 (1.7) which provided a statistically significant one-sided p-value of 0.010. There was also a numerical difference between drug and placebo at each timepoint in the study, as well as a nominally significant difference between drug and placebo on the primary outcome measure (mean MADRS total score) at each timepoint except for Day 15; and except for Day 8 there was

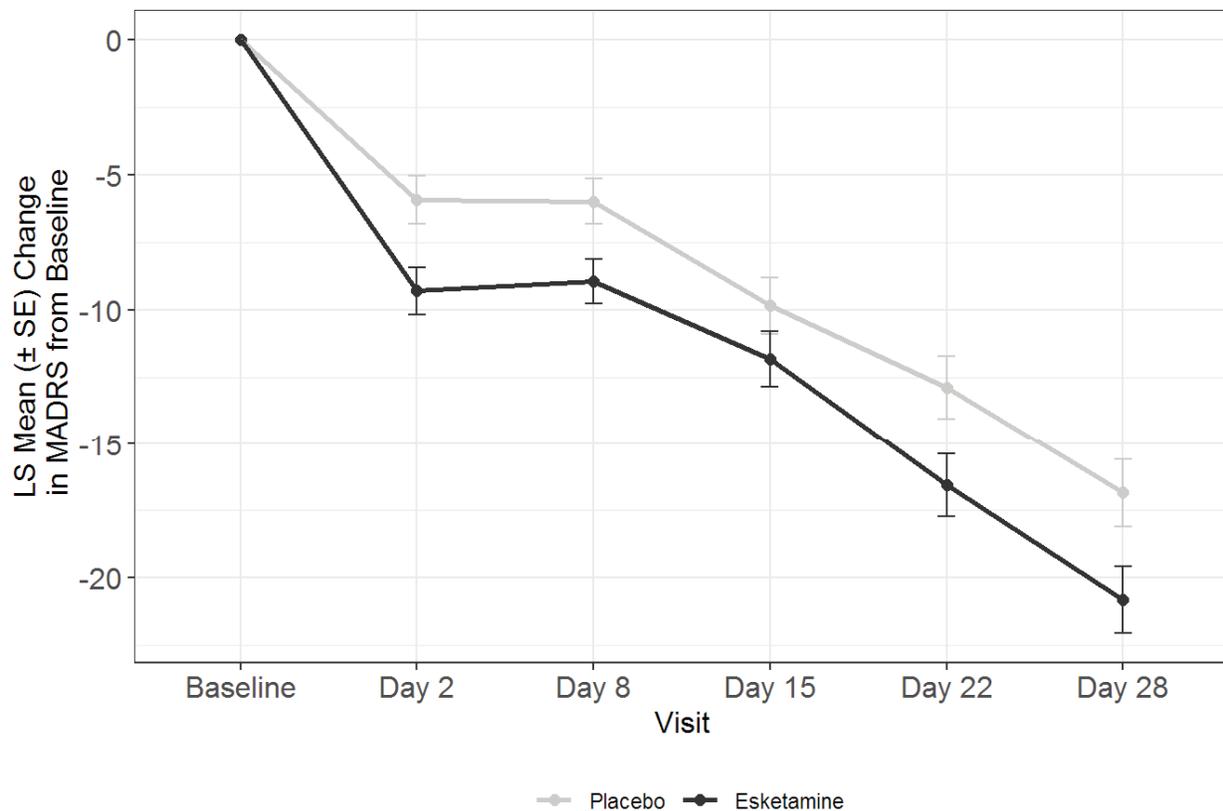
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progressive improvement in both groups through Day 28.

Table 28 Study 3002 Primary Efficacy Endpoint Results: MADRS Total Score LS Mean Change from Baseline at Week 4 (Day 28)

Treatment Arm	N	Baseline MADRS Total Score (SD)	Mean Change from Baseline (SD) at Week 4	LS Mean Change from Placebo (SE) at Week 4	1-Sided P-Value <0.025
Placebo+Oral AD	109	37.3 (5.7)	-17.0 (13.9)	--	--
Esketamine+Oral AD	114	37.0 (5.7)	-21.4 (12.3)	-4.0 (1.7)	0.010

Figure 13 Study 3002 Primary Efficacy Endpoint Results: MADRS Total Score LS Mean Change from Baseline at Week 4 (Day 28)



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Source: Andrew Potter, PhD, Statistical Reviewer

The same result trend was confirmed via ANCOVA/LOCF analysis, with an LS mean square

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difference of -3.5 (1.63) between treatment groups, and a 1-sided p-value statistically significant at 0.017.

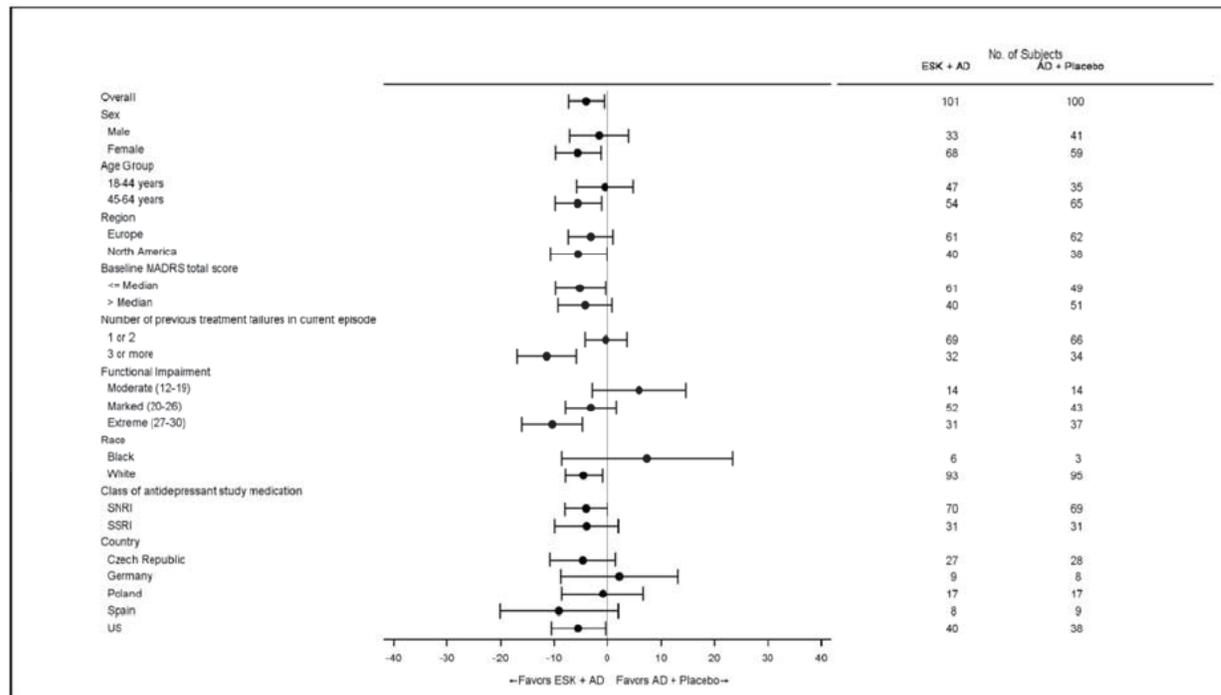
Subgroup Analyses

The Applicant conducted a Forest Plot analysis looking at demographic, diagnostic, and treatment-related subgroups with the primary endpoint.

Some of the subgroups that did not show a mean trend towards improvement on the primary endpoint in this study were: black race and subjects in Germany (although interpretability is limited by the very small n for these two subgroups (9 and 17 respectively)), and moderate functional impairment at baseline on SDS (12 to 19) (also a smaller n subgroup at 28 subjects). Some of the following notable subgroups showed greater mean improvement than the overall group on the primary endpoint: female gender, older age (45 to 64 years), North American region, three or more prior antidepressant failures, extreme functional impairment at baseline on SDS (27 to 30), and US sites. The larger degree of improvement in the more severely ill subgroups is particularly impressive for this study.

Figure 14 Study 3002 Subgroup Forest Plot

Forest Plot for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Least Squares Mean Treatment Difference of Change From Baseline (95% Confidence Interval) to Day 28 MMRM by Subgroup; Double-blind Induction Phase (Study ESKETINTRD3002: Full Analysis Set)



Note: Subgroups with fewer than 5 subjects not presented.

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Source: Figure 4, CSR Study 3002

The Applicant also conducted a sensitivity analysis for the primary endpoint using ANCOVA with baseline observation carried forward (BOCF) and worst observation carried forward (WOCF) data. The results showed consistency with the overall ANCOVA/LOCF analysis in terms of result trends.

Data Quality and Integrity

OSI decided to inspect sites that appeared to contribute heavily to primary efficacy results and had larger subject enrollment. The statistical reviewer notes that in this study a single site did not affect the overall study result (see his review for more details). He noted that there were multiple sites (at least four) that if excluded would affect the primary result, which provides some reassurance that 3002's study result was more generalizable across its study population.

The Applicant also conducted internal audits for GCP compliance and cancelled one site with nine subjects due to quality breaches. The study-specific monitoring guidelines and oversight activities were recorded in a trial master file and reviewed by study personnel periodically.

Site PL10002's enrolled subjects were not included in any analysis populations for this study. Site personnel did not properly document the administered treatments or properly follow protocol guidelines; source data could not be considered reliable. The Applicant conducted sensitivity analyses including this site for the primary efficacy endpoint analysis and found no significant effect on or changes to the overall result. (Inclusion of the excluded subjects slightly increased the trend towards efficacy, with overall LS mean CFB of -4.2 (1.7) between groups with a 1-sided p-value of 0.006.)

Efficacy Results – Secondary and other relevant endpoints

There were three key secondary endpoints, to be analyzed using a serial gatekeeping (fixed sequence) approach to adjust for multiplicity and control type I error. As the primary endpoint was statistically significant, the key secondary endpoints were to be analyzed in a prespecified order as follows: onset of clinical response by Day 2 (24 hours), change in SDS total score, change in PHQ-9 total score.

Due to the first key secondary endpoint not being statistically significant, the subsequent key secondaries could not be formally tested for statistical significance. Both of those two subsequent key secondaries would have been nominally significant and also showed numerical improvement in the esketamine group versus placebo for their respective endpoints. The SDS and PHQ-9 results here would provide limited evidence of a greater trend towards efficacy in functional improvement and confirmatory improvement in self-reported depression symptoms on IN esketamine versus IN placebo, plus an oral antidepressant, by Day 28.

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- Onset of Clinical Response by Day 2 (24 Hours)

For this endpoint, a clinical response by Day 2 was defined as at least 50% improvement (decrease) from baseline in MADRS total score with onset by Day 2 that was maintained to Day 28. One non-response excursion at a subsequent visit was allowed, if at least 25% improvement was measured. Subjects who did not meet these criteria or who discontinued before Day 28 for any reason were deemed non-responders.

There were 8% in the esketamine group versus 5% in the placebo group who met criteria for Day 2 response. This difference was not statistically significant (1-sided p-value of 0.161), so the next two key secondary endpoints could not be formally tested afterwards.

The difference in rapid response (i.e., Day 2) between the two groups was not evident on the first key secondary endpoint as per the clinical response definition. However, as noted earlier, on the primary efficacy measure, there was a nominally significant difference on esketamine versus placebo; however this was not a formally prespecified secondary endpoint or controlled for multiplicity. It is unclear if the lack of expected rapid response on esketamine in this study (as defined by the $\geq 50\%$ MADRS improvement measure) is in part due to the lower initial dosing (56 mg on Day 1, and flexible increases afterwards) in this study. (The results of Study 3001, where the lower dose was more effective, would not corroborate this theory.)

- Change in SDS Total Score

The LS mean CFB difference for SDS total score between treatment groups was -4.0 (1.17) using MMRM analysis, favoring the esketamine group over placebo. An exploratory 1-sided p-value would have been nominally significant at <0.001 but could not be formally evaluated due to the pre-specified analysis parameters correcting for multiplicity. A similar trend was seen on ANCOVA analysis.

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Table 29 Study 3002 SDS Total Score Change from Baseline at Day 28

Sheehan Disability Scale (SDS) Total Score: Change From Baseline to Day 28 MMRM; Double-blind Induction Phase (Study ESKETINTRD3002: 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	
1-sided p-value	<0.001 (b)	

Source: Table 30, CSR Study 3002

- Change in PHQ-9 Total Score

The LS mean CFB difference between treatment groups was -2.4 via MMRM analysis, favoring the esketamine group over placebo. As with the previous key secondary endpoint, the p-value could not be formally tested due to the negative p-value on the first key secondary endpoint as per the prespecified analysis parameters. The exploratory 1-sided p-value would have been nominally significant at 0.003. A similar trend was seen on ANCOVA analysis.

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Table 30 Study 3002 PHQ-9 Total Score Change from Baseline at Day 28

Patient Health Questionnaire (PHQ-9) Total Score: Change From Baseline to Day 28 MMRM Double-blind Induction Phase (Study ESKETINTRD3002: 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	
1-sided p-value	0.003 (b)	

(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 + 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 analysis can be considered statistically significant at the 1-sided 0.025 level only if the change in MADRS total score, onset of clinical response, and change in SDS total score analyses are also significant. If not statistically significant, the change in PHQ-9 total score cannot be formally evaluated and the p-value should not be referenced.

Note: PHQ-9 total score ranges from 0 to 27; a higher score indicates greater depression.

Note: Negative change in score indicates improvement.

Source: Table 32, CSR Study 3002

Other Secondary Endpoints

The other secondary endpoints listed here were either not controlled for multiplicity and/or compared statistically.

- Response Rates Based on MADRS Total Score

Please see Study 3001 for responder criteria. At Day 28, 69% of 101 subjects on esketamine versus 52% of 100 subjects on placebo, with oral antidepressant ongoing in both arms, met criteria for being responders. The number-needed-to-treat (NNT, 95% CI) was 6 (1.3 to 10.2). A larger percentage met responder criteria at each earlier timepoint on esketamine versus placebo, with an increasing overall trend (except for Day 8).

- Remission Rates Based on MADRS Total Score

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Please see Study 3001 for remission criteria. At Day 28, 53% of 101 subjects on esketamine were in remission versus 31% of 100 subjects on placebo, with oral antidepressant ongoing in both arms. The NNT was 5 (1.8 to 7.5). The greater trend towards remission on esketamine versus placebo was not seen until Day 22 in this study. It is unclear how to interpret that trend, although it may correspond to the lack of expected rapid full clinical response to esketamine versus placebo on earlier timepoints in this study; there may or may not be a possible correlation as well to lower esketamine doses used earlier in the study.

- Response Rates Based on SDS Score

See Study 3001 for responder criteria. The esketamine arm showed higher percentages of response on SDS scores versus the placebo arm at both Day 15 and Day 28.

Table 31 Study 3002 SDS Responders

Response Based on Sheehan Disability Scale (SDS) Over Time; Double-blind Induction Phase (Study ESKE TINTRD3002: Full Analysis Set)		
	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Day 15		
N	46	45
Yes	18 (39.1%)	7 (15.6%)
No	28 (60.9%)	38 (84.4%)
Day 28		
N	86	86
Yes	49 (57.0%)	34 (39.5%)
No	37 (43.0%)	52 (60.5%)

Source: Table 36, CSR Study 3002

- Remission Rates Based on SDS Score

See Study 3001 for remission criteria. As with response rates, a higher percentage of remission was seen in the esketamine arm versus placebo at both Day 15 and Day 28.

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Table 32 Study 3002 SDS Remitters

Remission Based on Sheehan Disability Scale (SDS) Over Time: Double-blind Induction Phase (Study ESKETINTRD3002: Full Analysis Set)		
	Intranasal Esk + Oral AD (N=114)	Oral AD + Intranasal Placebo (N=109)
Day 15		
N	46	45
Yes	7 (15.2%)	2 (4.4%)
No	39 (84.8%)	43 (95.6%)
Day 28		
N	86	86
Yes	34 (39.5%)	18 (20.9%)
No	52 (60.5%)	68 (79.1%)

Source: Table 37, CSR Study 3002

- Onset of Clinical Response by Day 8

See Study 3001 for responder criteria. By Day 8, 10.5% of 114 subjects on IN esketamine met responder criteria versus 6.4% of 109 subjects on IN placebo, with oral antidepressant ongoing in both arms. The odds ratio (95% CI) was 1.74 (0.65 to 4.70) for esketamine versus placebo. The difference between groups per exploratory p-value is not nominally significant at 0.137.

- CGI-S

The median change from baseline to endpoint for either treatment arm was the same, -2.0. The numerical result is difficult to interpret due to the use of median values with a categorical variable. The Applicant utilized an exploratory analysis using ranks of change from baseline as the response variable on ANCOVA. However, the calculated p-values do not appear fully interpretable due to the use of LOCF with a variable that has limited granularity and is more prone to skewing.

- GAD-7 Total Score

The LS mean CFB difference between treatment arms on this endpoint was -1.0 (0.7) and did not meet nominal significance on an exploratory 1-sided p-value. There was numerical improvement on the scale in both arms, indicating that, given its different mechanism of action, at least as measured by GAD-7, esketamine did not worsen anxiety in this study for subjects.

- EQ-5D-5L

The mean (SD) CFB in health status index (HSI) at endpoint of the double-blind induction phase was +0.29 (0.23) for the esketamine group versus +0.23 (0.25) for the placebo group. (The scale reports +0.03 to 0.07 as thresholds for meaningful improvement on HSI.) The mean sum score

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CFB was -23.2 (16.6) for the esketamine group versus -17.1 (19.7) for the placebo group. The mean CFB for EQ-VAS score was +29.1 (26.3) for the esketamine group versus +20.9 (26.6) for the placebo group. (The scale reports +7 to 10 as thresholds for meaningful improvement on EQ-VAS.) All of these indices appear to indicate meaningful patient-reported functional improvement for both treatment groups by study endpoint, with a slightly greater improvement on esketamine versus placebo, although these values were not statistically compared.

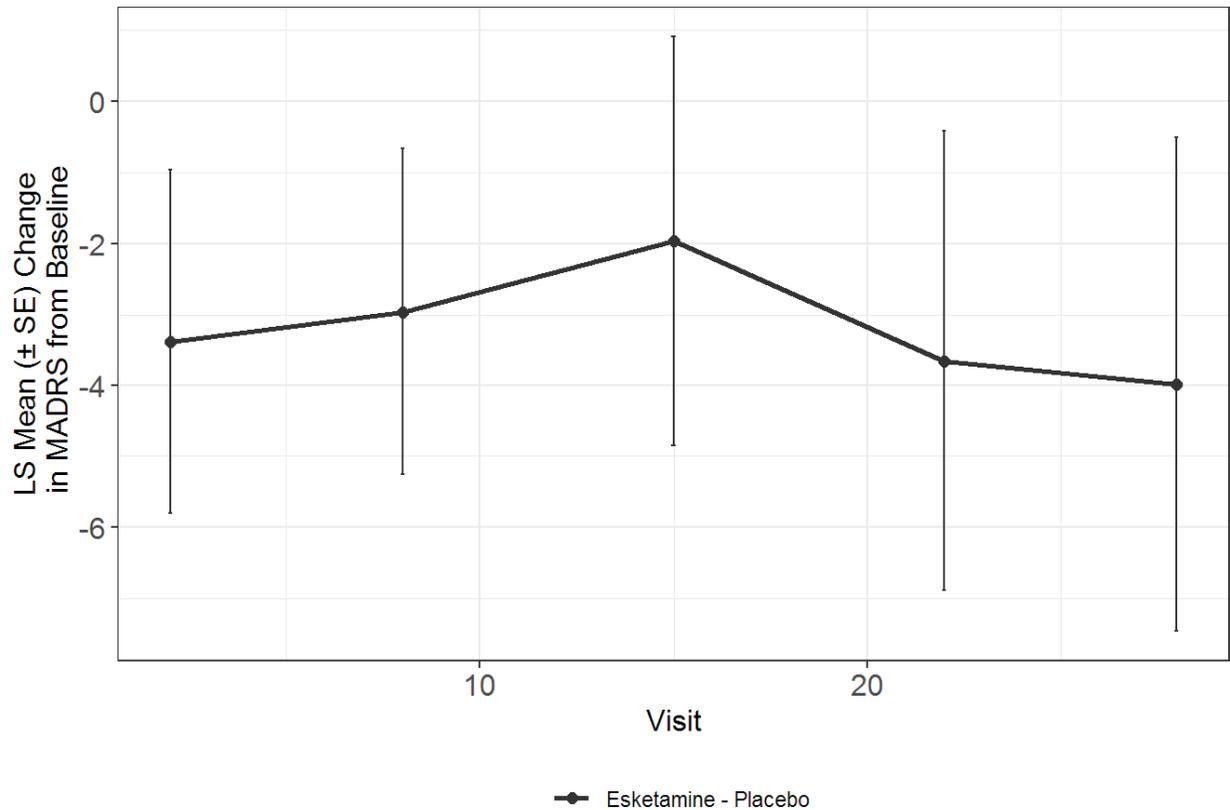
Dose/Dose Response

This study used flexible dosing for IN esketamine, with everyone in the esketamine arm starting at 56 mg on Day 1, and then having the option to increase to 84 mg as of Day 4 based on both efficacy and tolerability, and to sometimes decrease dosing due to tolerability issues at certain timepoints. Accordingly, there is no clear way to compare the efficacy of each dose in this study. An exploratory analysis to stratify efficacy results based on each dose is not feasible per the statistical reviewer, due to each visit having the option to change doses not just due to tolerability but efficacy as well, which makes modeling efficacy expectations difficult via stratification. About 2/3rds of subjects ended up taking 84 mg by Day 28 versus 1/3rd on 56 mg in the esketamine arm. See the Integrated Efficacy Analysis in this review and the statistical review for more details.

Durability of Response

Except for Day 8, there appeared to be a progressive improvement in both treatment groups on the primary endpoint, and many of the secondary endpoints, by Day 28. (See Figure 13 Study 3002 Primary Efficacy Endpoint Results: MADRS Total Score LS Mean Change from Baseline at Week 4 (Day 28).) The effect did not appear to be diminishing at study endpoint, with the effect curve indicating a likely continuation of improvement were the study to have continued for at least a few more weeks. This may correspond in part to the newly initiated oral antidepressant fully taking effect by that time, as expected. However, the esketamine arm also appeared to consistently show a numerically larger effect versus the placebo arm at each visit (although the degree of add-on esketamine effect greater than the placebo arm at each visit timepoint was not increasing, see the figure below). This trend appears to provide evidence that esketamine dosed twice weekly has some additive durability of response combined with an oral antidepressant over several weeks (as opposed to a one-time-only immediate rapid effect), versus treatment with oral antidepressants alone.

Figure 15 Study 3002 Placebo Subtracted LS Mean Change from Baseline in MADRS Total Score



Source: Andrew Potter, PhD, Statistical Reviewer

Persistence of Effect

Subjects in this study were eligible to enroll in Study 3003, a maintenance-of-effect study, which will be reviewed in the next study section and can provide more information on persistence of effect. The other remaining subjects could enter the follow-up study phase up to 24 weeks; while IN study medication was discontinued after Day 28, daily oral antidepressants were to be continued for at least 2 weeks and encouraged to continue throughout the follow-up phase as clinically warranted. Some efficacy results were recorded for the follow-up phase as follows (but only for a small number of subjects, and the follow-up total endpoint included subjects who withdrew early and had shorter drug exposures and is not interpretable):

- MADRS Total Score: mean MADRS Total Score CFB continued to increase in magnitude at the 2-week follow-up visit for subjects previously in the esketamine arm, with -13.3 (11.5). However the n was very small at 15, affecting interpretability of this result. For those previously in the placebo arm, the 2-week visit value was -6.7 (1.3) (n=31).

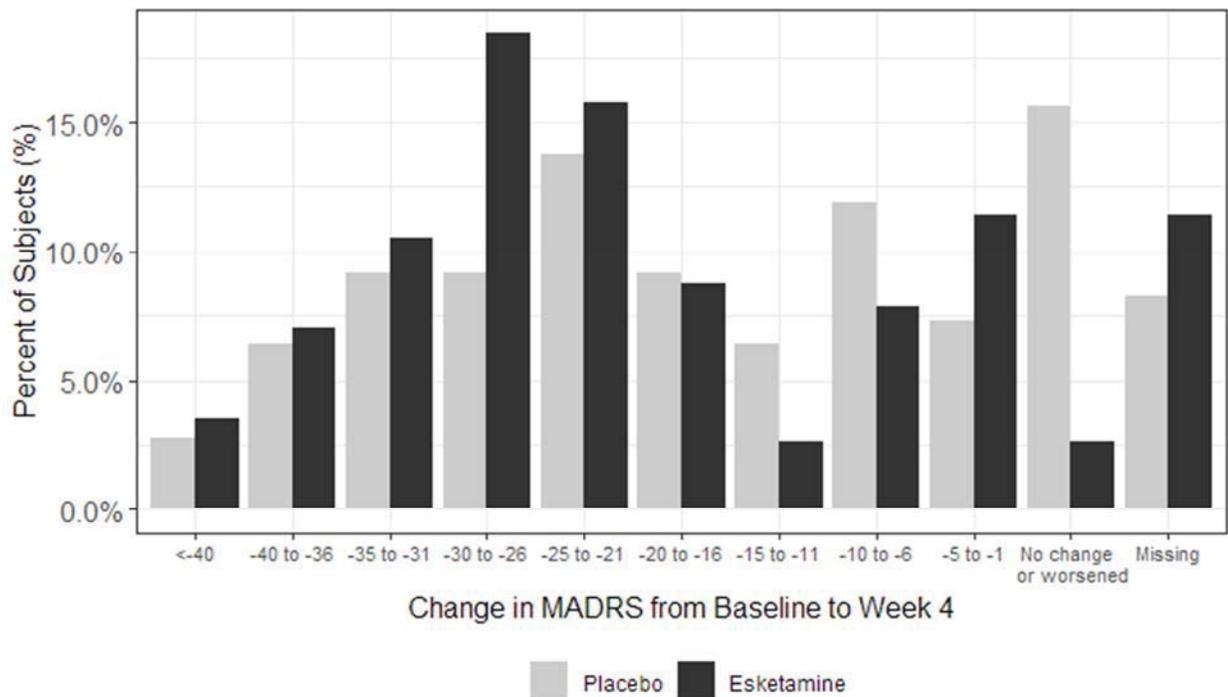
Overall, the significance of these follow-up period results was not interpretable due to small n's, no formal statistical analysis, and unclear exposure time.

Additional Analyses Conducted on the Individual Trial

- Distribution of Response

Distribution of response, as with Study 3001, indicated a trend towards higher magnitudes of change in MADRS total scores for subjects in the esketamine arm versus the placebo arm. In this study, corroborating the primary outcome result, esketamine's superior response to placebo was quite consistent across the score categories, especially the ones with greater decreases in score. This result provides additional supportive evidence that TRD patients may clinically respond robustly to esketamine plus an oral antidepressant and at rates superior to placebo plus an oral antidepressant.

Figure 16 Study 3002 Distribution of Response for MADRS Total Score CFB



Study TRD3002

Source: Andrew Potter, PhD, Statistical Reviewer

6.3. Study 3003 (SUSTAIN-1)

6.3.1. Study Design

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Overview and Objective

A Randomized, Double-Blind, Multicenter, Controlled Study of Intranasal Esketamine plus an Oral Antidepressant for Relapse Prevention in Treatment-Resistant Depression: Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-1)

Trial Design

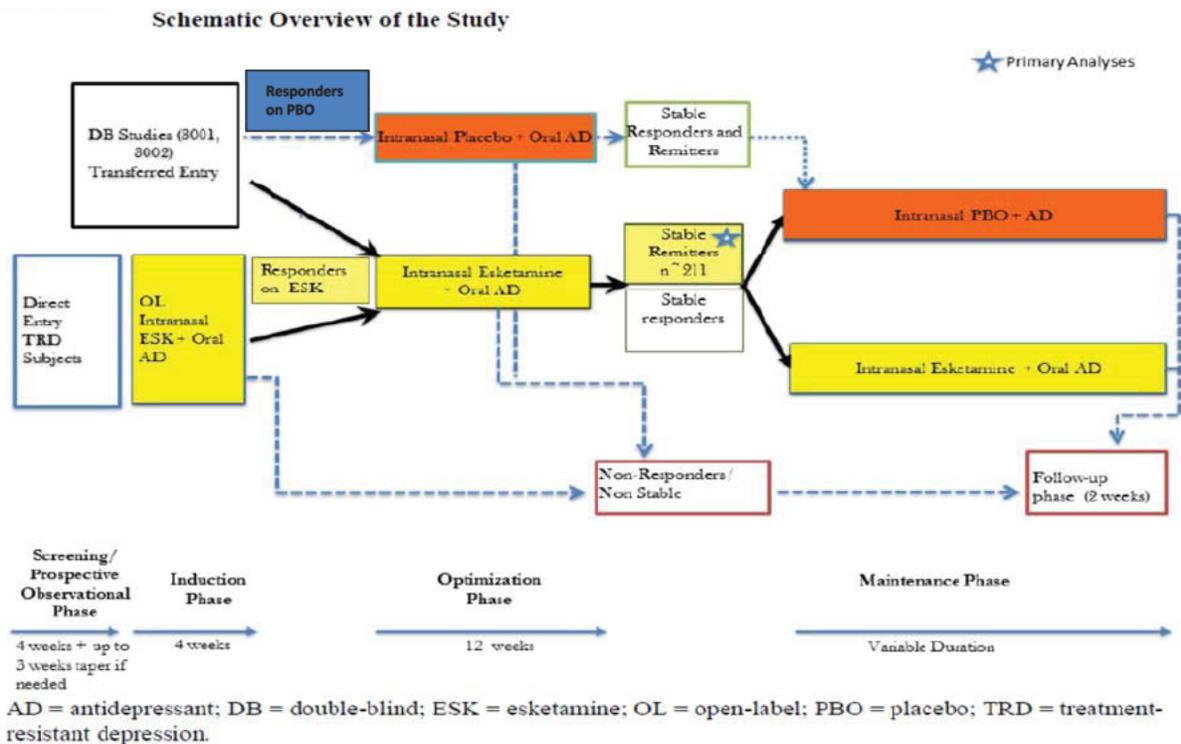
- *Basic study design:*

Study 3003 utilized a randomized withdrawal design to assess whether IN esketamine delays relapse of depressive symptoms over time versus placebo, with oral antidepressant ongoing for both arms, in subjects who reached stable remission or response on esketamine treatment.

The study had five phases:

- Screening/Prospective Observational Phase (direct-entry subjects only): 4 weeks + optional 3-week taper for oral antidepressant
- Open-Label Induction Phase (direct-entry subjects only): 4 weeks. IN treatment twice weekly + newly initiated oral antidepressant.
- Optimization Phase (both direct-entry and transferred-entry subjects): 12 weeks. IN treatment once weekly for first 4 weeks, then once weekly or once every other week based on clinical status. Oral antidepressant ongoing for all subjects.
- Maintenance Phase (both direct-entry and transferred-entry subjects): time to relapse. IN treatment once weekly or once every other week based on clinical status, reassessed every 4 weeks (3 regimen switches permitted, otherwise remained on weekly regimen). Oral antidepressant ongoing for all subjects.
- Follow-Up Phase: 2 weeks (IN treatment ended; oral antidepressant ongoing for all subjects).

Figure 17 Study 3003 Design Schematic



Source: Adapted from Figure 1, CSR Study 3003

The study was to end when a maximum of 84 relapses occurred. An interim analysis was to be performed after 30 relapses. This design permits a blinded comparison of time to depressive relapse for subjects on IN esketamine versus IN placebo, with oral antidepressant ongoing in both arms. A difference would indicate that IN esketamine dosed at least every other week has longer-term maintenance efficacy and may provide additional protection from future depressive relapse than oral antidepressant alone.

- *Choice of Control Group:*

The randomized withdrawal design meant that subjects entering the maintenance phase were randomized in a 1:1 ratio to receive either IN esketamine or IN placebo, with oral antidepressant ongoing. (Transferred-entry subjects continued the same randomization group they entered in Studies 3001 and 3002. Subjects originally randomized to placebo were still continued in the study to maintain blinding but would not be included in the primary analysis population.) The oral antidepressant was also randomly assigned during the induction phase, to one of four choices (escitalopram, sertraline, duloxetine, and venlafaxine XR.)

- *Trial Location:*

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This study was conducted at 164 sites, located in North America, Europe, and Turkey. The sites were: 4 sites in Belgium, 13 sites in Brazil, 2 sites in Canada, 11 sites in Czech Republic, 1 site in Estonia, 5 sites in France, 4 sites in Germany, 12 sites in Hungary, 4 sites in Italy, 6 sites in Mexico, 15 sites in Poland, 3 sites in Slovakia, 10 sites in Spain, 4 sites in Sweden, 54 sites in the US, 16 sites in Turkey. There appears to be adequate US representation in this study.

- *Diagnostic and Key Inclusion/Exclusion Criteria:*

The study population was diagnosed with TRD; see Study 3001, Section 6.1.1 for more details. The other key inclusion and exclusion criteria were generally the same as those for Studies 3001 and 3002.

The subjects who transferred over from Studies 3001 and 3002 must have completed the double-blind induction phase of their study and must have demonstrated response at the end of that phase ($\geq 50\%$ reduction in MADRS total score from baseline (Day 1) to induction phase endpoint (Day 28)). (They were still on either IN esketamine or IN placebo, plus oral antidepressant in both groups.)

For the maintenance phase of Study 3003, subjects had to meet criteria for either stable remission or stable response:

- Stable Remission: MADRS total score ≤ 12 for at least 3 of the last 4 weeks of the optimization phase, with 1 excursion of a MADRS total score > 12 or one missing MADRS assessments permitted at optimization week 13 or 14 only
- Stable Response: $\geq 50\%$ reduction in MADRS total score from baseline (Day 1 of induction phase prior to first IN dose) in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

(There were some adjustments to these criteria midway through the study, including removing the requirement for not missing ≥ 3 MADRS assessments; see the Protocol Amendments section.)

- *Dose Selection:*

See study 3001 for the rationale for selecting 56 mg and 84 mg as the tested doses for IN esketamine. For the direct-entry subjects, subjects underwent flexible dosing in a similar fashion to Study 3002. Doses were to be kept the same from the end of the induction phase throughout the optimization and maintenance phases.

- *Assignment to Treatment and Blinding:*

Transferred subjects from Studies 3001 and 3002 were to maintain the same IN medication assignment and oral antidepressant to maintain those subjects' blinding into the maintenance

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phase. The direct-entry subjects who achieved stable remission after the optimization phase were randomized in a 1:1 ratio at the start of the maintenance phase via computer-generated randomization schedule prepared before the study. (Direct-entry subjects who achieved stable response but not remission also were randomized in a 1:1 ratio via computer-generated randomization schedule.) Both randomizations were balanced using randomly permuted blocks (block size=4) and were stratified by country. The oral antidepressant assignment was also entered into IWRS.

Investigators were not provided with randomization codes, which were only maintained within IWRS. The blind could be broken for emergency situations only.

Of note, there was no additional monitoring or assessment with regard to potential unblinding concerns for both site investigators and subjects with subjects who were switched to placebo from IN esketamine during the maintenance phase. With this study design, there was the potential for both investigators and subjects to notice a change in common side effects and/or adverse events, as placebo would not have esketamine's degree of sedation, dissociation, or blood pressure changes. A subject familiarized with IN esketamine's effects for 16 weeks who is now switched to placebo may notice the difference. At least one protection against unblinding for efficacy assessments was the use of remote independent raters who contacted subjects via telephone to perform MADRS and other assessments. (See further discussion of this issue in the study results section for 3003.)

- *Dose Modification and Discontinuation:*

For direct-entry subjects in the open-label induction phase, IN esketamine started at 56 mg on Day 1, and was subsequently flexibly dosed in the same manner as Study 3002, with an option to increase to 84 mg by Day 4 based on efficacy and tolerability. The dose could be adjusted at subsequent visits between 56 or 84 mg accordingly.

During the optimization phase, direct-entry subjects continued IN esketamine, and transferred-entry subjects continued either IN esketamine or IN placebo as previously assigned in Studies 3001 or 3002. The dose was continued from the dose at the end of their previous study. A remote independent rater performed MADRS assessments weekly. After starting weekly dosing during the first 4 weeks of the optimization phase (Week 5 to Week 8), the MADRS score was used to determine the subsequent dosing frequency, either weekly, or every other week, at Week 8 and Week 12.

- Subjects with a MADRS total score >12 at Week 8 (or the last MADRS total score available) were to continue to receive weekly intranasal 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), frequency of intranasal

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- 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 intranasal 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 subject was to remain on an intranasal treatment session frequency of every other week for the next 4 weeks (i.e., through Week 16).

For the maintenance phase, a remote independent rater continued to assess MADRS scores weekly. The following dosing schedule depended on MADRS score updates:

Subjects who were currently receiving intranasal treatment sessions on a weekly basis stayed at the same weekly intranasal treatment session frequency for the first 4 weeks of this phase. For subjects who were currently receiving intranasal treatment sessions on an every other week basis, if the MADRS total score was >12 at Week 16, the frequency of intranasal treatment sessions was to be increased to weekly for the next 4 weeks. If the MADRS total score was ≤ 12 at Week 16, the subject was to stay at the same every other week intranasal treatment session frequency for the next 4 weeks.

Thereafter, changes to the intranasal 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 three changes in intranasal treatment session frequency from weekly to every other week was permitted during the maintenance phase. After this time, if a given subject was unable to sustain improvement on every other week dosing, they were to remain on a weekly intranasal dosing frequency for the duration of this phase.

No IN medication was administered during the follow-up phase.

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- *Administrative structure:*

An Independent Data Monitoring Committee (IDMC) oversaw the conduct of this study. There was also a Relapse Adjudication Committee (RAC). There were contract research organizations (CRO) involved with the randomization system, (b) (4) and site rater training and qualifications (b) (4); data monitoring (b) (4); independent MADRS rating (b) (4); the interim analysis (b) (4) and medical monitoring (b) (4).

- *Procedures and schedule:*

Please see Section 13.1.3 in the appendices.

- *Dietary Restrictions/Instructions:*

As with Studies 3001 and 3002, subjects were not allowed to eat at least 2 hours before and during intranasal dosing sessions. This precaution was reasonable to prevent nausea or vomiting or aspiration issues.

- *Concurrent medications:*

See Study 3001 for more details. Prior failed oral antidepressants were tapered off during an optional 3-week phase during screening. Prior non-antidepressant therapies administered up to 30 days before the screening phase were recorded at the start of screening.

- *Treatment compliance:*

As with Studies 3001 and 3002, investigators directly observed and recorded all IN doses in the eCRF, and oral antidepressant adherence was assessed using the PAQ. Missing 4 or more days of antidepressant medication in the prior 2-week period was considered inadequate adherence. Pill counts and drug accountability at specified time points were to be performed. Subjects who missed 21 days or more of their oral antidepressant in the optimization phase were not eligible to continue into the maintenance phase.

- *Rescue medication:*

See Study 3001.

- *Subject completion, discontinuation, or withdrawal:*

See Study 3001.

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Study Endpoints

The primary efficacy endpoint was time to relapse between subject randomization into the maintenance phase and first documentation of a relapse event, in subjects who were in stable remission at the end of the optimization phase after IN esketamine + oral antidepressant. Relapse was defined as MADRS Total Score ≥ 22 for 2 consecutive assessments separated by 5 to 15 days and/or hospitalization for worsening depression or other clinically relevant event per clinical judgment (i.e., suicide attempt, completed suicide, etc.) For clinically relevant events that occurred without meeting the score cutoff or hospitalization criteria, a relapse adjudication committee (RAC) reviewed those cases to determine if it was a relapse.

Other secondary endpoints measured were PHQ-9, SDS, CGI-S, GAD-7, EQ-5D-5L. See prior studies for list of safety endpoints. Other exploratory endpoints included HRUQ and biomarker relationships to depressive episode response to treatment.

Statistical Analysis Plan

The maximum number of relapses in subjects with stable remission required by this study was 84, which would provide 90% power to detect a hazard ratio of 0.493 at the 1-sided significance level of 0.025 for a fixed-sample design to detect superiority of the esketamine group versus the placebo group on the primary endpoint. The sample size calculation assumed that time to first relapse follows an exponential distribution, with a median time of 6 months for the placebo arm and 12.17 months for the esketamine arm. The corresponding 6-month relapse rates are 50% for the placebo group and 28.95% for the esketamine group.

Assumptions were made for accrual period and rate, maximum study duration, and dropout rate. Based on these assumptions, a total of approximately 211 subjects in stable remission needed to be randomized (in a 1:1 ratio) in order to obtain 84 relapses.

An interim analysis (IA) was to be performed to evaluate these assumptions during the study. The relapse rates were to be monitored sequentially during the maintenance phase, using a 2-stage group sequential design. One IA was to be performed when at least 33 relapse events occurred in stable remitters (with at least 30 relapses in the esketamine group, signaled by IWRS notification). If 33 relapses occurred without IWRS notification, the IA timing would be reassessed at every third relapse, to maintain the blind for transferred-entry subjects. Early termination of the maintenance phase for efficacy would be based on IA results. If the IA determined that the study was not to be stopped for efficacy, a sample size re-estimation was to be performed to ensure a conditional power of stage 2 of at least 90% with a minimum number of relapses after interim of 29 and maximum after interim of 54.

Protocol Amendments

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There were four global protocol amendments. The first (April 21, 2015) occurred before any subject enrollment, and the others occurred during the study (January 13, 2016; June 9, 2016; and April 4, 2017). Amendment 2 was instituted after 94 subjects were enrolled. Amendment 3 was instituted after 188 subjects were enrolled. Amendment 4 was instituted after 680 subjects were enrolled.

Amendment 2 and 3 added inclusion and exclusion criteria generally aligning with amendments for Studies 3001 and 3002 (such as inclusion of subjects failing only one antidepressant before screening but having started the second for at least 2 weeks before screening). Amendment 3 also clarified some parameters around stable response during the optimization phase for this study (i.e., $\geq 50\%$ reduction on MADRS total score from baseline in each of last 2 weeks of optimization phase, with at least one MADRS total score >12 in those 2 weeks). Amendment 4 further modified and clarified stable remission and response criteria during the optimization phase as follows:

- The definition of stable remission was revised from a MADRS total score ≤ 12 to a MADRS total score ≤ 12 for at least 3 of the last 4 weeks of the optimization phase, but with one excursion of a MADRS total score >12 or one missing MADRS assessment permitted at Optimization Week 13 or 14 (only); a MADRS total score of ≤ 12 at Weeks 15 and 16 was still required to be considered a stable remitter.
- The definition of stable response was revised, broadening it to include subjects that have $\geq 50\%$ reduction in the MADRS total score from baseline (Day 1 of induction phase; pre-randomization/prior to the first intranasal dose) in each of the last 2 weeks of the optimization phase, but who do not meet criteria for stable remission.
- Missing ≥ 3 MADRS assessments during Weeks 5 to 12 of the optimization phase was deleted from the determination of a subject's eligibility to participate in the maintenance phase of the study.
- Clarification was made that subjects in the optimization phase at the time the study closes were not required to complete the phase.

Other minor adjustments were made to dose adjustment criteria during the open-label induction phase and follow-up completion requirements. Modafinil and armodafinil were deleted as permitted medications during the study due to being potent CYP3A4 inducers.

It is unclear what overall effect on the study the later amendments would have had, given the high enrollment already in the study when these amendments were implemented. The number of subjects affected will be examined in the following section.

6.3.2. Study Results

Compliance with Good Clinical Practices

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The Applicant provided attestation that this study was conducted in accordance with good clinical practice (GCP) as per CFR requirements.

Financial Disclosure

There are no major concerns. See Appendix 13.2 for more details.

Patient Disposition

A total of 1097 subjects were screened for this study across 164 sites in 16 countries (Belgium, Brazil, Canada, Czech Republic, Estonia, France, Germany, Hungary, Italy, Mexico, Poland, Slovakia, Spain, Sweden, Turkey, and the US). 378 subjects were screen failures and 14 from one site with GCP violations (PL10002) were later excluded. There were 705 total enrolled subjects, with 437 from direct-entry and 268 transferred-entry from Studies 3001 (150 subjects: 112 esketamine arm and 38 placebo arm) and 3002 (118 subjects: 70 esketamine arm and 48 placebo arm).

Transferred-entry subjects originally in the placebo + oral antidepressant arm were not included in the efficacy analysis population but were included in the safety population. The total population of both direct-entry and transferred-entry subjects originally on IN esketamine was 455 subjects, with 175 meeting criteria for stable remission and 124 for stable response after the optimization phase (as per CSR page 87). These 299 subjects were initially due to enter the randomized withdrawal maintenance phase (although the Safety Maintenance Population is listed as 297 subjects; see explanation below).

The primary efficacy analysis was performed on the Full Analysis stable remitter population (175 subjects plus 1 direct-entry stable responder who was incorrectly randomized as a stable remitter, for 176 total). The Full Analysis stable responder population is listed as 121 subjects out of the original 124.

The Applicant later explained in an Information Request Response (Nov. 13, 2018) that there were three stable responder subjects who were discontinued at their sites before being randomized into the maintenance phase:

“These 3 subjects are listed below:

1. **ESKETINTRD3001**-^{(b) (6)}; Discontinuation reason was “Other” with the explanation “the site in error misunderstood and thought the subject was not eligible to proceed when in fact she was eligible.”

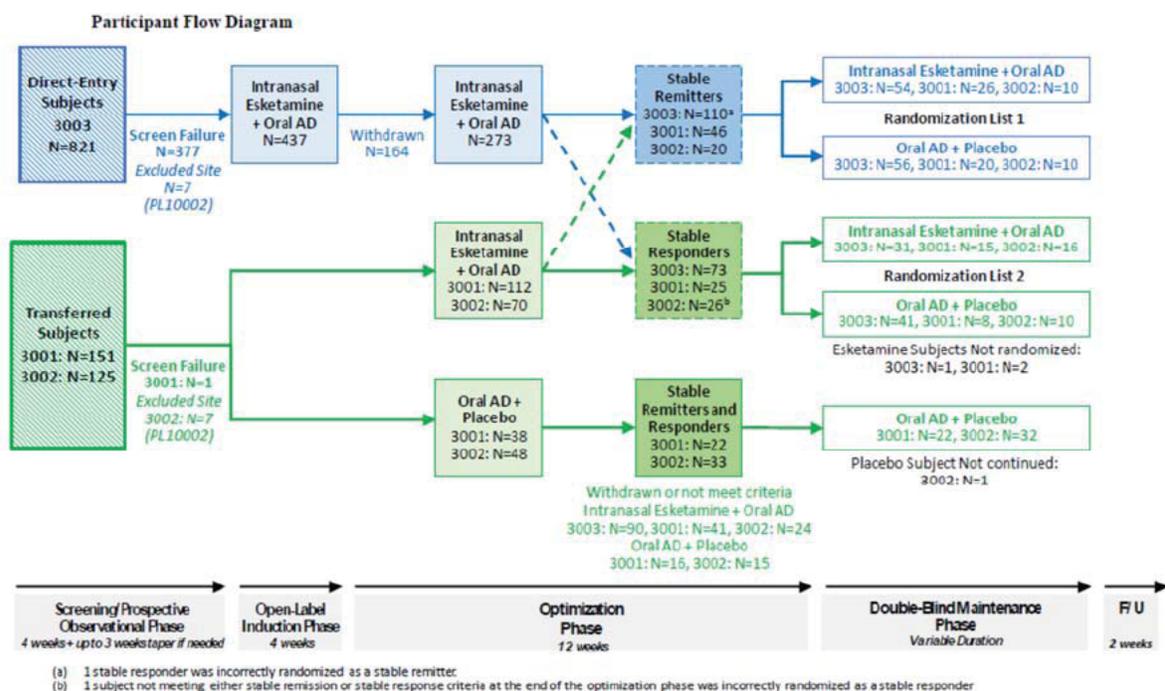
2. **ESKETINTRD3001**-^{(b) (6)}; Discontinuation reason was “MADRS total score ≥ 22 for 2 consecutive assessments separated by 5 to 15 days” during the Optimization Phase. The subject had MADRS total score of ≥ 22 only on one visit (OP week 8) and was discontinued

in error by site due to misunderstanding of the protocol which required 2 consecutive visits.

3. **ESKETINTRD3003** (b) (6) Discontinuation reason was “adverse event.” This subject had an adverse event of tinnitus (mild severity), starting on Day 82 of optimization phase, and was withdrawn from the Optimization Phase on Day 108 as the adverse event had not resolved. It was reported to have resolved after discontinuation of esketamine and duloxetine. Day 82 and 108 are relative to the study start date.

Additionally, 1 stable responder was incorrectly randomized as a stable remitter (Subject **ESKETINTRD3003**- (b) (6)) and 1 subject was randomized as a stable responder but did not meet the criteria for either stable response or stable remission (Subject **ESKETINTRD3002**- (b) (6)).”

Figure 18 Study 3003 Patient Disposition



Source: Figure 2, CSR Study 3003

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Table 33 Study 3003 Subjects in Each Phase

Number of Subjects in Each Phase and Analysis Set (Study ESKETINTRD3003: All Enrolled Analysis Set)			
	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo	Total
Open-label induction phase			
Full (IND)	430	N/A	430
Safety (IND)	437	N/A	437
Optimization phase			
Full (OP)	452	0	452
Safety (OP)	455	0	455
Safety transfer-entry placebo (OP_TEP) (a)	0	86	86
Maintenance phase			
Interim full (stable remitters) (b)	49	47	96
Full (stable remitters)	90	86	176
Full (stable responders)	62	59	121
Safety (MA)	152	145	297
Safety (stable remitters)	90	86	176
Safety transfer-entry placebo (MA_TEP) (a)	0	54	54
Follow-up phase			
Follow-up	481	64	545

Source: Table 6, CSR Study 3003

Subject withdrawals during each phase (excluding Studies 3001 and 3002 phases) were as follows:

Table 34 Study 3003 Subject Withdrawals for Each Phase

Study Completion/Withdrawal Information; Open-label Induction Phase (Study ESKETINTRD3003: Safety (IND) Analysis Set)	
	Intranasal Esk + Oral AD (N=437)
Continued to optimization phase	273 (62.5%)
Withdrawn during open-label induction phase	164 (37.5%)
Adverse event	22 (5.0%)
Lack of efficacy	2 (0.5%)
Lost to follow-up	1 (0.2%)
Protocol violation	2 (0.5%)
Withdrawal by subject	15 (3.4%)
Other	8 (1.8%)
Subject does not meet criteria for continuing into the next phase	114 (26.1%)

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Study Completion/Withdrawal Information; Optimization Phase (Study ESKETINTRD3003: Safety (OP) Analysis Set)

	Intranasal Esk + Oral AD (N=455)
Continued to maintenance phase	297 (65.3%)
Withdrawn during optimization phase	158 (34.7%)
Adverse event	5 (1.1%)
Lack of efficacy	8 (1.8%)
Lost to follow-up	2 (0.4%)
MADRS total score \geq 22 for 2 consecutive visit (a)	14 (3.1%)
Protocol violation	4 (0.9%)
Withdrawal by subject	8 (1.8%)
Other	10 (2.2%)
Subject does not meet criteria for continuing into the next phase	107 (23.5%)
Subject does not meet criteria for stable remission or stable response	106 (23.3%)
Subject missed \geq 3 MADRS assessments (b)	1 (0.2%)

Study Completion/Withdrawal Information; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
Completed maintenance phase	82 (91.1%)	77 (89.5%)	159 (90.3%)
Subjects who relapsed	24 (26.7%)	39 (45.3%)	63 (35.8%)
Subjects who completed maintenance phase due to study termination (a)	58 (64.4%)	38 (44.2%)	96 (54.5%)
Withdrawn during maintenance phase	8 (8.9%)	9 (10.5%)	17 (9.7%)
Adverse event	1 (1.1%)	1 (1.2%)	2 (1.1%)
Pregnancy	1 (1.1%)	0	1 (0.6%)
Withdrawal by subject	3 (3.3%)	3 (3.5%)	6 (3.4%)
Other	3 (3.3%)	5 (5.8%)	8 (4.5%)

(a) Subjects were considered completers if they were relapse free at the time of the study termination

Source: Tables 7, 8, 9 in CSR Study 3003

The withdrawals during direct-entry treatment phases were mainly due to not achieving adequate response and therefore not meeting prespecified criteria for entry into the next phase (26% during the open-label induction phase, and 23% during the optimization phase). For entry into the optimization phase, subjects had to meet responder criteria (\geq 50% reduction from baseline in MADRS total score). For entry into the maintenance phase, subjects had to meet criteria for either stable remission or stable response (see previous inclusion criteria section) and also could not have missed \geq 3 MADRS assessments.

For the maintenance phase, there were no predominant reasons for subject withdrawal (the highest reason was "other" at 4.5%), with about 10% of subjects leaving early.

About 75% of all enrolled subjects (532 of 705 subjects) completed the study and entered the 2-week follow-up phase.

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Table 35 Study 3003 Withdrawals in Follow-Up Phase

Study Completion/Withdrawal Information; Follow-up Phase (Study ESKETINTRD3003: Follow-up Analysis Set)			
	Intranasal Esk + Oral AD (N=481)	Oral AD + Intranasal Placebo (N=64)	Total (N=545)
Completed	470 (97.7%)	62 (96.9%)	532 (97.6%)
Withdrawn	11 (2.3%)	2 (3.1%)	13 (2.4%)
Lost to follow-up	1 (0.2%)	0	1 (0.2%)
Pi decision to discontinue fu and proceed to 54135419trd3008	5 (1.0%)	1 (1.6%)	6 (1.1%)
Withdrawal by subject	3 (0.6%)	0	3 (0.6%)
Other	2 (0.4%)	1 (1.6%)	3 (0.6%)

Source: Table 10, CSR Study 3003

Overall there are no clear trends or unexpected reasons for subject withdrawal in this study. The number of misrandomized subjects was too low to have significantly impacted overall efficacy results.

Protocol Violations/Deviations

There were 90 out of 705 (13%) enrolled subjects who reported one or more major protocol deviations. Of those, 52 involved entry criteria-related deviations, with 47 ending up enrolled in this study despite not satisfying certain entry criteria. Criteria that were not followed involved a wide range of issues including: 16 subjects who did not meet oral antidepressant treatment criteria, required documentation, or MGH-ATRQ compliance criteria; seven subjects who did not meet (b) (4) 20 subjects who did not meet clinical laboratory, ECG, HTN, or other medical criteria; four subjects who did not demonstrate response after completing Studies 3001 or 3002; and more.

Table 36 Study 3003 Major Protocol Deviations

Major Protocol Deviations (Study ESKETINTRD3003: All Enrolled Analysis Set)	
	Total (N=705)
No. of subjects with protocol deviations	90 (12.8%)
Developed withdrawal criteria but not withdrawn	8 (1.1%)
Entered but did not satisfy criteria	47 (6.7%)
Received a disallowed concomitant treatment	5 (0.7%)
Received wrong treatment or incorrect dose	21 (3.0%)
Other	15 (2.1%)

Source: Table 13, CSR Study 3003

For the maintenance phase, the number and type of major protocol deviations was not

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significantly imbalanced between treatment arms, for either the stable remitter or stable responder groups. These deviations were unlikely to have majorly affected primary endpoint efficacy results.

Table 37 Study 3003 Major Protocol Deviations in Stable Remitters vs. Responders

TSIDEM04A_3003: Major Protocol Deviations (Study ESKE TINTRD3003: Full (Stable Remitters) Analysis Set)			
	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
No. of subjects with protocol deviations	8 (8.9%)	6 (7.0%)	14 (8.0%)
Developed withdrawal criteria but not withdrawn	1 (1.1%)	0	1 (0.6%)
Entered but did not satisfy criteria	2 (2.2%)	3 (3.5%)	5 (2.8%)
Received a disallowed concomitant treatment	0	1 (1.2%)	1 (0.6%)
Received wrong treatment or incorrect dose	3 (3.3%)	3 (3.5%)	6 (3.4%)
Other	2 (2.2%)	1 (1.2%)	3 (1.7%)

TSIDEM04B_3003: Major Protocol Deviations (Study ESKE TINTRD3003: Full (Stable Responders) Analysis Set)			
	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)	Total (N=121)
No. of subjects with protocol deviations	5 (8.1%)	7 (11.9%)	12 (9.9%)
Developed withdrawal criteria but not withdrawn	1 (1.6%)	0	1 (0.8%)
Entered but did not satisfy criteria	4 (6.5%)	5 (8.5%)	9 (7.4%)
Received wrong treatment or incorrect dose	0	2 (3.4%)	2 (1.7%)

Source: Response to FDA Information Request; November 13, 2018

Table of Demographic Characteristics

The demographic characteristics of each randomized arm of the maintenance stable remitters population (used for the primary efficacy analysis) were generally similar, and also similar to the original all-enrolled population for Study 3003. As with Studies 3001 and 3002, the majority of subjects tended to be middle-aged, white, overweight to obese females. Most subjects were in Europe (58%) with about 23% US representation (30% North American).

Table 38 Study 3003 Demographic Characteristics of the Primary Efficacy Analysis

Demographic Parameters	All Enrolled Group (N=705) n (%)	Maintenance Group: Stable Remitters (FA Pop'n for Primary Endpoint)		
		Esketamine +Oral AD (N=90) n (%)	Placebo +Oral AD (N=86) n (%)	Total Stable Remitters (N=176) n (%)
Sex				
Male	248 (35%)	32 (36%)	27 (31%)	59 (34%)

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Demographic Parameters	All Enrolled Group (N=705) n (%)	Maintenance Group: Stable Remitters (FA Pop'n for Primary Endpoint)		
		Esketamine +Oral AD (N=90) n (%)	Placebo +Oral AD (N=86) n (%)	Total Stable Remitters (N=176) n (%)
Female	457 (65%)	58 (64%)	59 (67%)	117 (67%)
Age				
Mean years (SD)	46.1 (11.1)	45.4 (12.1)	46.2 (11.2)	45.8 (11.6)
Median (years)	47.0	47.5	45.0	46.5
Min, max (years)	(18; 64)	(19; 64)	(19; 64)	(19; 64)
Age Group				
18 to 44 years	292 (41%)	38 (42%)	37 (43%)	75 (43%)
45 to 64 years	413 (59%)	52 (58%)	49 (57%)	101 (57%)
Race				
White	635 (90%)	80 (89%)	76 (88%)	156 (89%)
Black or African American	31 (4.4%)	4 (4.4%)	6 (7.0%)	10 (5.7%)
Asian	3 (0.4%)	0	0	0
American Indian or Alaska Native	1 (0.1%)	0	1 (1.2%)	1 (0.6%)
Multiple	4 (0.6%)	1 (1.1%)	0	1 (0.6%)
Other	22 (3.1%)	2 (2.2%)	1 (1.2%)	3 (1.7%)
Ethnicity				
Hispanic or Latino	94 (13%)	14 (16%)	12 (14%)	26 (15%)
Not Hispanic or Latino	600 (85%)	73 (81%)	72 (84%)	145 (82%)
Not Reported/Unknown	11 (1.5%)	3 (3.3%)	2 (2.3%)	5 (2.8%)
Region				
United States	190 (27%)	21 (23%)	20 (23%)	41 (23%)
Rest of the World	515 (73%)			
Canada	5 (0.7%)	1 (1.1%)	0	1 (0.6%)
Brazil	64 (9.1%)	11 (12%)	11 (13%)	22 (13%)
Mexico	35 (5.0%)	5 (5.6%)	5 (5.8%)	10 (5.7%)
Europe	411 (58%)	52 (58%)	50 (58%)	102 (58%)
Belgium	14 (2.0%)	1 (1.1%)	1 (1.2%)	2 (1.1%)
Czech Republic	99 (14%)	14 (16%)	14 (16%)	28 (16%)
Estonia	1 (0.1%)	0	0	0
France	10 (1.4%)	3 (3.3%)	3 (3.5%)	6 (3.4%)
Germany	7 (1.0%)	0	1 (1.2%)	1 (0.6%)
Hungary	35 (5.0%)	2 (2.2%)	2 (2.3%)	4 (2.3%)
Italy	21 (3.0%)	2 (2.2%)	1 (1.2%)	3 (1.7%)
Poland	132 (19%)	19 (21%)	18 (21%)	37 (21%)
Spain	16 (2.3%)	2 (2.2%)	3 (3.5%)	5 (2.8%)
Slovakia	7 (1.0%)	2 (2.2%)	1 (1.2%)	3 (1.7%)

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Demographic Parameters	All Enrolled Group (N=705) n (%)	Maintenance Group: Stable Remitters (FA Pop'n for Primary Endpoint)		
		Esketamine +Oral AD (N=90) n (%)	Placebo +Oral AD (N=86) n (%)	Total Stable Remitters (N=176) n (%)
Sweden	16 (2.3%)	3 (3.3%)	3 (3.5%)	6 (3.4%)
Turkey	53 (7.5%)	4 (4.4%)	3 (3.5%)	7 (4.0%)
BMI				
Underweight <18.5	6 (0.9%)	2 (2.2%)	0	2 (1.1%)
Normal 18.5 to <25	195 (28%)	19 (21%)	18 (21%)	37 (21%)
Overweight 25 to <30	259 (37%)	32 (36%)	33 (38%)	65 (37%)
Obese 30 to <40	212 (30%)	33 (37%)	30 (35%)	63 (36%)
Morbidly Obese ≥40	33 (4.7%)	4 (4.4%)	5 (5.8%)	9 (5.1%)
HTN Status				
Yes	147 (21%)	23 (26%)	19 (22%)	42 (24%)
No	558 (79%)	67 (74%)	67 (78%)	134 (76%)
Antidepressant Class/Type				
SNRI	440 (63%)	62 (69%)	58 (67%)	120 (68%)
SSRI	259 (37%)	28 (31%)	28 (33%)	56 (32%)
Duloxetine	323 (46%)	47 (52%)	38 (44%)	85 (48%)
Escitalopram	128 (18%)	13 (14%)	14 (16%)	27 (15%)
Sertraline	130 (19%)	15 (17%)	14 (16%)	29 (17%)
Venlafaxine XR	118 (17%)	15 (17%)	20 (23%)	35 (20%)

The stable responders who were randomized in the maintenance phase also displayed a generally even distribution of demographic characteristics between treatment arms. (The stable responders group (n=121) had 62 subjects randomized to the esketamine arm and 59 subjects randomized to the placebo arm.) There was a slightly higher percentage of males in the esketamine arm (39%) versus the placebo arm (29%).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

For the full analysis (FA) stable remitters group from the maintenance phase (N=176), the baseline psychiatric characteristics were generally similar between treatment groups. The mean MADRS total score was 37.5 (4.93). For subjects who had failed three or more prior antidepressants, the esketamine arm had 21% versus 26% in the placebo arm.

For the FA stable responders group (N=121), the baseline MADRS score was higher at 39.5 (5.27) which might partly explain why, being a more severely depressed population at baseline, these subjects were responders versus remitters. The baseline psychiatric characteristics for this group was also generally even between treatment arms, although trending towards slightly more illness severity in the esketamine arm versus the placebo arm on multiple indices (i.e., mean baseline MADRS score was 40.1 in the esketamine arm versus 38.9 in the placebo arm). There was also a slightly higher rate of suicidal ideation and behavior (SI/B) lifetime history in the esketamine arm (42%) versus the placebo arm (34%), and also a slightly higher rate of SI events in the last 6 months in the esketamine arm (32%) versus the placebo arm (24%). (However, for subjects who had failed 3 or more prior antidepressants, the esketamine arm had 34% versus 42% in the placebo arm.) The slight trend towards more illness severity in the esketamine arm for this stable responder group might reflect one reason why this group was not as responsive to esketamine as the stable remitters, after undergoing the initial induction and optimization phases.

For the stable remitters group, a higher percentage of the esketamine arm came into the maintenance phase on every other week dosing (59%) versus the placebo arm (52%), as opposed to weekly dosing. For the stable responders group, the opposite was the case, with the esketamine group having 16% on every other week dosing versus 27% for the placebo group. (This data indicates that the majority of the stable responders group was getting more frequent dosing (i.e., weekly), as per protocol for less treatment response.)

On Day 1 of the maintenance phase, 40 out of 90 stable remitters (44%) were receiving esketamine 56 mg, and 50 out of 90 (56%) were on esketamine 84 mg. For stable responders, 20 out of 62 (32%) were initially on esketamine 56 mg, and 41 out of 62 (66%) were on 84 mg.

In terms of subject origination from direct-entry (3003 open-label) versus transferred-entry (3001 and 3002) phases, 62% (110 subjects) of stable remitter subjects came from direct-entry and 38% (66) from transferred-entry. For stable responders, 65% (72) came from direct-entry and 35% (39) from transferred entry. The distribution across treatment arms was generally consistent. (Stable Remitters: 54 direct-entry and 36 transferred-entry on esketamine and 56 direct-entry and 30 transferred-entry on placebo; Stable Responders: 31 direct-entry and 21 transferred-entry on esketamine and 41 direct-entry and 18 transferred-entry on placebo.)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- Treatment Compliance:

Due to the randomized withdrawal design, with time to relapse as the study endpoint, exposure duration comparisons between treatment arms naturally varied and would not provide meaningful information on compliance differences between groups during the maintenance phase. (The mean total duration for the IN esketamine arm was 22.0 weeks (18.0) and for the IN placebo arm was 14.9 weeks (15.1).) Also, the prior phases were open-label for the direct-entry subjects, so no comparative exposure data is available for those phases.

The data on total number of days dosed during the maintenance phase for both groups indicates the esketamine arm received more days of IN dosing than the placebo arm (because the subjects in the esketamine arm on average stayed longer in the study than those on placebo).

Table 39 Study 3003 Esketamine Exposure Days (Stable Remitters and Stable Responders)

TSIEXPE07E: Number of Days Dosed with Intranasal Study Medication; Maintenance Phase (Study ESKE TINTRD3003: Full (Stable Remitters) Analysis Set)		
	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)
Number of days dosed		
1-7	27 (30.0%)	43 (50.0%)
8-14	31 (34.4%)	20 (23.3%)
15-21	14 (15.6%)	11 (12.8%)
22-28	10 (11.1%)	7 (8.1%)
29-35	5 (5.6%)	3 (3.5%)
36-42	2 (2.2%)	1 (1.2%)
64-70	1 (1.1%)	1 (1.2%)

TSIEXPE07F: Number of Days Dosed with Intranasal Study Medication; Maintenance Phase (Study ESKE TINTRD3003: Full (Stable Responders) Analysis Set)		
	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)
Number of days dosed		
1-7	16 (25.8%)	27 (45.8%)
8-14	15 (24.2%)	15 (25.4%)
15-21	10 (16.1%)	8 (13.6%)
22-28	9 (14.5%)	6 (10.2%)
29-35	7 (11.3%)	3 (5.1%)
36-42	2 (3.2%)	0
57-63	1 (1.6%)	0
71-77	1 (1.6%)	0
85-91	1 (1.6%)	0

Source: Response to FDA Information Request; November 13, 2018

For the oral antidepressant, again, a meaningful comparison between treatment arms for treatment compliance using exposure time is not possible, because of the varying times to

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relapse for each arm. Similar issues would arise with a PK comparison, although that was not available.

- Concomitant Medications:

For prior antidepressants, venlafaxine was the most common one taken in the current depressive episode by direct-entry subjects in the safety population for the induction phase (41%) followed by escitalopram (33%).

During the open-label induction phase, 81% of safety population subjects reported using concomitant medications, with alprazolam (11%) the most common one followed by levothyroxine (10%). During the optimization phase, 82% reported concomitant medications, with the most common ones being clonazepam (13%), ibuprofen (13%), levothyroxine (11%), and alprazolam (9%). During the maintenance phase, 82% reported concomitant medications, with the most common ones being ibuprofen (14%), acetaminophen (13%), clonazepam (10%), levothyroxine (10%), alprazolam (8%), lorazepam (6%), and zolpidem (6%). (For stable remitters in the maintenance phase, 83% in the esketamine arm used concomitant medications versus 79% in the placebo arm. For stable responders, 79% used in the esketamine arm and 86% in the placebo arm.)

These percentages appear generally similar to the rates of concomitant medication use in the other studies.

One concern during the maintenance phase is a higher number of subjects who started or took additional antidepressant medications in the esketamine arm versus the placebo arm (11/152 (7.2%) versus 1/145 (0.7%)). However, all but 2 of these medications were administered at the very end of the maintenance phase (likely in the context of starting post-study treatment), so they were unlikely to have confounded the study results.

For the total maintenance phase group, there was also a slightly higher number of subjects on benzodiazepines, anxiolytics, benzodiazepine-related medications, and centrally-acting medications in the esketamine arm versus the placebo arm (30/152 (20%) versus 22/145 (15%)). However, when looking at stable remitter and stable responder groups specifically, the distribution showed no major discrepancy between treatment arms. For the maintenance phase with stable remitters, the distribution of the most commonly used sedative-hypnotic medications was similar across treatment arms, with 26% on clonazepam, alprazolam, lorazepam, and zolpidem in the esketamine arm and 31% in the placebo arm. For stable responders, it was 34% in both arms.

- Rescue Medication:

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During the open-label induction phase, 21% (92/437) of subjects used medication to treat an AE. During the optimization phase, 30% (138/455) used medication to treat an AE.

The following were the number of subjects during the open-label induction phase who required medication to treat specific AEs of interest: anxiety AEs (3.2%: 14/437), depression AEs (including irritability, crying) (5.3%: 23/437), suicidal ideation AEs (0.9%: 4/437), regressive behavior/agitation/akathisia/disorientation (0.9%: 4/437), BP/HTN (2.5%: 11/437).

The following were the number of subjects during the open-label optimization phase who required medication to treat specific AEs of interest: anxiety AEs (4.2%: 19/455), BP/HTN (3.3%: 15/455), nausea/vomiting/motion sickness (2.9%: 13/455). There were no medications used for depression or agitation or dissociative AEs in this phase.

For all subjects in the maintenance phase, 36% (54/152) of subjects in the esketamine arm used medication to treat an AE versus 27% (39/145) in the placebo arm. (Of note, in this phase esketamine dosing is only weekly or every other week in the esketamine arm, and oral AD is ongoing in both arms.) While the rates of rescue medication use were higher in the esketamine versus the placebo arm for this phase of the study, usage was low overall and unlikely to have affected study efficacy results.

Table 40 Study 3003 Subjects Who Used Medication for AEs of Interest During Maintenance Phase

AE	Esketamine+Oral AD (N=152)	Placebo+Oral AD (N=145)
Anxiety/Panic Attack	5.3%	3.4%
BP Increased/HTN	1.3%	0
Dissociation	0.7%	0
Nausea/Vomiting	0.7%	0
Depression	5.9%	0.7%

Source: Applicant Response to IR, November 12, 2018

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the difference in time to relapse between two groups of stable remitters during the maintenance phase, those who were re-randomized at the start of the maintenance phase to receive IN esketamine versus those on IN placebo, with oral antidepressant ongoing in both arms. Subjects had to have received at least one dose of IN study drug and one dose of oral antidepressant during the maintenance phase to be included in the FA set. (Transferred-entry subjects who were originally on IN placebo during the previous phases and continued into the maintenance phase were not included in the FA set.)

The primary analysis was statistically significant for a longer time to relapse in subjects

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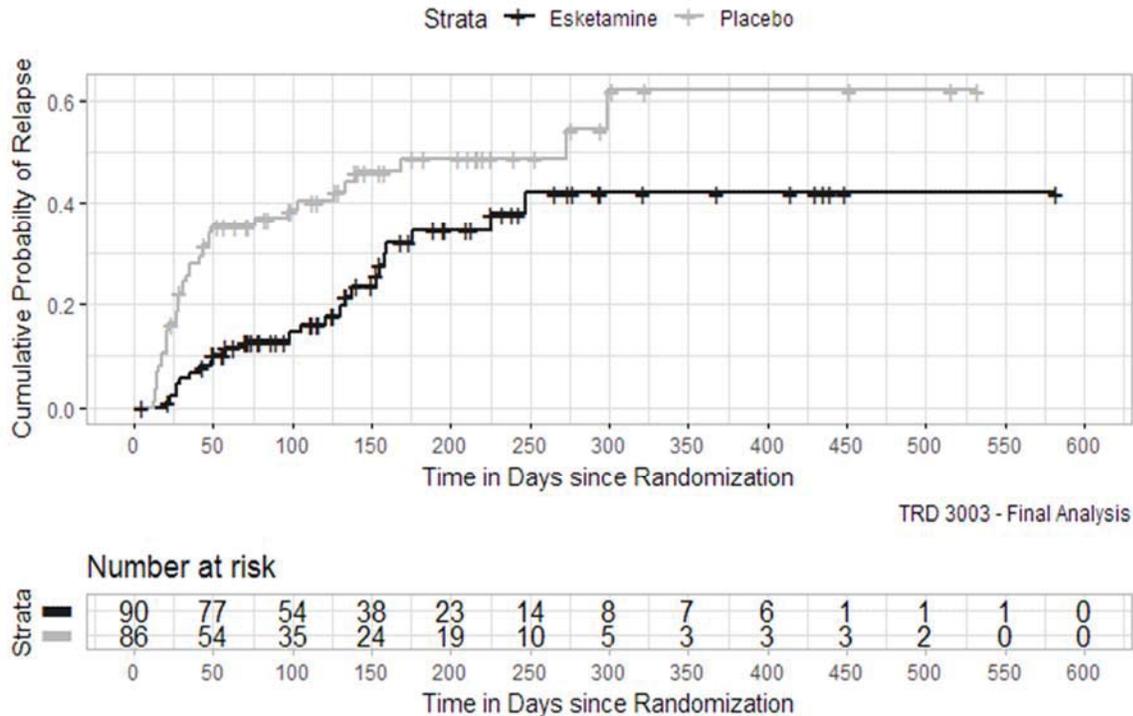
randomized to continue esketamine versus those randomized to placebo (discontinuation of previous esketamine), at a 2-sided p-value of 0.003. The analysis examined the summary statistic of the hazard ratio, using a weighted combination log-rank test. The number of subjects who relapsed during the maintenance phase was 24 (27%) in the esketamine group versus 39 (45%) in the placebo group. The estimated hazard ratio of the esketamine group relative to the placebo group was 0.49 (95% CI: 0.29 to 0.84). The most common reason for relapse was a MADRS total score ≥ 22 for two consecutive assessments separated by 5 to 15 days. Almost half the relapses in the placebo arm occurred in the first 4 weeks of the maintenance phase.

Table 41 Study 3003 Primary Endpoint of Time to Relapse in Stable Remitters in Maintenance Phase

	Esketamine + Oral AD	Placebo + Oral AD
<i>Number Assessed</i>	90	86
<i>Number Censored (No Relapse)</i>	66 (73%)	47 (55%)
<i>Number of Relapses</i>	24 (27%)	39 (45%)
<i>Time to Relapse (Days)</i>		
25% percentile (95% CI)	153 (105 to 225)	33 (22 to 48)
Median (95% CI)	NE	273 (97 to NE)
75% percentile (95% CI)	NE	NE
<i>Hazard Ratio (HR) (95% CI)</i>	0.49 (0.3 to 0.8)	--
<i>2-sided P-value (<0.05)</i>	0.003	--

Source: Table 20, CSR Study 3003, page 111, NE=not estimable

Figure 19 Study 3003 Primary Efficacy Analysis (Time to Relapse in Stable Remitters)



Source: Andrew Potter, PhD, Statistical Reviewer

The reasons for relapse are listed in the table below. Nearly all the placebo arm relapses were due to MADRS total score failure (97%) versus the esketamine arm (75%). The esketamine arm also had 13% subjects who were adjudicated as having clinically relevant relapse events (i.e., hospitalizations for depression for 3 subjects, versus 1 subject in the placebo arm). These numbers are too small to say if there were any significant hospitalization-related relapse trends in one arm versus the other.

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Table 42 Study 3003 Reasons for Relapse

Frequency Distribution of Reason for Relapse: Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)

	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)	Total (N=176)
Total number of subjects with relapse	24	39	63
Reason for relapse			
MADRS total score ≥ 22 for 2 consecutive assessments (a)	18 (75.0%)	38 (97.4%)	56 (88.9%)
Hospitalization	3 (12.5%)	0	3 (4.8%)
Depression	2 (8.3%)	0	2 (3.2%)
Major depression	1 (4.2%)	0	1 (1.6%)
Other clinically relevant event determined as a relapse (not hospitalized) (b)	3 (12.5%)	1 (2.6%)	4 (6.3%)
Depression	2 (8.3%)	1 (2.6%)	3 (4.8%)
Depressive symptom	1 (4.2%)	0	1 (1.6%)

(a) Based on 2 consecutive assessments separated by 5 to 15 days.
 (b) All such cases were assessed by the Relapse Adjudication Committee (RAC).

Source: Table 21, CSR Study 3003

Interim Analysis:

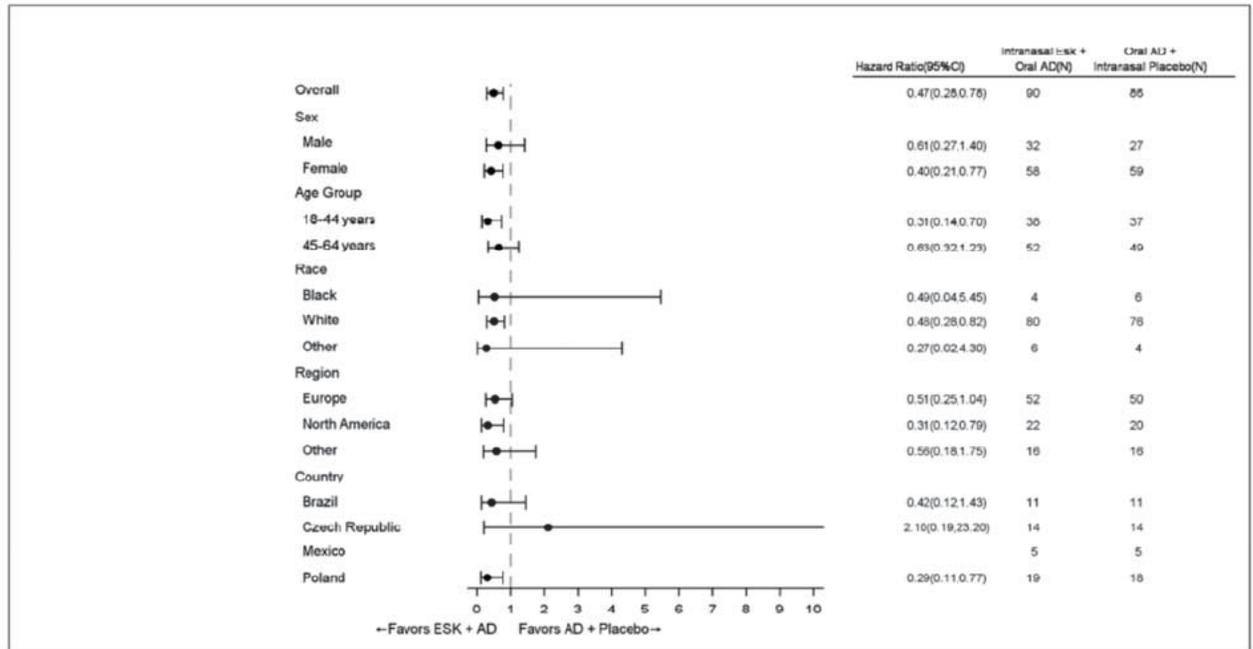
The Applicant conducted a pre-planned interim analysis (IA) during the study to allow for early stopping in case of statistically significant evidence of efficacy after 33 relapse events in stable remitters. The IA examined the data after 31 relapses (August 23, 2017 cutoff date). Afterwards, the Applicant decided to continue the study with a goal of reaching 59 total relapses to detect a statistically significant difference; this number was only recorded in IWRS and not revealed to other study staff (except Clinical Supplies staff) until this number of relapses was reached. The IA showed 11 relapses out of 49 subjects (22%) in the esketamine group versus 20 out of 47 (43%) in the placebo group with a preliminary 2-sided p-value of 0.03. (The prespecified IA significance level goal was 0.0097.)

Subgroup Analyses:

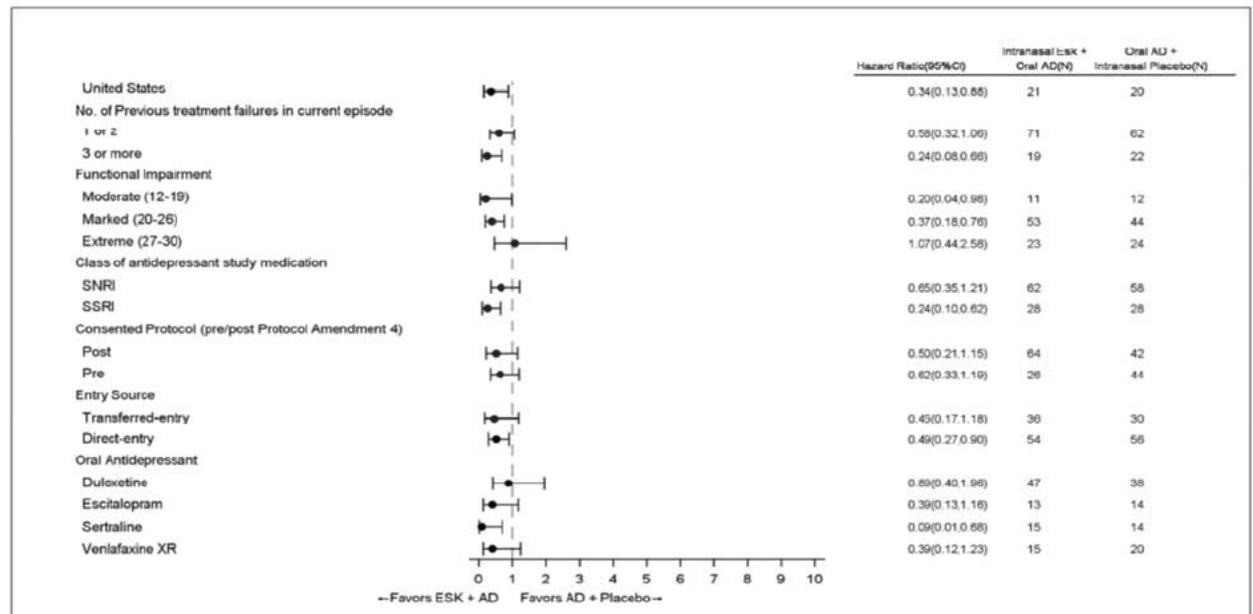
The Applicant conducted subgroup analyses using Cox regression analysis of hazard ratios. Most of the subgroups still favored the esketamine arm versus the placebo arm for time to relapse. The main exception was the Czech Republic subgroup (who had an even number of relapses in both arms). Also, subjects with an extreme baseline functional impairment score (27 to 30) and subjects on duloxetine showed a more equivocal relapse response between esketamine and placebo. Other subgroups with confidence intervals crossing into the placebo range were too small to interpret meaningfully.

Figure 20 Study 3003 Subgroup Forest Plots

Forest Plot of Hazard Ratio by Subgroup: Cox Regression (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)



Forest Plot of Hazard Ratio by Subgroup: Cox Regression (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)



Note: Hazard ratio estimates for subgroups with no event in either arm not displayed.

Note: Subgroups with fewer than 5 subjects not presented.

Note: All subjects had to have non-response to at least 2 antidepressants per protocol; some subjects required confirmation of non-response to the second antidepressant during the screening prospective observational period.

Source: Figure 4, CSR Study 3003

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Sensitivity and Other Analyses:

- Withdrawal Effect Analysis

One concern about randomized withdrawal study designs with antidepressant medications is whether antidepressant withdrawal can affect the relapse rates in the early weeks of the study. Discontinuing a medication early may amplify the tendency to relapse in the placebo arm of a randomized withdrawal study. Esketamine withdrawal can lead to rebound depressive-type symptoms, but more typically after stopping high and frequent doses per the literature⁷. For this study, esketamine doses were relatively low and infrequent (weekly or every other week) and an oral antidepressant was also still ongoing, rendering significant withdrawal effects from esketamine discontinuation to be likely minimal to none. MADRS assessments (covering the previous 7 days) were performed the same day a weekly esketamine dose was administered before the dose, so any acute next-day withdrawal effects would not be a concern.

The Applicant conducted a post-hoc analysis looking at time to relapse after censoring subjects who relapsed within Weeks 1 to 4 of the maintenance phase. The hazard ratios favored a higher number of relapses in the placebo arm in this group, but closer to esketamine with each week.

This trend may confirm this vulnerability to early relapse for subjects discontinuing esketamine. Instead of esketamine withdrawal, this trend may be due to other factors such as increased illness risk and vulnerability in the TRD population without treatment, and more infrequent esketamine dosing (although the esketamine dose was stable at weekly or every other week for at least 12 weeks during the previous optimization phase and only increased to weekly if MADRS response was waning). The early relapse rate may also reflect unblinding bias, as subjects previously on esketamine notice the difference when switched to placebo (and on-site investigators may also notice the difference between symptoms and AEs although they do not rate the MADRS). Typically, in other maintenance-of-effect studies for approved drugs for MDD, relapses are noted to increase at a slower rate, after about a month post-randomization⁸. As compared to oral antidepressants, esketamine has noted immediate effects such as dissociation (for a majority of subjects, with rates as high as 75%) and sedation upon dosing, that do not dissipate with time according to the safety data reviewed (see the safety review section). A perceived difference after receiving placebo could possibly adversely affect subjects who assume negative consequences from no longer receiving active drug, even with an ongoing background oral antidepressant.

⁷ Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry* 2013; 73(12):1133-1141.

⁸ Borges, S, 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.

Table 43 Study 3003 Rates of Relapse Censoring Early Relapse Subjects (Weeks 1 to 4)

Time to Relapse Censoring Subjects with a Relapse within Weeks 1,2,3 and 4; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)			
	Number of relapses (%) (a)		Hazard ratio (95% CI)
	Intranasal Esk + Oral AD	Oral AD + Intranasal Placebo	
Week 1	0	0	0.47 (0.28; 0.78)
Week 2	0	6 (15.4%)	0.54 (0.32; 0.91)
Week 3	1 (4.2%)	13 (33.3%)	0.64 (0.37; 1.12)
Week 4	4 (16.7%)	19 (48.7%)	0.71 (0.38; 1.31)

(a) The number of relapses occurred within weeks 1,2,3 and 4.

Note: Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor. The oral AD + intranasal placebo is the reference group.

Source: Table 22, CSR Study 3003

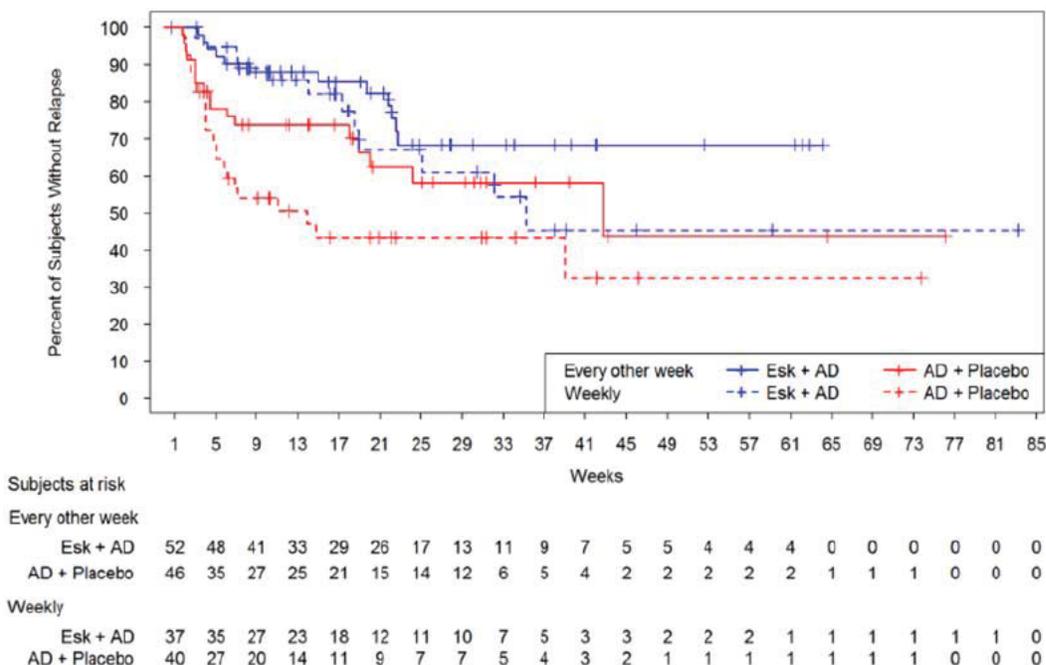
Our statistical reviewer also conducted subgroup analyses looking at the relapse trend curves after omitting the early weeks; reportedly there was no difference in the overall relapse trend favoring esketamine maintenance versus placebo, even when censoring the early relapsers. (See Section 7.3 and the statistical review for more details.)

- Dosing Frequency Analysis

The Applicant examined post-hoc whether there was a difference between subjects who remained in remission with weekly dosing versus every other week dosing. Subjects who required weekly dosing tended to relapse more quickly than those who did not. This trend corroborates that the group requiring more frequent dosing to sustain remission was more vulnerable to relapse.

Figure 21 Study 3003 Time to Relapse by Dosing Frequency

Cumulative Proportion of Subjects Who Remained Relapse Free by Dosing Frequency; Maintenance Phase (Kaplan-Meier Estimates) (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)



Source: Figure 5, CSR Study 3003

- Awareness of Change from Study Drug Analysis

Another concern was whether esketamine’s dissociative and sedative effects relative to placebo unblinded this study to subjects who could notice the difference when randomized to placebo. A post-hoc analysis of CADSS and MOAA/S total scores over time for subjects who relapsed on placebo within the first 4 weeks of the maintenance phase was conducted. There were 19 subjects who met these criteria.

The CADSS total score in 63% of these subjects was 0 in the 4 weeks before and after randomization, indicating a majority did not seem to notice a difference in dissociation before or after discontinuation. Of the 7 other subjects who had a CADSS score >0 before randomization, only 3 showed a change after randomization. Removing these 3 subjects and conducting an analysis on the remaining population did not show a difference in trend from the primary efficacy analysis.

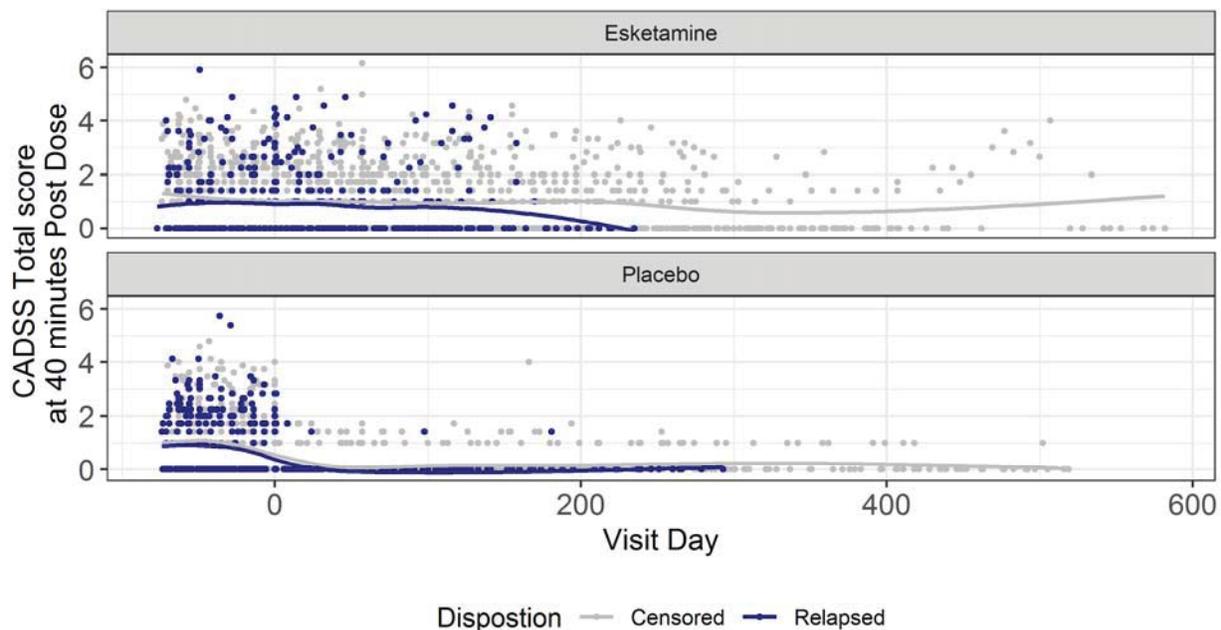
The MOAA/S scores reportedly did not show sedation before randomization in any of the 19 subjects. There were 2 subjects in this group who reported sedation AEs in the 4 weeks before randomization (which seems to indicate that MOAA/S scores are not always reliable in

detecting clinically significant sedation). An analysis of the remaining population without these 2 subjects did not show a difference in trend from the primary efficacy analysis.

Blood pressure elevations were not analyzed as investigators were instructed not to tell subjects about such findings as they occurred (only afterwards if clinical intervention was required) and were usually asymptomatic. It is unknown if site personnel would potentially alter their behavior in response to suspecting subjects were on drug instead of placebo, after detecting expected side effects, or if any behavior changes would affect subject results at all.

Our statistical reviewer conducted further exploratory analysis of dissociation symptom trajectories as measured by the CADSS and their association to the time to relapse of depression. In the figure below, CADSS scores decline rapidly in the placebo arm when patients are randomized to stopping esketamine. Dr. Potter used a joint model of both CADSS score trajectories and time to depression relapse. This analysis found that both esketamine treatment (HR = 0.45, $p = 0.0032$) and CADSS score (HR = 0.63 per unit increase in square root CADSS, $p = 0.0448$) are associated with time to relapse of depression.

Figure 22 Treatment Arm Average CADSS score Trajectories Stratified by Relapse Status (TRD3003: FAS - Remitter Set)



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Source: Andrew Potter, PhD, Statistical Reviewer

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The presence of an association between dissociation and time to relapse introduces the possibility of alternative interpretations of the esketamine to placebo hazard ratio. Potential interpretations include:

- Despite the association of dissociative symptoms with increasing time to relapse, the potential change in perception of assigned treatment does not change the evidence that esketamine delays time to depression relapse.
- The efficacy of esketamine in delaying time to relapse depends on the subject feeling some dissociative symptoms. The subject may worsen either due to suspecting they are no longer taking active drug, or because there is some primary antidepressant effect from or association with dissociation.

Our exploratory analysis cannot distinguish between these possibilities. It is possible, but not conclusive, that change in perception of treatment assignment based on esketamine's active symptom profile has partially impacted this study's results.

- Other Sensitivity Analyses

The Applicant conducted several prespecified sensitivity analyses to confirm the methodology used relative to the efficacy results.

One analysis used an unweighted log-rank test and Cox proportional hazards model after a cutoff date when 59 events occurred (with 61 relapses recorded as 3 events occurred on the cutoff date) and also after 63 events. The estimated hazard ratio of the esketamine arm relative to the placebo arm was 0.46 (95% CI: 0.27 to 0.77) after 61 events and 0.47 (95% CI: 0.28 to 0.78) after 63 events. These results are consistent with the primary analysis.

Another analysis used stress-testing to examine the assumption of ignorable censoring, where subjects on treatment who discontinued prematurely from the maintenance phase had a higher relapse hazard compared to similar subjects who remained in this phase. The single sensitivity parameter Delta represented this ratio between early discontinuers and those who remained at any given point t . A sequence of Delta values for 8 subjects was used until a tipping point was reached for non-significant results. For this study, the tipping point reached 50, implying that even for hazard inflation up to 50 times, statistical significance was maintained.

Finally, after Amendment 4 revised the definition of stable remission to allow a single excursion or missed MADRS assessment at Week 13 or 14 due to non-illness-related life event, a post-hoc analysis examined the subgroups pre- and post-Amendment 4 criteria. Of 176 stable remitters, 167 met pre-Amendment 4 criteria, and 8 met post-Amendment 4 criteria (1 other subject was a misrandomized stable responder). The results for the pre-Amendment 4 subgroup remained similar to the primary efficacy results, with a hazard ratio of 0.44 (0.26 to 0.74) with a 2-sided p -

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value of 0.002.

Overall these sensitivity analyses seem to corroborate the primary efficacy analysis results.

Data Quality and Integrity

See the previously discussed concerns about functional unblinding. There were also possible concerns about one large site in Poland driving the efficacy result, with 100% placebo relapse rate (12 out of 12 subjects versus 2 out of 9 for stable remitters). However, the OSI inspection of the site did not yield any significant conduct-related concerns aside from a few cases of subjects possibly receiving lower amounts of esketamine due to nasal spray administration issues. If subjects received less than expected esketamine doses, the results of the study, if impacted at all, would have likely trended more strongly in a positive efficacy direction if the correct doses were received.

Efficacy Results – Secondary and Other Relevant Endpoints

The following secondary endpoints were not controlled for multiplicity.

- Time to Relapse in Stable Responders

For the stable responders group in the maintenance phase, there was a statistically significant difference for time to relapse between the esketamine and placebo groups, with a 2-sided p-value of <0.001 using a 2-sided log-rank test. There were 16 (26%) of subjects in the esketamine group and 34 (58%) of subjects in the placebo group who relapsed during the maintenance phase. Nearly all the relapses (98%) were due to MADRS total score ≥ 22 not being met at 2 consecutive assessments (with only one subject being hospitalized for depression in the placebo arm).

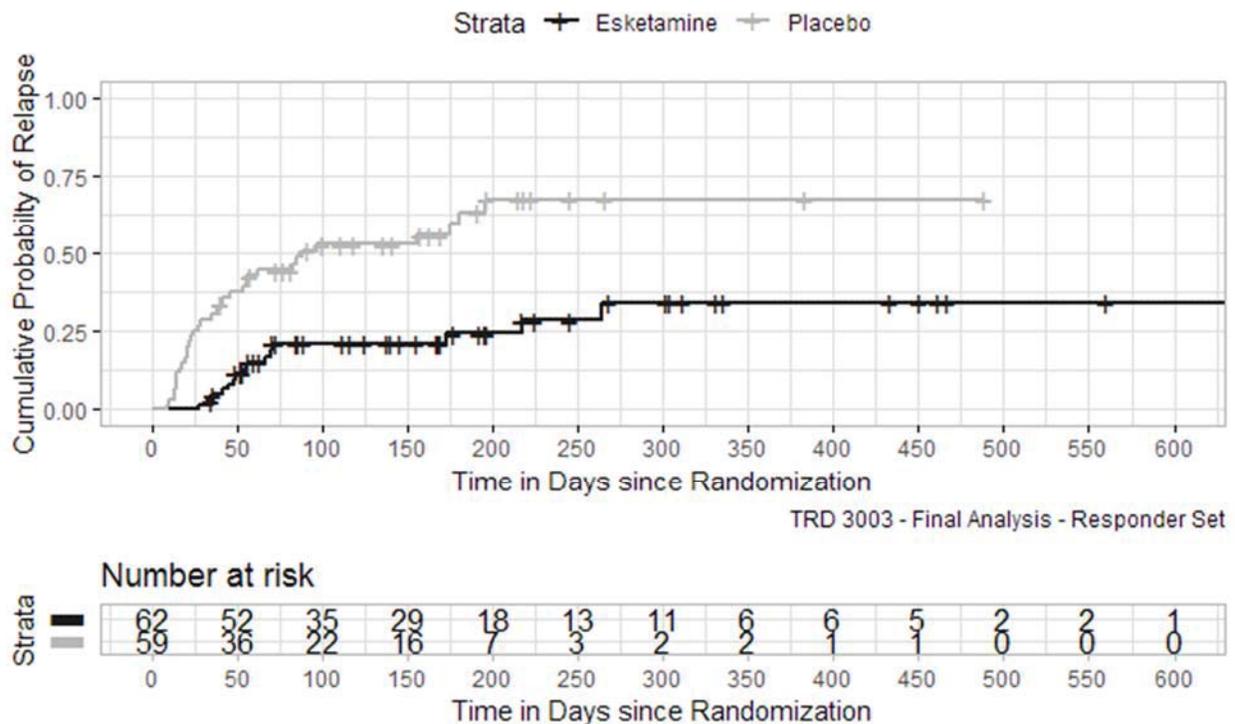
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Table 44 Study 3003 Secondary Efficacy Endpoint of Time to Relapse in Stable Responders

	Esketamine + Oral AD	Placebo + Oral AD
Number Assessed	62	59
Number Censored	46 (74%)	25 (42%)
Number of Relapses	16 (26%)	34 (58%)
Time to Relapse (Days)		
25% percentile (95% CI)	217 (56 to 635)	24 (17 to 46)
Median (95% CI)	635 (264 to 635)	88 (46 to 196)
75% percentile (95% CI)	635 (NE)	NE
Hazard Ratio (HR) (95% CI)	0.30 (0.16 to 0.55)	--
2-sided P-value (<0.05)	<0.001	--

Source: Study 3003 CSR, NE=not estimable

Figure 23 Study 3003 Secondary Efficacy Endpoint of Time to Relapse in Stable Responders



Source: Andrew Potter, PhD, Statistical Reviewer

- MADRS Total Score

The mean MADRS total score change from baseline to endpoint showed a decrease for the direct-entry subjects treated with open-label IN esketamine during the induction phase (37.7

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(5.50) to 15.4 (12.4), **-22**) and a slight increase during the optimization phase (8.5 (5.9) to 12.2 (10.6), **+3.7**). (The slight mean increase may reflect the less frequent IN esketamine dosing regimen, stepped down to weekly or every other week.)

As an exploratory analysis, the Applicant compared the mean MADRS total score change during the maintenance phase between the esketamine and placebo arms, using ANCOVA/LOCF. Both arms showed a gradual mean increase by study endpoint, although the esketamine arm showed a lower mean score than the placebo arm (as would be expected given the higher relapse rate in the placebo arm). (A nominally significant p-value for the difference between treatment arms is noted, although it was not corrected for multiplicity.) It is somewhat unclear how to interpret the overall gradual MADRS mean total score increase for the esketamine arm during the maintenance phase; perhaps the maintenance dosing, while sufficient to prevent more relapses than the placebo arm, was still too infrequent to fully sustain the improvements from the previous induction and optimization phases, or the scores reflect the natural course of TRD over a longer period of time, or it is a regression to the mean phenomenon.

Table 45 Study 3003 MADRS Total Score Mean Change from Baseline (Stable Remitters) for Maintenance Phase (ANCOVA/LOCF)

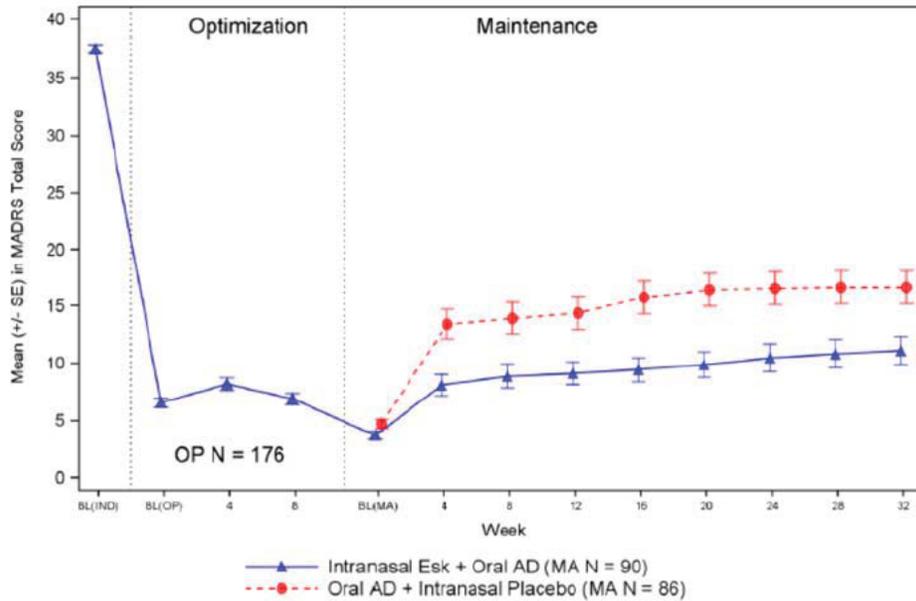
Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)		
	Intranasal Esk + Oral AD (N=90)	Oral AD + Intranasal Placebo (N=86)
Baseline(MA)		
N	90	86
Mean (SD)	3.7 (3.29)	4.7 (3.73)
Median (Range)	3.0 (0; 12)	5.0 (0; 15)
End point(MA)		
N	89	86
Mean (SD)	11.3 (11.66)	17.2 (13.22)
Median (Range)	6.0 (0; 36)	15.5 (0; 47)
Change from baseline(MA) to end point(MA)		
N	89	86
Mean (SD)	7.5 (11.59)	12.5 (13.63)
Median (Range)	2.0 (-8; 35)	12.5 (-12; 47)
ANCOVA (a)		
Diff. of LS means (SE) (Esk+AD minus AD+Placebo)	-5.2 (1.82)	
95% confidence interval on diff.	-8.77; -1.58	
Two-sided p-value (b)	0.005	

Source: Table 25, CSR Study 3003, page 126

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Figure 24 Study 3003 MADRS Total Score Mean Change from Baseline for Stable Remitters

Arithmetic Means (\pm SE) for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score Over Time LOCF (Study ESKETINTRD3003: Full (Stable Remitters) Analysis Set)



Source: Figure 7, CSR Study 3003, page 128

A similar trend was seen in the stable responders group, although the mean increase for the esketamine arm was smaller (probably given that the baseline MADRS mean score was higher than the stable remitters baseline).

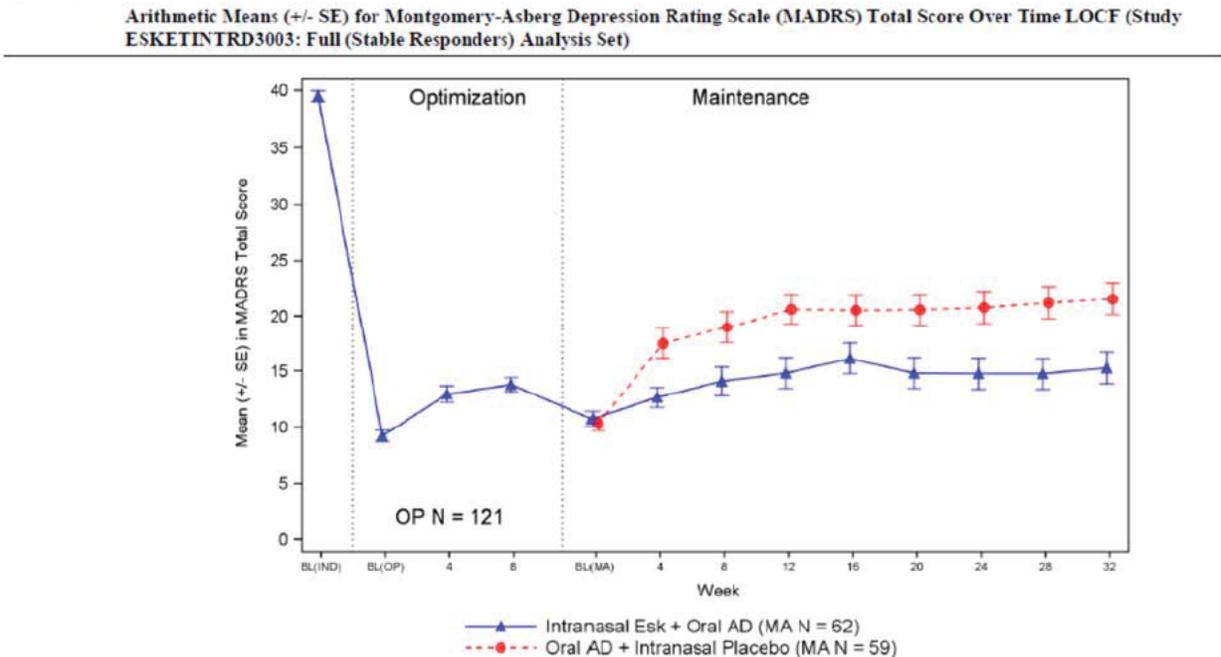
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Table 46 Study 3003 MADRS Total Score Mean Change from Baseline (Stable Responders) in Maintenance Phase (ANCOVA/LOCF)

Montgomery-Asberg Depression Rating Scale (MADRS) Total Score: Change from Baseline (MA) to Endpoint (MA) LOCF ANCOVA; Maintenance Phase (Study ESKETINTRD3003: Full (Stable Responders) Analysis Set)		
	Intranasal Esk + Oral AD (N=62)	Oral AD + Intranasal Placebo (N=59)
Baseline(MA)		
N	62	59
Mean (SD)	10.7 (5.27)	10.3 (4.86)
Median (Range)	10.5 (0; 22)	11.0 (0; 19)
End point(MA)		
N	62	59
Mean (SD)	15.1 (11.39)	21.8 (11.25)
Median (Range)	13.0 (0; 44)	25.0 (0; 40)
Change from baseline(MA) to end point(MA)		
N	62	59
Mean (SD)	4.4 (11.38)	11.4 (12.00)
Median (Range)	3.5 (-18; 35)	14.0 (-13; 40)
ANCOVA (a)		
Diff. of LS means (SE) (Esk+AD minus AD+Placebo)	-7.4 (1.95)	
95% confidence interval on diff.	-11.30; -3.55	
Two-sided p-value (b)	<0.001	

Source: Table 26, CSR Study 3003

Figure 25 Study 3003 MADRS Total Score Mean Change from Baseline for Stable Responders



Source: Figure 8, CSR Study 3003, page 129

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At the end of the maintenance phase, a greater percentage of stable remitters and stable responders in the esketamine group (65% and 47% respectively) met criteria for remission (MADRS total score ≤ 12 at endpoint) compared to the placebo group (42% and 25% respectively). The same trends were seen for criteria for response ($\geq 50\%$ improvement from baseline MADRS total score) with the stable remitters and stable responders with the esketamine group (75% and 66% respectively) versus the placebo group (56% and 34% respectively).

The MADRS mean difference trends and the larger percentages for both stable remitters and responders achieving remission and response at study endpoint during the maintenance phase for the esketamine arm versus the placebo arm provide supporting evidence of a subgroup of subjects who benefit from esketamine plus oral antidepressant for the treatment of TRD versus placebo plus oral antidepressant alone. (However, there is the caveat with this study design that the maintenance study endpoint reflected longer overall treatment exposure time (including oral antidepressant exposure) in the esketamine arm versus the placebo arm. Nonetheless, that time difference is mainly due to the higher relapse rate in the placebo arm, again reflecting an overall trend towards greater maintenance efficacy in the esketamine group for this study.)

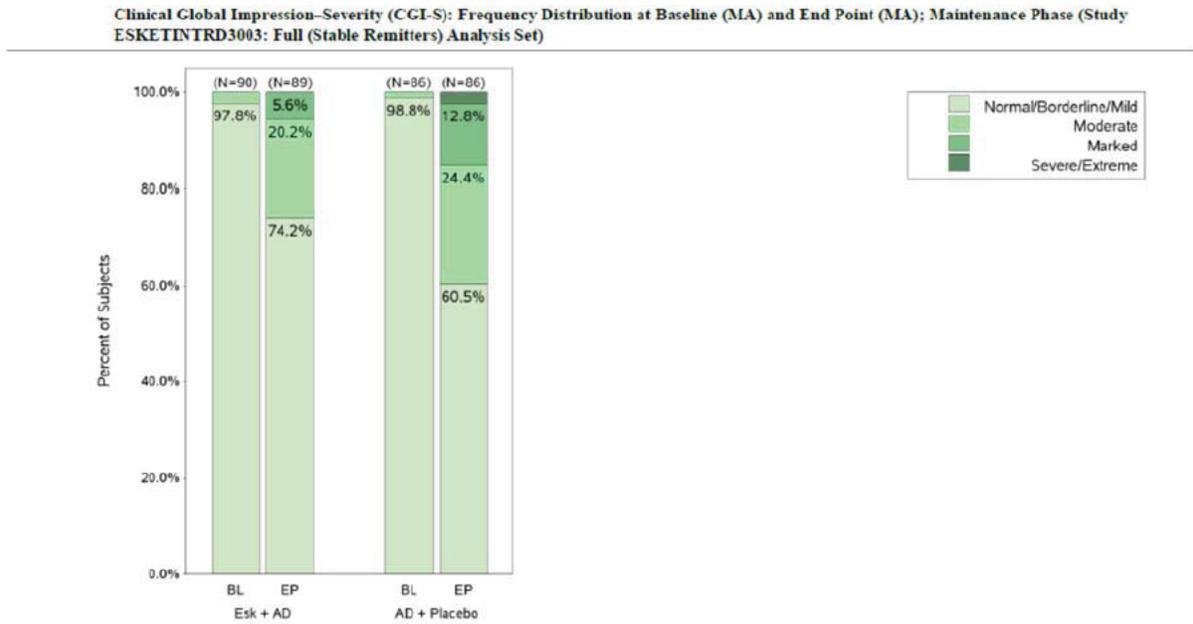
- PHQ-9 Total Score

Mean score changes from baseline to endpoint during the maintenance phase for several other secondary scales were measured in each treatment arm and compared on an exploratory basis, for the stable remitter and stable responder populations. For the PHQ-9 Total Score, mean scores slightly increased in both arms for stable remitters, but the esketamine arm remained lower than placebo at endpoint (LS Mean Difference of -2.4 (0.9)) with a nominally significant p-value of 0.008 via ANCOVA/LOCF. For stable responders, the same trend was seen (LS Mean Difference of -3.0 (0.9) with a nominally significant p-value of 0.002). Remission and response rates at study endpoint for both stable remitters and stable responders showed similar trends, with higher percentages meeting criteria in the esketamine arm versus the placebo arm, although these were not statistically compared.

- CGI-S Total Score

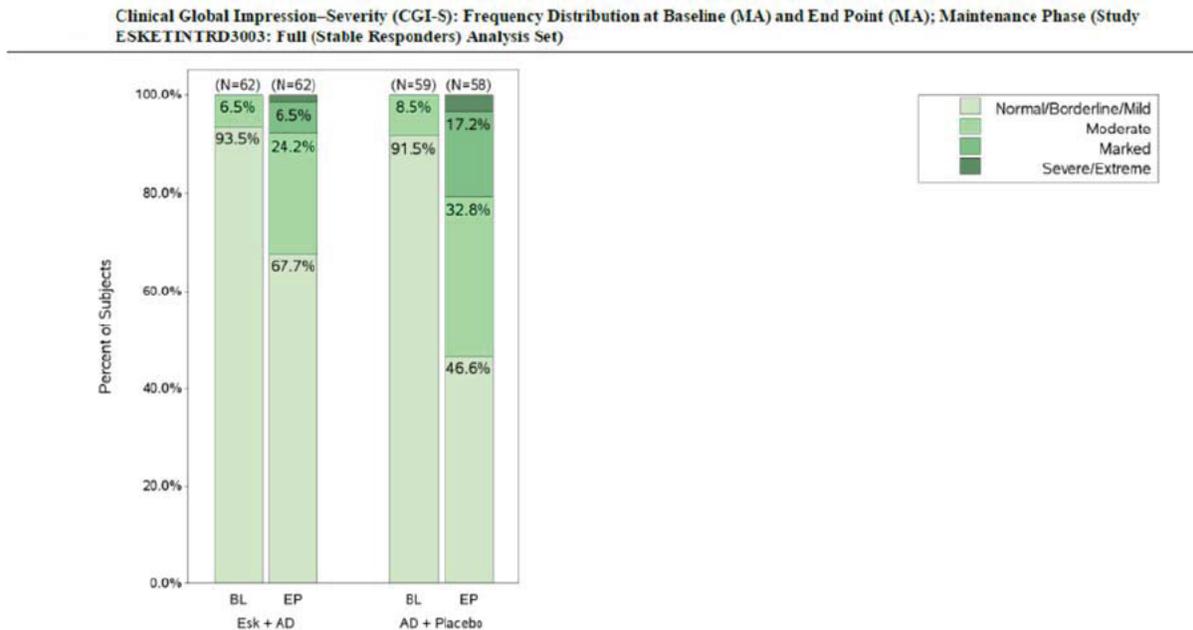
The Applicant provided a frequency distribution of CGI-S levels that indicated a higher percentage of normal to moderate subjects versus marked to severe in the esketamine arm versus the placebo arm at study endpoint for the maintenance phase for stable remitters and stable responders. These were not statistically compared values.

Figure 26 Study 3003 CGI-S Frequency Distribution in Stable Remitters, Maintenance Phase



Source: Figure 11, CSR Study 3003

Figure 27 Study 3003 CGI-S Frequency Distribution in Stable Responders, Maintenance Phase



Source: Figure 12, CSR Study 3003

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- GAD-7 Total Score

Mean GAD-7 total scores overall improved during this study for direct-entry subjects during the induction (13.6 to 4.5) and optimization (2.7 to 3.2) phases. For the maintenance phase, both mean scores increased in each treatment arm (1.0 to 3.2 in the esketamine arm, and 1.2 to 5.1 in the placebo arm; LS mean difference -1.7) for the stable remitters group. Similar trends were seen in the stable responders group (LS mean difference -1.1). It is unclear how to interpret these findings, given the inclusion of open-label subjects, and the ongoing improvement even in the placebo arm.

- SDS Score

SDS total scores ≤ 6 indicate remission and ≤ 12 indicate response. Mean SDS scores overall improved during this study for direct-entry subjects during the induction (23.7 to 10.7) and optimization (8.6 to 7.3) phases. For the maintenance phase, both treatment groups showed an increase in mean SDS score from baseline to endpoint (2.6 to 6.6 in the esketamine arm and 3.6 to 10.3 in the placebo arm; LS mean difference -2.9) in the stable remitters group. An exploratory 2-sided p-value via ANCOVA was nominally significant at 0.025. A similar trend was seen in the stable responders group (LS mean difference -4.7, a nominally significant p-value < 0.001).

Remission and response rates based on SDS total score during the maintenance phase in the stable remitters group were as follows: remission rates from baseline to endpoint were 81% to 58% in the esketamine arm, and 75% to 39% in the placebo arm; response rates were 94% to 70% in the esketamine arm, and 88% to 55% in the placebo arm. For the stable responders group, remission rates went from 47% to 42% in the esketamine arm, and 53% to 21% in placebo arm; response rates went from 75% to 70% in the esketamine arm, and 84% to 43% in the placebo arm. Overall, these results support esketamine's greater maintenance efficacy in sustaining remission and response, measured via SDS total score, compared to subjects who have esketamine withdrawn to placebo, with oral antidepressant ongoing in both arms. However, these remission and response rate values were not statistically compared.

- EQ-5D-5L

Increases in EQ-VAS score indicate improvement in respondents' self-assessment of health status, on a scale of 0 to 100. For Study 3003, direct-entry subjects showed increases during induction and optimization phases on esketamine. During the maintenance phase, stable remitters and stable responders both showed decreases, but the decrease was greater in the placebo arm compared to the esketamine arm in both groups. This information corroborates the trends seen on the other secondary endpoints for this study, although again the values were not statistically compared.

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Table 47 Study 3003 EQ-VAS Mean Scores

Mean (SD) EQ-VAS Scores (Study ESKETINTRD3003 Full Analysis Sets)			
	Induction	Mean (SD) EQ-VAS score Optimization	Maintenance
	Intranasal Esk + Oral AD	Baseline: 40.8 (22.31) End point: 68.9 (22.82)	
	Intranasal Esk + Oral AD	Baseline: 77.5 (15.59) End point: 76.4 (19.39)	
Stable responders:	Intranasal Esk + Oral AD		Baseline: 77.0 (17.37) End point: 76.0 (17.67)
	Oral AD + Intranasal Placebo		Baseline: 79.1 (14.27) End point: 65.4 (18.99)
Stable remitters:	Intranasal Esk + Oral AD		Baseline: 88.4 (9.23) End point: 77.9 (20.80)
	Oral AD + Intranasal Placebo		Baseline: 86.6 (9.77) End point: 70.6 (21.51)

AD= antidepressant; Esk= esketamine; EQ-VAS= EuroQol Group visual analogue scale; SD= standard deviation

Source: Attachment [TEFEQ5D01A](#), Attachment [TEFEQ5D01B](#), Attachment [TEFEQ5D01C](#), Attachment [TEFEQ5D01D](#)

Source: Table 31, CSR Study 3003

Dose/Dose Response

The following are the mean doses for subjects entering the maintenance phase for each of the analysis populations:

Table 48 Study 3003 Mean Esketamine Doses Entering Maintenance Phase

	Randomized to continue esketamine	Randomized to discontinue esketamine
Total Group	72.9 mg (n=152)	74.0 mg (n=145)
Stable Remitters	71.6 mg (n=90)	73.3 mg (n=86)
Stable Responders	75.0 mg (n=62)	75.0 mg (n=59)

Source: Applicant Response to IR, November 26, 2018

Subjects remained on the same dose they began in the maintenance phase throughout that phase. The majority of subjects were on 84 mg (about 2/3rds) esketamine in both stable remitters and stable responders, and the rest were on 56 mg.

There were no major differences between treatment arms in terms of mean dose before entering the maintenance phase, so prior esketamine exposure can be considered generally even between groups.

Durability of Response

This maintenance-of-effect study shows that a higher number of subjects show worsening depression on several endpoint measures after esketamine is discontinued compared to those

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who remain on esketamine, even with an oral antidepressant ongoing in both treatment arms. The rate of decline was most noticeable in the first 4 weeks of withdrawal but continued to steadily increase past that time throughout the full maintenance phase until study termination. (The Kaplan-Meier curves stopped declining at Week 35 for esketamine arm, and Week 43 for placebo arm.)

Persistence of Effect

See primary efficacy results for this randomized withdrawal study.

Additional Analyses Conducted on the Individual Trial

See the Statistical Review for more details.

6.4. Study 3005 (TRANSFORM-3)

6.4.1. Study Design

Overview and Objective

Randomized, Double-Blind, Multicenter, Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-Resistant Depression: Trial of Rapid-Acting Intranasal Esketamine for Treatment-Resistant Major Depressive Disorder (TRANSFORM-3)

Trial Design

- *Basic study design:*

Study 3005 is a randomized, double-blind, active-controlled, multicenter study in geriatric subjects with TRD (ages 65 and older).

This study had 3 phases:

- **Screening Phase:** Up to 4 weeks duration to prospectively observe and assess treatment response to subject's current oral antidepressant treatment. Non-responders were deemed eligible to move on to the next phase, after tapering and discontinuing their oral antidepressant over an additional optional 3-week period or via clinical judgment.
- **Treatment Phase (Double-Blind Induction):** 4 weeks total duration where subjects were switched to a new oral antidepressant for daily administration, and then also randomized to either receive intranasal esketamine 28 mg, 56 mg, or 84 mg, or placebo, twice a week. Subjects who completed this phase were eligible to enter long-term safety study 3004.

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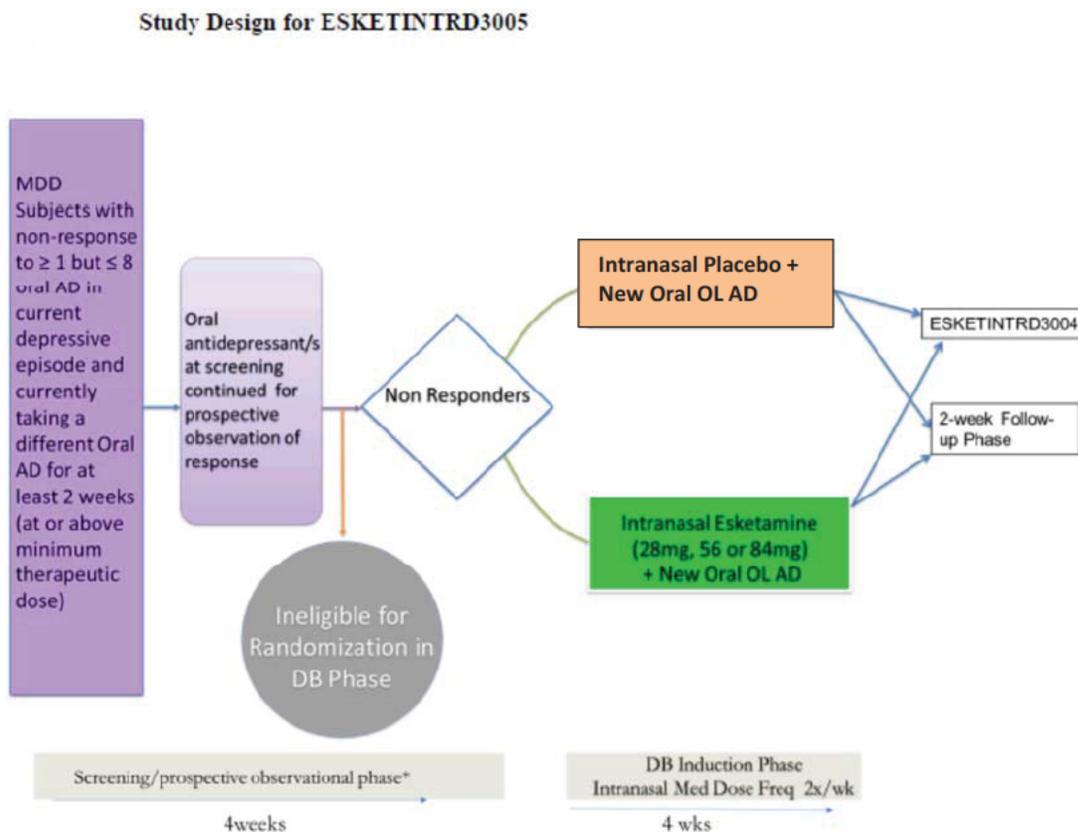
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- Follow-Up Phase: 2 weeks total duration to assess safety and tolerability of the study medication, including any withdrawal concerns. (The oral antidepressant had to also be continued for at least 2 weeks into follow-up, unless not deemed clinically appropriate by the investigator.) This phase included all subjects who received at least 1 dose of IN study medication in the previous phase, including those who withdrew early during that phase or chose not to enter the long-term safety study 3004.

Figure 28 Study 3005 Study Design Schematic



Source: Adapted from Figure 1, CSR Study 3005, page 26

- *Choice of control group:*

As with Studies 3001 and 3002, the study design incorporates currently accepted treatment algorithms for TRD involving a complete switch in treatment after lack of response, as opposed to an adjunctive treatment modality. The newly initiated oral antidepressant plus intranasal placebo serves as a control relative to the other treatment arm with the new oral antidepressant plus intranasal ketamine, given via flexible dosing. Several different oral antidepressants (two SSRIs and two SNRIs) were permitted as the background oral antidepressant. (The justification for doing so may be that all oral antidepressants have shown

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comparable effect sizes for treatment response in clinical trials.) They are: escitalopram, sertraline, duloxetine, and venlafaxine XR.

- *Trial location:*

Study 3005 was conducted at 57 total sites (3 in Belgium, 3 in Brazil, 2 in Bulgaria, 1 in Finland, 7 in France, 4 in Italy, 1 in Lithuania, 5 in Poland, 4 in South Africa, 6 in Spain, 6 in Sweden, 2 in UK, 13 in US).

- *Diagnostic criteria:*

See Study 3001 for the diagnostic criteria used for TRD. The TRD study entry cutoff scores for the MADRS total score and IDS-C₃₀ total score are lower for the elderly population than the other studies (as per Protocol Amendment 3, see that section for more details).

- *Key inclusion/exclusion criteria:*

The criteria were similar to those for the previous studies, with the exception that the age group would be subjects 65 years and older.

- *Dose selection:*

The esketamine arm was to be flexibly dosed, ranging from 28 mg to 56 mg to 84 mg twice weekly for 4 weeks during the double-blind induction phase. After Amendment 1, the lower dose of esketamine (28 mg) was permitted past Day 1; this dose was used due to PK study data in the elderly and concerns about safety and tolerability.

The doses used for the oral antidepressants were lower than those used for the non-geriatric studies. See the dose modification section below.

- *Study treatments:*

See Study 3001.

- *Assignment to treatment:*

As with the other studies, central randomization was used. Subjects were assigned to one of 2 treatment groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study. The randomization was balanced via randomly permuted blocks (block size = 4) and stratified by country and class of newly-initiated oral antidepressant. IWRS was used to assign a unique treatment code dictating the treatment assignment and matching

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study drug kits for each subject. IWRS managed study agent inventory without unblinding investigators.

- *Blinding:*

See Study 3001. As with the other studies, there were no additional blinding methods provided for the known effects of esketamine versus placebo, aside from the bitter flavoring.

- *Dose modification, dose discontinuation:*

Dosing protocols for previous antidepressants during the screening phase were the same as Study 3002, with adherence assessed using the PAQ.

Non-responders ($\leq 25\%$ MADRS improvement from Week 1 to Week 4 of screening phase and total score ≥ 24 at Week 2 and Week 4; this definition was modified in Amendment 3, see that section for more details) who had discontinued their previous antidepressant were eligible to enter the double-blind induction phase. During the double-blind induction phase, on Day 1 a newly assigned open-label oral antidepressant was initiated for daily use during this phase.

Subjects in the esketamine arm could be dosed flexibly from 28 to 84 mg with the following titration schedule.

Table 49 Study 3005 Intranasal Esketamine Flexible Dose Titration Schedule

Dose Titration of Intranasal Esketamine ^a		
Day	Dose	Dose Titration Guidance
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability
Days 8, 11, 15	28, 56 or 84 mg	The dose may be maintained, or increased or reduced by 28 mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. No dose increase is permitted beyond Day 15.
Days 18, 22 and 25	28, 56 or 84 mg	No dose increase is permitted beyond Day 15. If needed for tolerability, dose reduction by 28 mg from the previous dose is permitted on Days 18, 22 and 25.

^a Dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.

Source: Table 4, CSR Study 3005, page 42

No dose increases were permitted past Day 15. Reductions for tolerability were permitted.

The oral antidepressant could not be lowered below the minimum therapeutic doses as noted below:

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- Sertraline 25 mg daily
- Venlafaxine XR 75 mg daily
- Escitalopram 5 mg daily
- Duloxetine 30 mg daily

These doses are lower than the minimum therapeutic doses used in the previous non-geriatric studies.

- *Administrative structure:*

See the previous studies.

- *Procedures and schedule:*

Please see Section 13.1.4 in the appendices.

- *Dietary restrictions/instructions:*

As with the previous studies, the only major restriction was no intake 2 hours before IN medication.

- *Concurrent medications:* List or describe the concurrent medications/treatments that were expected, encouraged, permitted, and not permitted, as applicable. Discuss tapering and discontinuation schedules along with any washout periods.

See Study 3001.

- *Treatment compliance:*

See Study 3001. PK levels were drawn during this study.

- *Rescue medication:*

See Study 3001.

- *Subject completion, discontinuation, or withdrawal:* Describe the definitions that were used to consider patients trial completers. Discuss how subjects who discontinued or withdrew from the study were handled in statistical analyses and whether this was fully specified in the pooled or SAP. Discuss whether subjects withdrawn from the study were replaced, regardless of the reason for withdrawal. Discuss whether any follow-up procedures and/or assessments were provided for subjects who discontinued or were withdrawn from the study. You may refer to the table of study procedures and

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assessments or the study schedule of events.

See Study 3001. Subjects in this study were eligible to enter the long-term safety study 3004 but not Study 3003.

Study Endpoints

The primary efficacy endpoint was the difference between treatment groups on change from baseline in the MADRS total score from Day 1 to Day 28 of the double-blind induction phase.

Secondary efficacy endpoints included:

- Proportion of responders ($\geq 50\%$ reduction from baseline in MADRS total score) at Day 28 of the double-blind induction phase
- Proportion of remitters (MADRS ≤ 12) at Day 28 of the double-blind induction phase
- Change from baseline (Day 1 to Day 28) on CGI-S
- Change from baseline (Day 1 to Day 28) on EQ-5D-5L

Additional efficacy assessments included:

- SDS
- PHQ-9

Safety and other assessments were the same as the previous studies.

Statistical Analysis Plan

The maximum sample size planned for Study 3005 was calculated assuming a treatment difference after 4 weeks of treatment in the double-blind induction phase of 6.5 points on the MADRS total score between treatment groups with an SD of 12, a one-sided significance level of 0.025, and a dropout rate of 25%. A maximum of 74 subjects was to be randomized to each treatment group to achieve 80% power using a fixed design assuming no interim analysis. These treatment effect estimations were derived from Panel A results of Study 2003 and clinical judgment.

An interim analysis was planned 4 weeks after randomizing 50 subjects (25 per treatment group) in order to determine if sample size re-estimation was necessary or if the study should be halted due to futility. It was projected that at that time about 36 subjects in the FA set would have completed the induction phase (about 18 per treatment group). The dropout rate was monitored to ensure sufficient subjects were included in the IA.

There were two analysis phases planned in this study: double-blind induction phase and follow-up (posttreatment) phase. The following analysis sets were to be used: all randomized, full, safety, and follow-up. The all randomized group included anyone randomized, regardless of

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whether treatment was received. The FA group received at least one dose of IN study medication and one dose of oral antidepressant medication during the double-blind induction phase. The safety group was the same, but with at least one dose of IN study medication OR one dose of oral antidepressant, and subjects with at least one post-baseline observation during the double-blind induction phase. (Subjects who received an unplanned treatment were still grouped under their planned treatment arm.)

Protocol Amendments

There were three protocol amendments, dated June 8, 2015; January 10, 2016; and July 18, 2016. Amendment 1 added 28 mg of esketamine as a continuous study dose, not just on Day 1, to improve safety and tolerability. There were minor adjustments to other inclusion and exclusion criteria. Amendment 2 revised specifications to the TRD inclusion criteria definition (similar to the ones in the previous studies). Subjects with at least 7 prior ECT treatments and/or VNS were to be excluded. Some additional medical conditions were excluded (sleep apnea, uncontrolled diabetes, severe renal impairment, etc.) Amendment 3 reduced the MADRS total score inclusion criteria from ≥ 28 to ≥ 24 and IDS-C₃₀ total score from ≥ 34 to ≥ 31 to better align with lower scores typically reported by the elderly. The number of previous antidepressant non-response episodes was revised to ≥ 1 to 8. Like the other phase 3 studies, the criteria were revised to allow subjects who had recently started a second antidepressant in the current episode (at least 2 weeks) to participate in the screening phase and see if they later met criteria for study entry after a minimum of 6 weeks of treatment. Other modifications to inclusion and exclusion criteria were added (inclusion of patients with Parkinson's Disease without cognitive impairment, allowing concomitant use of psychostimulants if restricted within 12 hours of dosing sessions, excluding subjects with MMSE < 22 if they had less than a high school education, etc.)

Amendment 1 was added before study enrollment began. Amendment 2 was added after 17 subjects had already enrolled. Amendment 3 was added after 31 subjects had enrolled. It does not seem that these criteria would significantly affect study results, although it is worth noting the softening of TRD criteria for post-Amendment 3 subjects.

6.4.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with good clinical practice (GCP) as per CFR requirements. One site (US10009) with three screened subjects (one of whom was initially randomized) was excluded from the analysis population after an audit revealed GCP noncompliance.

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There are no major concerns. See Appendix 13.2 for more details.

Patient Disposition

Out of 302 subjects initially screened, a total of 138 subjects were randomized into Study 3005, with 72 in the esketamine arm and 66 in the placebo arm. Except for one subject originally assigned to placebo, the same subjects were included in the FA and safety populations.

There were two subjects (one in each arm) still included in the FA population who did not have a post-baseline MADRS score and received at least one dose of study medication.

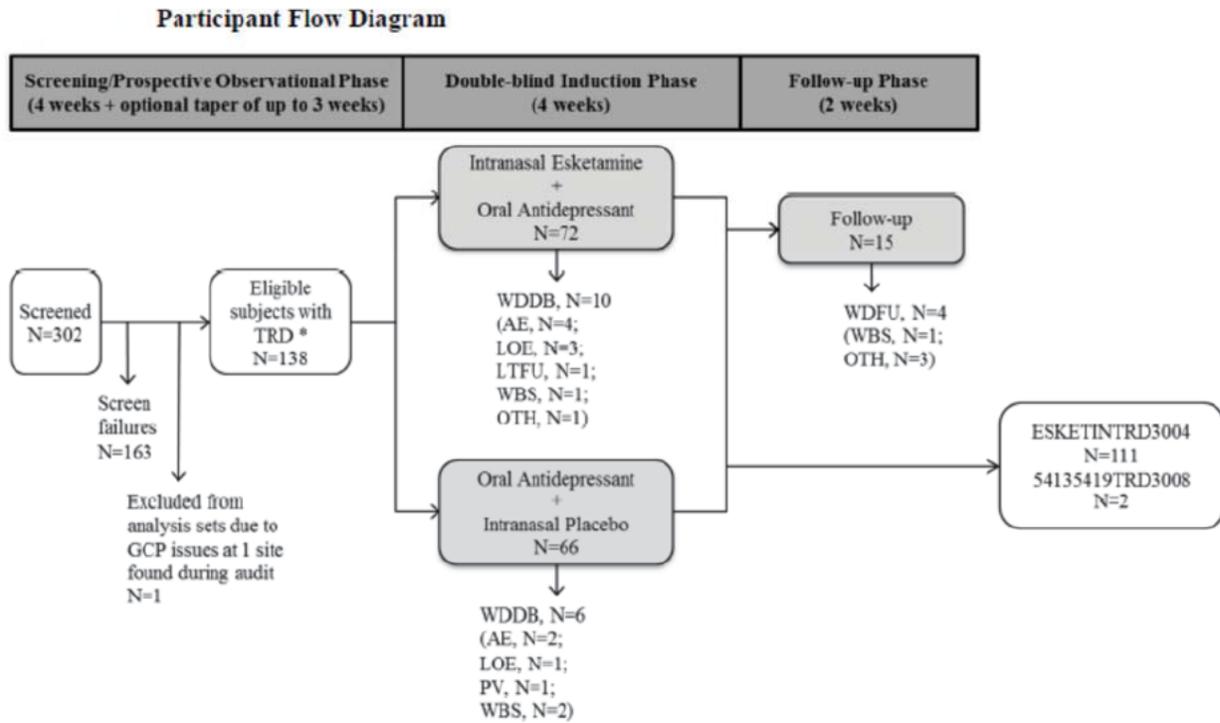
There were 124 subjects (89%) who completed the study (including follow-up), with 14 subjects (10%) who withdrew. Only 15 subjects (11%) entered the follow-up phase, with the majority entering long-term safety Studies 3004 (111 subjects) and 3008 (2 subjects).

Table 50 Study 3005 Patient Disposition

Number of Subjects in Each Analysis Set (Study ESKETINTRD3005: All Randomized Analysis Set)			
	Intranasal Esk + Oral AD (N=72)	Oral AD + Intranasal Placebo (N=66)	Total (N=138)
All randomized	72 (100.0%)	66 (100.0%)	138 (100.0%)
Full	72 (100.0%)	65 (98.5%)	137 (99.3%)
Safety	72 (100.0%)	65 (98.5%)	137 (99.3%)
Follow-up	12 (16.7%)	3 (4.5%)	15 (10.9%)

Source: Table 5, CSR Study 3005, page 71

Figure 29 Study 3005 Patient Disposition



Source: Figure 2, CSR Study 3005, page 73

The majority of subject withdrawals from the study were due to AEs or lack of efficacy. A slightly higher percentage withdrew from the esketamine arm (14%) versus the placebo arm (9%).

Table 51 Study 3005 Subject Withdrawals

Study Completion/Withdrawal Information; Double-blind Induction Phase (Study ESKETINTRD3005: All Randomized Analysis Set)			
	Intranasal Esk + Oral AD (N=72)	Oral AD + Intranasal Placebo (N=66)	Total (N=138)
Completed	62 (86.1%)	60 (90.9%)	122 (88.4%)
Withdrawn	10 (13.9%)	6 (9.1%)	16 (11.6%)
Adverse event	4 (5.6%)	2 (3.0%)	6 (4.3%)
Lack of efficacy	3 (4.2%)	1 (1.5%)	4 (2.9%)
Lost to follow-up	1 (1.4%)	0	1 (0.7%)
Protocol violation	0	1 (1.5%)	1 (0.7%)
Withdrawal by subject	1 (1.4%)	2 (3.0%)	3 (2.2%)
Other	1 (1.4%)	0	1 (0.7%)

Source: Table 6, CSR Study 3005

Protocol Violations/Deviations

There were 31 subjects (23%) with one or more protocol deviations in Study 3005, with an even distribution between treatment arms (22% in the esketamine arm, 21% in the placebo arm). The main deviation reported was entering the study without meeting criteria (17% in the esketamine arm, 15% in the placebo arm). One subject in each arm received escitalopram as their new antidepressant, despite reporting prior treatment failure on it.

As noted earlier, one subject who was initially randomized (to the placebo arm) was excluded from the final analysis population (all sets) after one US site was audited and found to be GCP-noncompliant. This subject was withdrawn after Day 8 of the induction phase. It was unlikely that this incident would have affected the study’s results, as it only involved one subject.

There was an addendum to the CSR noting 17 additional subjects who had major protocol deviations, with 15 of them not meeting the TRD inclusion definition (mostly due to not continuing their oral antidepressant during the screening phase), and two not discontinuing their previous oral antidepressant medication on Day 1 of the induction phase. (11 were on esketamine (including the two who didn’t discontinue their antidepressants) and six were on placebo.) This may indicate a slightly higher number of patients in the esketamine arm who did not quite meet criteria for TRD, based only on lower number of treatment failures.

Table of Demographic Characteristics

Much like the other phase 3 studies, the majority of subjects in Study 3005 were white (95%), female (62%), and overweight or greater on BMI (76%). Unlike the other studies, more subjects were initiated on an SSRI (56%) than SNRI for their oral antidepressant. The mean age was 70 years, and 51% of subjects were from the United States.

Table 52 Study 3005 Demographic Characteristics of the Primary Efficacy Analysis

Demographic Parameters	Control Group (Placebo + Oral AD) (N=65) n (%)	Esketamine + Oral AD Group (N=72) n (%)	Total (N=137) n (%)
Sex			
Male	25 (39%)	27 (38%)	52 (38%)
Female	40 (62%)	45 (63%)	85 (62%)
Age			
Mean years (SD)	69.4 (4.2)	70.6 (4.8)	70.0 (4.5)
Median (years)	68.0	70.0	69.0
Min, max (years)	(65; 82)	(65; 86)	(65; 86)
Age Group			
65 to 74 years	57 (88%)	59 (82%)	116 (85%)

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Demographic Parameters	Control Group (Placebo + Oral AD) (N=65) n (%)	Esketamine + Oral AD Group (N=72) n (%)	Total (N=137) n (%)
75+ years	8 (12%)	13 (18%)	21 (15%)
Race			
White	64 (99%)	66 (92%)	130 (95%)
Black or African American	0	0	0
Multiple/Other	0	4 (5.6%)	4 (2.9%)
Unknown	1 (1.5%)	2 (2.8%)	3 (2.2%)
Ethnicity			
Hispanic or Latino	5 (7.7%)	10 (14%)	15 (11%)
Not Hispanic or Latino	59 (91%)	59 (82%)	118 (86%)
Region			
United States	36 (55%)	34 (47%)	70 (51%)
South Africa	5 (7.7%)	2 (2.8%)	7 (5.1%)
Europe	24 (37%)	35 (49%)	59 (43%)
Belgium	4 (6.2%)	2 (2.8%)	6 (4.4%)
Bulgaria	0	3 (4.2%)	3 (2.2%)
Poland	3 (4.6%)	4 (5.6%)	7 (5.1%)
Spain	4 (6.2%)	4 (5.6%)	8 (5.8%)
Finland	1 (1.5%)	1 (1.4%)	2 (1.5%)
France	3 (4.6%)	4 (5.6%)	7 (5.1%)
Italy	3 (4.6%)	6 (8.3%)	9 (6.6%)
Lithuania	0	2 (2.8%)	2 (1.5%)
Sweden	6 (9.2%)	8 (11%)	14 (10%)
United Kingdom	0	1 (1.4%)	1 (0.7%)
BMI (kg/m²)			
Underweight (<18.5)	1 (1.5%)	0	1 (0.7%)
Normal (18.5 to < 25)	14 (22%)	18 (25%)	32 (23%)
Overweight (25 to <30)	21 (32%)	28 (29%)	49 (36%)
Obese (30 to <40)	24 (37%)	23 (32%)	47 (34%)
Morbidly Obese (40+)	5 (7.7%)	3 (4.2%)	8 (5.8%)
Hypertension Status			
Yes	32 (49%)	41 (57%)	73 (53%)
No	33 (51%)	31 (43%)	64 (47%)
Oral AD Class/Type			
SNRI	30 (46%)	31 (43%)	61 (44%)
SSRI	35 (54%)	41 (57%)	76 (56%)
Duloxetine	23 (35%)	25 (35%)	48 (35%)
Venlafaxine XR	7 (11%)	7 (9.7%)	14 (10%)

Demographic Parameters	Control Group (Placebo + Oral AD) (N=65) n (%)	Esketamine + Oral AD Group (N=72) n (%)	Total (N=137) n (%)
Sertraline	10 (15%)	15 (21%)	25 (18%)
Escitalopram	25 (39%)	25 (35%)	50 (37%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The mean baseline MADRS total score for the subjects in Study 3005 was 35.2 (6.16), ranging from 19 to 51, with a mean (SD) duration of the current episode of 215.8 (341.7) weeks. (Again as with 3001 and 3002, a few subjects with baseline MADRS total scores below the MADRS screening cutoff score of 25, as low as 19, were included due to improvement between screening and baseline. As there were only a few, and the overall means between groups remained similar, these subjects were unlikely to have significantly affected the overall results.) About 32% of subjects reported a lifetime history of suicidal ideation on the C-SSRS, and 14% reported a history of suicidal behavior. Most subjects reported having failed at least two or more antidepressants (85%), with 15% failing their second antidepressant during the screening phase. Subjects mostly reported their first MDD diagnosis onset in middle age (mean age 43.1 years).

The baseline characteristics between treatment arms did not vary significantly, with the mean baseline MADRS total score at 35.5 in the esketamine arm versus 34.8 in the placebo arm. The mean current episode duration was shorter though in the esketamine arm (163.1 weeks ± 277) versus the placebo arm (274.1 ± 395), although the SD range was large. For the esketamine arm, 36% had failed 3 or more antidepressants versus 41% in the placebo arm.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- Treatment Compliance:

Site investigators or designees directly observed the self-administration of intranasal medication doses. PK levels measured on Day 22 also verified the presence of esketamine and noresketamine at dose-appropriate levels in the esketamine arm for that visit. (The only unexpectedly elevated value was in one subject over 75 years old on 28 mg.)

Table 53 Study 3005 Plasma PK Esketamine Concentrations (Day 22)

Plasma Esketamine Concentrations (ng/mL) Following Administration of 28 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	5	51.5	21.1	105	33.0	64.1
65-74 y	2 h	5	25.5	8.61	46.6	14.6	57.1
≥ 75 y	40 min	1	45.7	-	-	-	-
≥ 75 y	2 h	1	42.9	-	-	-	-

Source: Attachment [TablePK01_ESKETINTRD3005](#)

Plasma Esketamine Concentrations (ng/mL) Following Administration of 56 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	10	86.2	42.2	158	43.3	50.3
65-74 y	2 h	9	73.9	25.0	174	57.1	77.3
≥ 75 y	40 min	3	33.7	12.5	44.9	18.3	54.5
≥ 75 y	2 h	3	28.1	17.3	43.8	13.9	49.5

Source: Attachment [TablePK02_ESKETINTRD3005](#)

Plasma Esketamine Concentrations (ng/mL) Following Administration of 84 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	34	105	33.3	220	49.9	47.5
65-74 y	2 h	34	61.1	30.5	129	25.2	41.3
≥ 75 y	40 min	6	84.4	48.4	133	33.3	39.4
≥ 75 y	2 h	6	58.7	42.8	83.1	16.1	27.4

Source: Attachment [TablePK03_ESKETINTRD3005](#)

Plasma Noresketamine Concentrations (ng/mL) Following Administration of 28 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	5	43.8	19.0	56.0	14.4	32.9
65-74 y	2 h	5	52.5	8.57	90.9	30.4	57.9
≥ 75 y	40 min	1	14.7	-	-	-	-
≥ 75 y	2 h	1	16.3	-	-	-	-

Source: Attachment [TablePK04_ESKETINTRD3005](#)

Plasma Noresketamine Concentrations (ng/mL) Following Administration of 56 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	10	70.7	15.8	181	51.9	73.4
65-74 y	2 h	9	59.0	18.1	93.2	26.0	44.1
≥ 75 y	40 min	3	41.5	2.82	61.6	33.5	80.7
≥ 75 y	2 h	3	63.7	8.15	131	62.3	97.8

Source: Attachment [TablePK05_ESKETINTRD3005](#)

Plasma Noresketamine Concentrations (ng/mL) Following Administration of 84 mg Intranasal Esketamine on Study Day 22

Subject Age	Time	n	Mean	Minimum	Maximum	Standard Deviation	%CV
65-74 y	40 min	34	124	19.1	508	111	89.0
65-74 y	2 h	34	148	18.8	301	77.8	52.5
≥ 75 y	40 min	6	70.3	23.7	205	70.5	100
≥ 75 y	2 h	6	143	27.4	220	72.1	50.3

Source: Attachment [TablePK06_ESKETINTRD3005](#)

Source: Tables 24 to 29, CSR Study 3005

The mean percentage of oral antidepressant treatment compliance during the double-blind induction phase was $\geq 90.6\%$ in both treatment groups. One subject in the placebo arm received the wrong IN medication (esketamine) during one session at Day 22, and one subject in each arm received less than the minimum oral antidepressant therapeutic dose once.

Overall, there are no concerns about treatment compliance's effects on the efficacy results.

- Concomitant Medications:

The most common prior antidepressant medication used in the study population was mirtazapine (31%), then sertraline (26%), venlafaxine (26%), bupropion (24%), and duloxetine (23%).

During the double-blind induction phase, 93% of subjects reported using concomitant medications. The most common ones used were levothyroxine (20%), lorazepam (19%), atorvastatin (16%), and simvastatin (15%). The use of concomitant medications did not vary much between treatment arms (93% in the esketamine arm versus 94% in the placebo arm). For lorazepam, zolpidem, alprazolam, and clonazepam (the most commonly used sedative-hypnotics in the study), 47% of the esketamine arm used these drugs, versus 46% in the placebo arm.

There are no major concerns about concomitant medication differences affecting this study's results.

- Rescue Medications:

There were 22% of subjects in the esketamine arm versus 25% of subjects in the placebo arm who required medication for an AE. No rescue medications were used for dissociative or depression AEs.

Table 54 Study 3005 Subjects Who Used Medication for AEs of Interest

AE	Esketamine+Oral AD (N=72)	Placebo+Oral AD (N=65)
Anxiety/Feeling of Despair	5.6%	4.6%
BP Increased/HTN	2.8%	1.5%
Nausea/Vomiting	2.8%	3.1%

Source: Applicant Response to IR, November 12, 2018

Overall, use of rescue medication for AEs of interest was low and not markedly worse in the esketamine arm for this geriatric study. Their use likely did not affect study efficacy results.

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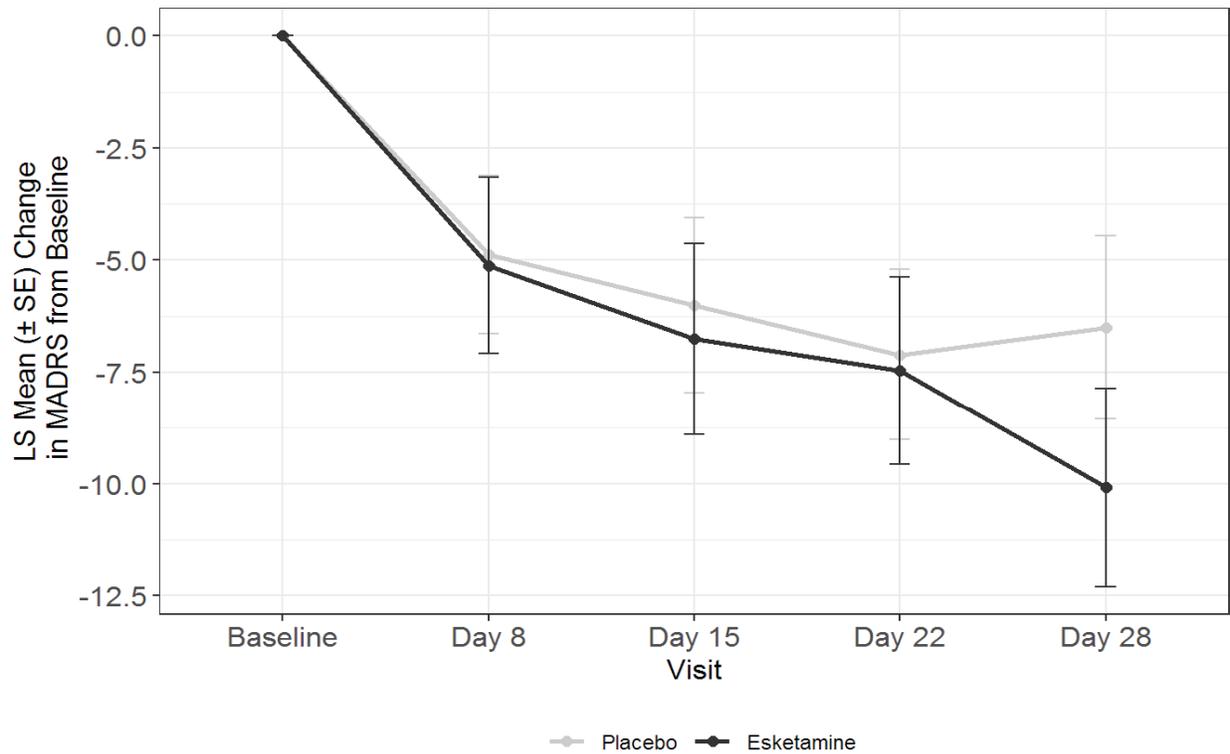
Efficacy Results – Primary Endpoint

Although there was a greater mean change from baseline on the primary endpoint of MADRS total score at study endpoint (Day 28) in the esketamine arm from placebo (LS mean difference of -3.6), the one-sided p-value via MMRM analysis was not statistically significant at 0.029. The placebo arm also showed an unexpected trend towards worsening only at Day 28. ANCOVA analysis showed the same trend and a one-sided p-value narrowly missing statistical significance at 0.026.

Table 55 Study 3005 Primary Endpoint MADRS Total Score CFB at Day 28 Using MMRM (Full Analysis Pop'n)

Treatment Arm	N	Baseline MADRS Total Score (SD)	Mean Change from Baseline (SD) at Week 4	LS Mean Change from Placebo (95% CI) at Week 4	1-Sided P-Value <0.025
Placebo+Oral AD	65	34.8 (6.4)	-6.3 (8.9)	--	--
Esketamine+Oral AD	72	35.5 (5.9)	-10.0 (13)	-3.6 (-7.2 to 0.07)	0.029

Figure 30 Study 3005 Primary Endpoint MADRS Total Score LS Mean CFB at Day 28 Using MMRM (Full Analysis Pop'n)



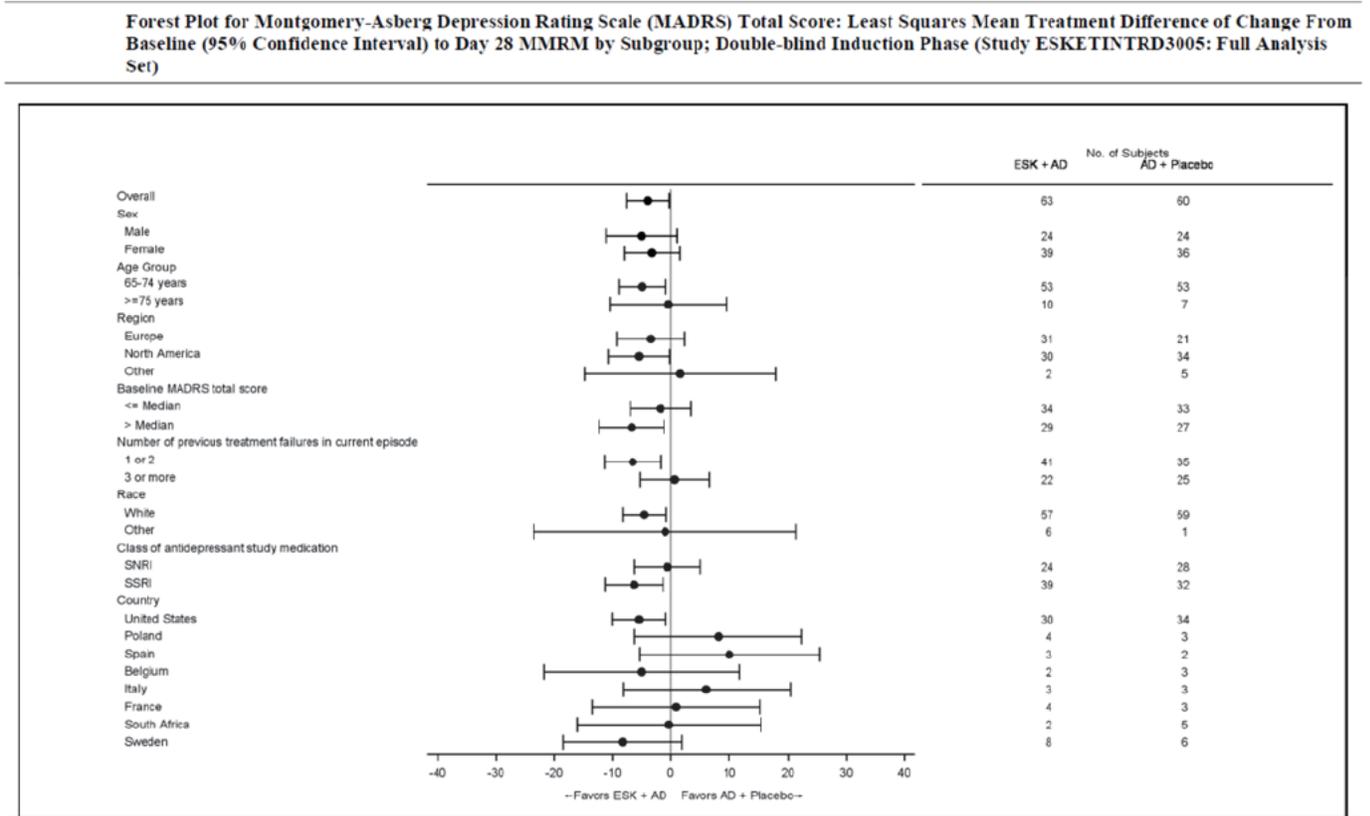
TRD 3005 - Combined Estimates

Source: Andrew Potter, PhD, Statistical Reviewer

Subgroup Analyses:

Overall, the subgroups generally favored the esketamine arm in terms of efficacy. The main exceptions were small sites in Poland, Spain, France, and Italy. Also the subgroup of subjects who had failed 3 or more antidepressants did not favor esketamine over placebo.

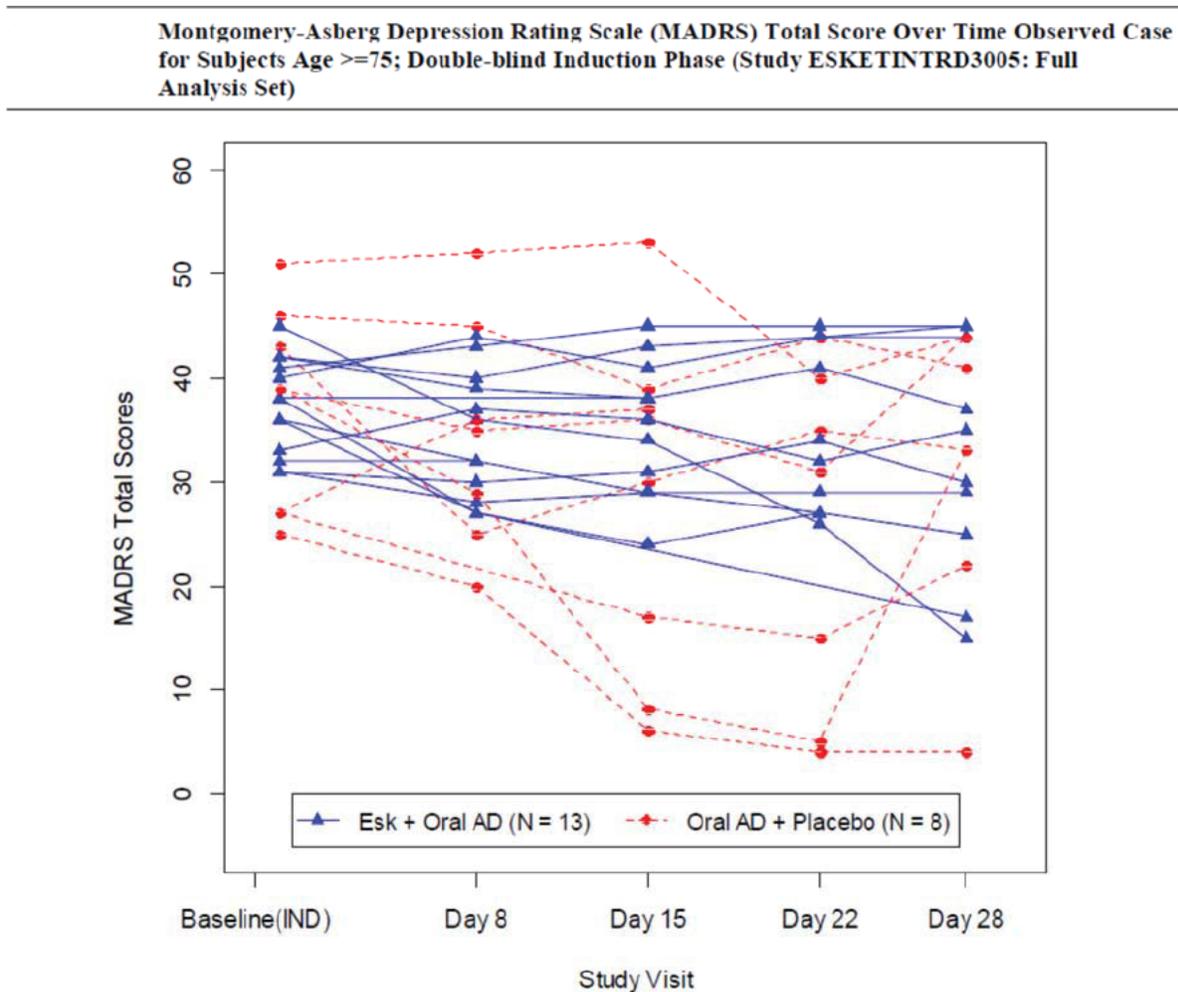
Figure 31 Study 3005 Subgroup Forest Plot



Source: Figure 4, CSR Study 3005, page 107

Results were also equivocal in the subgroup of subjects 75 years and older (n=21, with highly variable data from subject to subject and from visit to visit particularly in the placebo arm.

Figure 32 Study 3005 MADRS Total Score During Study for Subjects 75 Years and Older



Source: Figure 7, CSR Study 3005

Post-hoc analyses also showed that subjects with late-onset depression (55 years and older) showed worsening relative to placebo in this study as compared to age of onset prior to 55 years who showed improvement.

Overall, there were no clear efficacy subgroup trends, although the older subgroup (75 years and older) generally did not respond as well to esketamine versus placebo.

Data Quality and Integrity

The Applicant notes that one US site was excluded from the study after an audit detected GCP violations.

Although there were no other overt data integrity concerns, the study results give some pause, due to the unusual response curve throughout the induction phase. Unlike Studies 3001 and 3002, there was no early consistent differentiation between the esketamine and placebo treatment groups which continued to Day 28. The placebo arm suddenly worsened only on this last day relative to previous days, and the esketamine arm also suddenly improved relative to previous days. While the result still was not statistically significant, so any intentional bias is unlikely, the unusual trend possibly may indicate concerns with the integrity of the data collection at all timepoints or an inadequate sample size. The slower dosing titration for this study also does not explain the lack of differentiation between treatment groups by Days 15 and 22, where doses would have reached 56 to 84 mg for the majority of subjects.

There were also concerns raised about at least one outlier subject ([REDACTED] ^{(b) (6)}) who may have also skewed the study with multiple missing visits (please see the statistical review for more details) and highly variable subject data in the placebo arm with the 75 years and older subgroup. Finally, there was an issue with a set of reported discrepancies between the locked dataset and actual data, reported in an addendum to the CSR. These discrepancies mainly affected adverse events, protocol violations, and concomitant medication reporting and were corrected and included in the datasets for Study 3004 (long-term safety study).

Efficacy Results – Secondary and other relevant endpoints

The following secondary endpoint results are from page 126 of the Study 3005 CSR (and are either not corrected for multiplicity and/or compared statistically):

- **MADRS response rates:** The number of responders at Day 28 in the intranasal esketamine + oral antidepressant group was 17 of 63 (27.0%) subjects and 8 of 60 (13.3%) subjects in the oral antidepressant + intranasal placebo group. The NNT (95% CI) for response at Day 28 based on MADRS total score was 7.3 (-0.2; 14.8).
- **MADRS remission rates:** The proportion of subjects in remission at Day 28 was 11 of 63 (17.5%) subjects in the intranasal esketamine + oral antidepressant group and 4 of 60 (6.7%) subjects in the oral antidepressant + intranasal placebo group. The NNT (95% CI) for remission at Day 28 based on MADRS total score was 9.3 (-0.4; 19.0).
- **CGI-S:** Based on the analysis of the ranks of change in CGI-S score from baseline to the endpoint of the double-blind induction phase, results favored treatment with intranasal esketamine + oral antidepressant. The odds ratio for an improved CGI-S score was 5.3, suggesting that subjects treated with esketamine + oral antidepressant were 5.3 times more likely than those treated with oral antidepressant + intranasal placebo to have an improved CGI-S score at the end of the double-blind induction phase. However these analyses are of limited interpretability due to the use of LOCF with a categorical variable prone to skewing.
- **EQ-5D-5L:** The percentage of subjects who reported problems in 3 of the 5 individual dimensions (mobility, pain/discomfort, anxiety/depression) decreased from baseline to

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endpoint of the double-blind induction phase in both treatment groups. The percentage of subjects in the intranasal esketamine + oral antidepressant group who reported problems in the self-care and usual activities dimensions also decreased from baseline to endpoint of the double-blind induction phase.

- **SDS:** The SDS total score (mean change from baseline to study endpoint) improved for both treatment groups. Results based on MMRM and ANCOVA LOCF analysis for the change from baseline over time for SDS total score numerically favored treatment with intranasal esketamine + oral antidepressant.
- **PHQ-9:** The PHQ-9 total score (mean change from baseline to study endpoint) improved for both treatment groups. Results based on MMRM and ANCOVA LOCF analysis for the change from baseline over time for PHQ-9 total score favored treatment with intranasal esketamine + oral antidepressant.

Overall, as with the other parallel-group studies, the rates of remission and response were better in the esketamine arm than the placebo arm at Day 28 although these were not statistically compared. The other secondary outcome measures also corroborated trends towards more improvement in the esketamine arm than the placebo arm, although not within statistically significant ranges.

Dose/Dose Response

Study 3005 utilized flexible dosing for its esketamine arm. No definitive dose response data can be derived from this study.

Durability of Response

In this study, the effectiveness of esketamine in combination with an oral AD over placebo was unclear. The drug treatment response curve continues downward towards improvement through to Day 28 in the esketamine arm, but without much differentiation from the placebo arm until Day 28. The interpretability of this study's results is unclear.

Persistence of Effect

While some efficacy measures were administered during the 2-week follow-up period, the remaining sample size was very small and not interpretable. Therefore, no meaningful post-treatment efficacy information is available for this study.

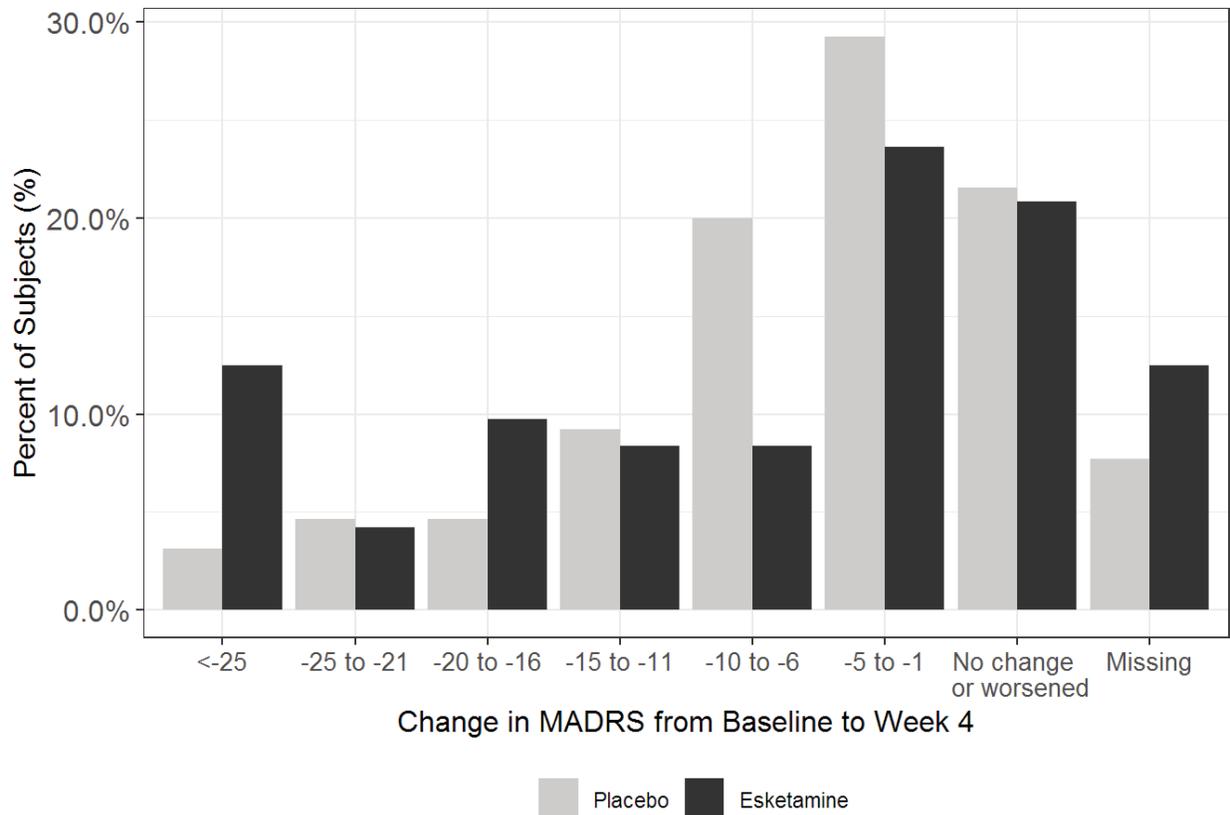
Additional Analyses Conducted on the Individual Trial

- Distribution of Response

The distribution of response of MADRS total scores in Study 3005 somewhat corroborate a greater trend towards higher magnitudes of change in MADRS total scores for esketamine-

treated subjects compared to placebo. However, unlike the other two parallel-group phase 3 studies, in Study 3005 there remains a high number of minimal (MADRS change -1 to -5) and nonresponders on esketamine. It is unclear if this trend indicates a higher degree of treatment resistance to esketamine in the geriatric population or some other issue.

Figure 33 Study 3005 MADRS Total Score Distribution of Response



Study TRD3005

Source: Andrew Potter, PhD, Statistical Reviewer

6.5. Relevant Phase 2 Studies

6.5.1. Study 2003 (SYNAPSE)

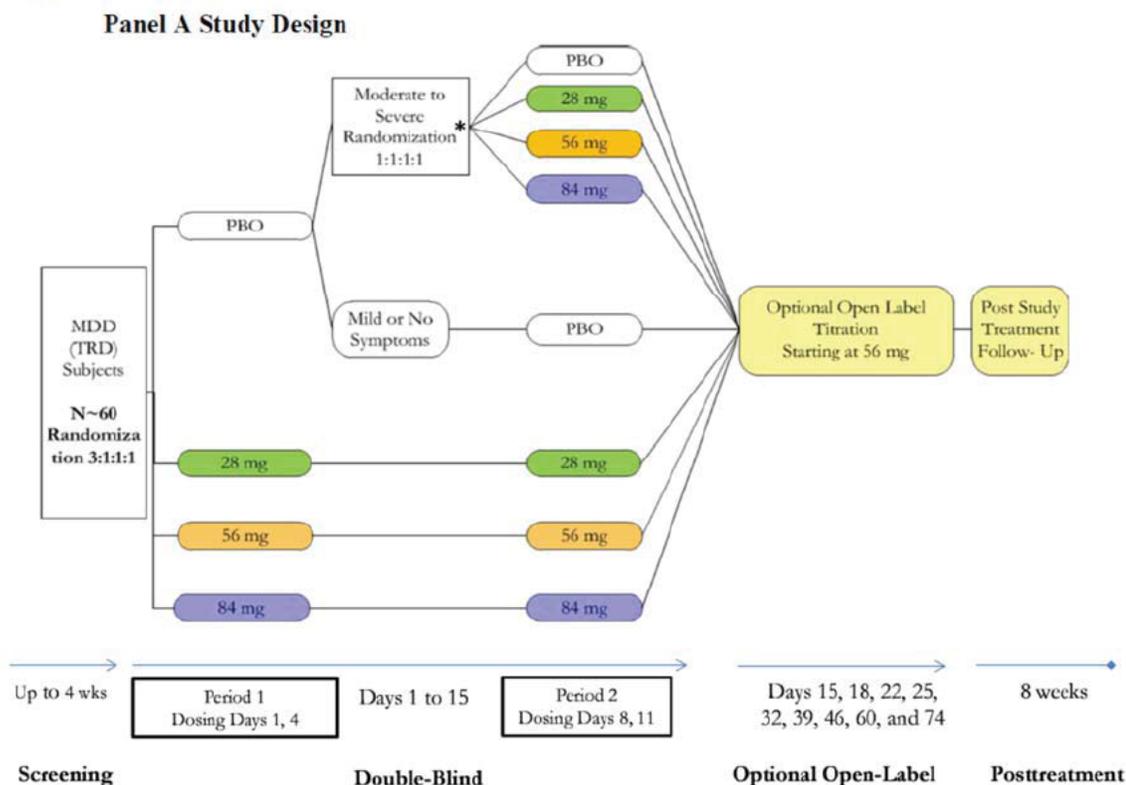
- Study Design

This phase 2 randomized, placebo-controlled, sequential parallel comparison design (SPCD), dose-response study consisted of two panels (A and B) and two one-week double-blind treatment periods (1 and 2) for each panel. Panel A studied 28, 56, and 84-mg doses of esketamine and Panel B studied 14 and 56-mg doses. Background oral antidepressant may or

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may not have been ongoing from previous treatment. The primary efficacy endpoint was the difference between IN esketamine and placebo for change from baseline in the MADRS total score for the combined double-blind treatment periods. The Applicant also analyzed pairwise comparisons of each esketamine dose versus placebo for dose response using a two different weighted combination tests based on estimates and standard errors from an ANCOVA model.

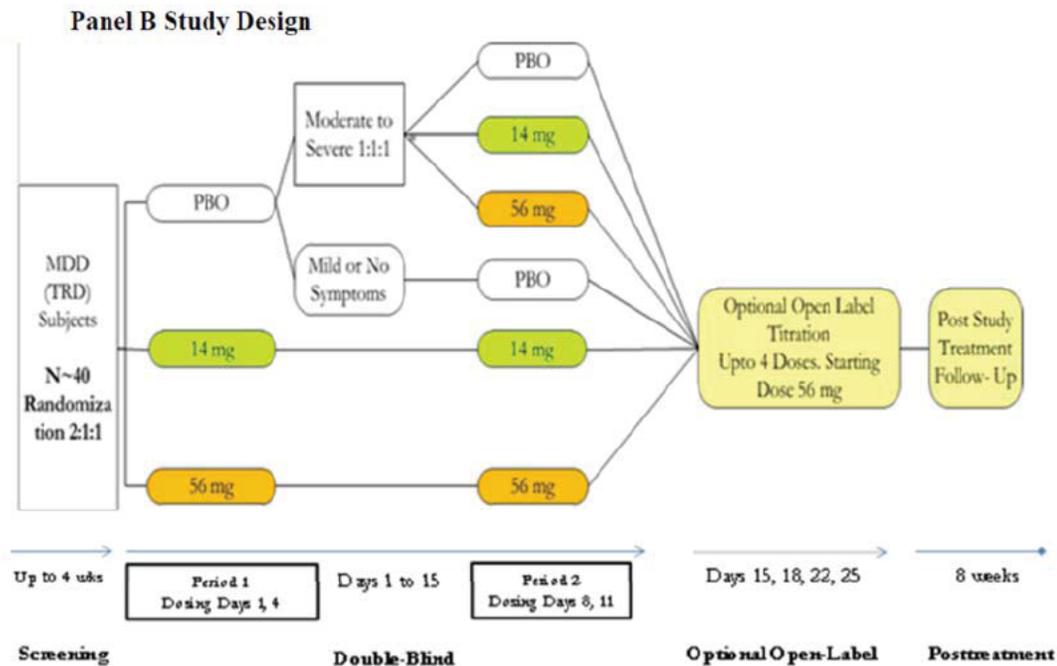
Figure 34 Study 2003 Study Design Schematic (Panel A)



* Randomization stratified by QIDS-SR₁₆ total score [Moderate = 11 to 16; Severe > 16]

Source: CSR Study 2003

Figure 35 Study 2003 Study Design Schematic (Panel B)



* Randomization stratified by QIDS-SR₁₆ total score [Moderate = 11 to 16; Severe > 16]

Source: CSR Study 2003

- Study Results

Patient were randomized to treatment (IN esketamine or placebo) at the beginning of Period 1. Placebo non-responders were re-randomized to treatment in Period 2. Panels A and B were analyzed separately for efficacy. Panel A randomized 67 subjects in the US and Belgium, and Panel B randomized 41 subjects in Japan. Baseline demographic characteristics were generally similar to the phase 3 studies, although the baseline MADRS mean total scores were lower at 34.1 in Panel A and 28.3 in Panel B.

For Panel A, there was a statistically significant difference in mean MADRS total score in all esketamine dose groups versus placebo for Periods 1 and 2 combined on ANCOVA (LOCF) analysis. In addition, all esketamine doses were statistically significantly better than placebo in Period 1 but not Period 2.

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Table 56 MADRS Total Score: Change from Baseline to End Point ANCOVA LOCF Analysis; Double-Blind Phase, Panel A, Periods 1 and 2 Combined

Esketamine Dose	28 mg	56 mg	84 mg
Mean diff. Placebo (SE)	-4.2 (2.09)	-6.3 (2.07)	-9.0 (2.13)
90% Confidence Interval for Mean diff. Placebo	(-7.67,-0.79)	(-9.71,-2.88)	(-12.53,-5.52)
One sided p-value <0.025	0.021	0.001	<0.001

Source: CSR Study 2003

Due to a failed consistency test between Periods 1 and 2, the combined analysis was not performed for Panel B. The individual period results showed no clear efficacy trends.

The results for Study 2003 also provide support for a dose response corresponding to higher doses, although Study 3001 did not confirm these results. (See the Clinical Pharmacology review for more details.)

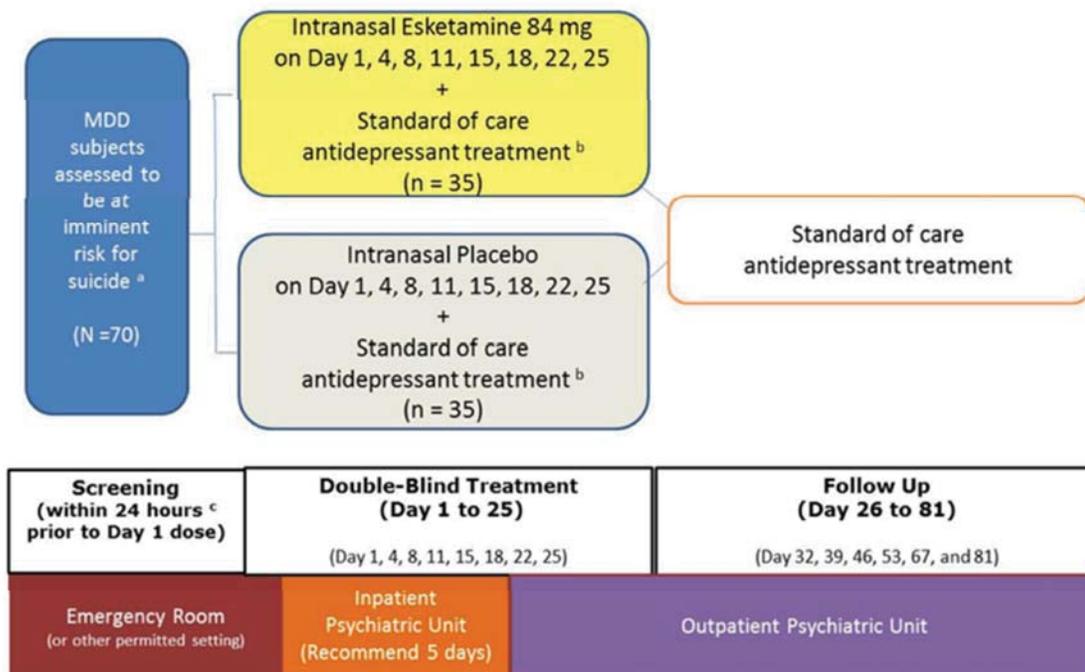
Due to the small sample size, the sequential parallel comparison design, the equivocal results for Panel B, the lack of consistency for background oral antidepressants, pre-specification of two weighted combination tests, and the shorter treatment period, I do not consider the results of this study adequate for a pivotal study but at least supportive of the overall efficacy result trends.

6.5.2. Study SUI2001

- Study Design

This was a phase 2 double-blind randomized placebo-controlled study to evaluate the efficacy and safety of IN esketamine for the rapid reduction of symptoms of MDD including suicidal ideation, in subjects at imminent risk of suicide (under a separate Investigational New Drug application). The study was conducted at ten US sites. The primary endpoint was the efficacy of IN esketamine 84 mg versus placebo as measured by mean change from baseline on the MADRS total score at 4 hours post-dose on Day 1, with secondary endpoints looking at other timepoints (24 hours post-dose (Day 2), Day 25 (end of double-blind treatment), and Day 81 (end of follow-up treatment)).

Figure 36 Study SUI2001 Design Schematic



Source: Study SUI2001 CSR

There were 68 subjects randomized to treatment after presenting to an emergency room (ER) for treatment of MDD and imminent suicidal risk. Subjects were screened for official study entry within 24 to 48 hours of receiving an initial IN dose in the ER on Day 1 of double-blind treatment (and subsequently being admitted to an inpatient psychiatric unit). After study entry, subjects were still to receive standard of care treatment for MDD and suicidal risk, including at least 5 days of hospitalization and initiation, continuation, or augmentation of oral antidepressants.

If accepted, subjects were to continue blinded treatment until Day 25, followed by a 56-day follow-up phase (Day 26 to Day 81). Subjects were randomized in a 1:1 ratio to either 84 mg IN esketamine or IN placebo, to be dosed twice weekly for 4 weeks.

Oral antidepressants were to be continued throughout the double-blind treatment phase at the same dose after reaching therapeutic range. Efficacy and safety rating assessments were to be conducted separately to improve blinding.

- Study Results

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There were 66 subjects (35 on esketamine, 31 on placebo) who received at least one dose of study medication and comprised the intent-to-treat (ITT) population. There were 49 completers (27 on esketamine, 22 on placebo). The majority of the 19 subjects who discontinued the study early were due to adverse events and lack of efficacy. Major protocol deviations occurred at similar rates across both treatment groups.

The majority of subjects were female (65%), with a mean age of 35.8 years (and a majority of subjects under age 35 at 55%). The mean MADRS score was 38.6 (± 6.5). All subjects had answered “yes” to having current suicidal ideation with intent on Question B5 of the Mini-International Neuropsychiatric Interview (MINI). These demographics reflect a severely ill study population, comparable to the one studied in the TRD adult phase 3 trials.

The efficacy results on the MADRS show numerical improvement at all timepoints on esketamine compared to placebo, although there was no statistically significant difference between treatment groups at Day 25. Day 1 (4 hours post-dose) was the primary efficacy endpoint for this study. (Day 2 and Day 25 were the secondary endpoints.)

Table 57 Study SUI2001 MADRS Mean Total Score Change from Baseline

	Day 1 (Primary Endpoint)	Day 2	Day 25
Esketamine (SD)	-13.4 (9.0)	-19.3 (12.0)	-26.4 (14.5)
Placebo (SD)	-9.1 (8.4)	-12.8 (9.8)	-23.0 (10.8)
LS Mean Difference (SE)	-5.3 (2.1)	-7.2 (2.9)	-4.5 (3.1)
2-sided p-value <0.05	0.015	0.015	0.159

Source: Study SUI2001 CSR

The percentage of responders and remitters was also numerically higher at all timepoints in the esketamine group versus the placebo group (including at Day 81). At Day 25, 83% in the esketamine group were responders versus 63% on placebo. For remitters, 67% were on esketamine versus 50% on placebo.

Overall, although the sample size is small, and the background oral antidepressant was not as consistently controlled as in the phase 3 studies, this study is of interest as a parallel-group study in a population with significant MDD illness severity and clinical morbidity; the study presents supportive evidence consistent with most of the prior TRD esketamine study results.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Study 3002 and Study 3003 were statistically significant on their primary efficacy endpoints, whereas Study 3001 and 3005 were not.

7.1.1. Primary Endpoints

The following information summarizes the primary endpoint efficacy results from the phase 3 esketamine studies:

Table 58 Primary Efficacy Results for Phase 3 Short-Term Esketamine Studies

Study Number	Treatment Group	N	Primary Efficacy Measure: MADRS Total Score			1-sided p-value (compared to 0.025)
			Mean Baseline Score (SD)	LS Mean Change from Baseline (95% CI)	LS Mean Difference from Placebo (95% CI)	
3001	ESK 56 mg ^a	115	37.4 (4.8)	-18.9 (-21.4 to -16.4)	-4.1 (-7.7 to -0.6)	0.013
	ESK 84 mg	114	37.8 (5.6)	-18.2 (-20.9 to -15.6)	-3.2 (-6.9 to 0.5)	0.044
	Placebo	113	37.5 (6.2)	-14.9 (-17.4 to -12.4)	--	--
3002	ESK (56 or 84 mg)*	114	37.0 (5.7)	-20.8 (-23.3 to -18.4)	-4.0 (-7.3 to -0.6)	0.010
	Placebo	109	37.3 (5.7)	-16.8 (-19.3 to -14.4)	--	--
3005	ESK (28, 56, or 84 mg)	72	35.5 (5.9)	-10.1 (-13.1 to -7.1)	-3.6 (-7.2 to 0.1)	0.029
	Placebo	65	34.8 (6.4)	-6.5 (-9.4 to -3.6)	--	--

^aLower dose could not be tested because the higher dose failed

*Arm is statistically significant compared to placebo

Source: CSRs for 3001, 3002, 3005

The maintenance-of-effect Study 3003 included responders from 3001 and 3002 as well as direct-entry subjects who underwent an open-label protocol and met response criteria. The primary efficacy endpoint was time to relapse for stable remitters who were randomized to continue IN esketamine versus those who were put on IN placebo, with oral antidepressant

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ongoing in both arms. The endpoint hazard ratio of 0.49 was statistically significant with a p-value of 0.003.

Clinical Relevance of Primary Endpoints:

The MADRS is a well-established scale for assessing symptom severity in MDD. Cutoff score correlations with symptom severity for the MADRS vary in the research literature, but one agreed-upon range follows:

- 0 to 6: normal/symptoms absent
- 7 to 19: mild depression
- 20 to 34: moderate depression
- >34: severe depression⁹.

The following definitions were used for response and remission after a given antidepressant regimen in the esketamine phase 3 studies (with adjusted criteria for occasional excursions or missing data):

- Remission: MADRS total score ≤ 12
- Response: $\geq 50\%$ reduction in MADRS total score from baseline (Day 1 of induction phase prior to first IN dose), without meeting criteria for stable remission.

While the responder definition is reasonably similar to the one found in most research literature¹⁰, the remission cutoff score of 12 may be on the higher side of the range studied in the literature (with some papers advocating for scores as low as 4 and below and as high as 11 and below)¹¹. A paper by Zimmerman et al noted that lower remission cutoff scores may provide a more accurate clinical standard, and that remission prevalence rates can increase with higher cutoff scores¹².

For the esketamine phase 3 studies 3001 and 3002, the mean numerical difference from baseline MADRS total score to study endpoint for Studies 3001 and 3002 (-18.8 to -21.4) roughly correspond to mean positive responder values (-18.5 to -18.9 indicating at least 50% reduction from mean baseline MADRS total scores) for the esketamine arms in those studies.

⁹ Herrmann, N, et al. "The Sunnybrook Stroke Study: A Prospective Study of Depressive Symptoms and Functional Outcome." *Stroke* 1998; 29(3):618-624.

¹⁰ Riedel M, et al. "Response and Remission Criteria in Major Depression: A Validation of Current Practice." *J Psychiatr Res* 2010; 44(15):1063-8.

¹¹ Zimmerman M, et al. "Defining Remission on the Montgomery-Asberg Depression Rating Scale." *J Clin Psychiatry* 2004; 65(2):163-8.

¹² Zimmerman M, et al. "Implications of Using Different Cut-Offs on Symptom Severity Scales to Define Remission from Depression." *Int Clin Psychopharmacology* 2004; 19(4):215-220.

The placebo arms' numerical change was smaller than positive responder values. Study 3005's mean numerical MADRS degree of change did not exceed positive responder values in either arm.

While the MADRS total score difference from placebo was not statistically significant for Study 3001, one might interpret the overall numerical score differences from baseline as within clinically significant responder ranges (especially when considering the mean baseline MADRS total score was higher in that study than the other phase 3 studies, and also much higher than baseline scores in other drug trials for other approved antidepressants). These numerical mean MADRS score reductions meeting the definition of clinical response may be a supportive consideration for esketamine's effect's clinical meaningfulness. I will discuss the study remission rates in the next section.

7.1.2. Secondary and Other Endpoints

Overall, none of the prespecified secondary endpoints was statistically significant. The other secondary endpoints were not controlled for multiplicity. Accordingly, none of these endpoints meet criteria for inclusion in labeling.

Table 59 Esketamine TRD Phase 3 Parallel-Group Study Secondary Endpoints

Study Treatment Arm	3001			3002		3005	
	ESK 56 mg	ESK 84 mg	Placebo	ESK	Placebo	ESK	Placebo
MADRS Sustained Response Day 2+	10%; p-value 0.010	9%; p-value 0.041	2%	8%; p-value 0.161	5%	n/a	n/a
SDS	-2.5; 0.036	-2.2; 0.059	n/a	-4.0; <0.001	n/a	-4.6; 0.007	n/a
PHQ-9	-2.3; 0.012	-2.2; 0.016	n/a	-2.4; 0.003	n/a	-2.8; 0.009	n/a
MADRS Responders at Day 28	54%	53%	39%	69%	52%	27%	13%
MADRS Remitters at Day 28	36%	39%	31%	53%	31%	18%	7%
MADRS Sustained Response Day 8+	13%; 0.005	11%; 0.009	4%	11%; 0.137	6%	n/a	n/a

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Study	3001			3002		3005	
Treatment Arm	ESK 56 mg	ESK 84 mg	Placebo	ESK	Placebo	ESK	Placebo
CGI-S*	-2.0; 0.006	-2.0; 0.021	-1.0; n/a	-2.0; 0.017	-2.0; n/a	-1.0; <0.001	0.0; n/a
GAD-7	-1.5; 0.012	-1.4; 0.016	n/a	-1.0; 0.061	n/a	n/a	n/a
EQ-5D-5L CFB Mean Sum Score**	-19.0	-19.4	-14.6	-23.2	-17.1	-6.6	-1.6

*Median Score Change from Baseline Only

**Mean Score Change from Baseline Only

(SDS, PHQ-9, and GAD-7 Values are Change from Baseline Difference from Placebo)

(P-values are one-sided compared to 0.025)

Source: Esketamine Study CSRs

However, a few secondary endpoints were nominally significant on exploratory p-values (uncontrolled for multiplicity or unable to be formally tested due to a prespecified testing sequence), and all showed numerical improvement for esketamine treatment arms versus placebo. The only prespecified secondary endpoint that was consistently in the nominally significant range for p-values across the phase 3 parallel-group studies was the PHQ-9, a self-reported measure. This result may indicate a confirmatory trend towards efficacy for depressive symptoms as also seen with the MADRS with esketamine. (The CGI-S was also nominally significant across all the studies, but the interpretability of the ANCOVA analysis using LOCF is questionable with a categorical variable that is more vulnerable to skewing. If valid, the results may provide additional supportive evidence that esketamine provides functional improvement for illness severity in subjects.)

The self-reported EQ-5D-5L also showed numerical improvement in all the phase 3 parallel group studies for the esketamine groups versus placebo, indicating a trend towards functional improvement. Also, remission (MADRS ≤ 12) and responder ($\geq 50\%$ MADRS Reduction from Baseline) rates are numerically better for esketamine arms versus placebo arms in all phase 3 short-term studies (although these values were not statistically compared):

Table 60 Esketamine TRD Phase 3 Responder and Remitter Rates at Day 28

Study	Esketamine 56 mg Fixed (or Flexible Combined with 84 mg)	Esketamine 84 mg Fixed	Placebo
3001 Responders	54%	53%	39%
3001 Remitters	36%	39%	31%
3002 Responders	69%	--	52%
3002 Remitters	53%	--	31%
3005 Responders	27%	--	13%
3005 Remitters	18%	--	7%

Source: Study CSRs

A similar trend is seen on the distribution of response based on MADRS total scores in the short-term studies, with subjects on esketamine showing higher percentages in the low MADRS total score categories at study endpoint compared to those on placebo, with oral antidepressant ongoing in both groups.

While one caveat to the remitter rates is the relatively high cutoff score of 12 compared to those recommended by research literature (see discussion in previous section), the numerically higher rate differentiation from placebo remains present, even with progressively lower MADRS cutoff scores in Studies 3001 and 3002.

Table 61 Study 3001 and 3002 Subjects in Remission at Endpoint Based on MADRS Total Score

			Subjects with MADRS Total Score (Percentage of Arm)						
Study	Arm	N	≤12	≤11	≤10	≤9	≤8	≤7	≤6
Study 3001	Esketamine 56 mg	115	40 (35%)	38 (33%)	36 (31%)	36 (31%)	32 (28%)	30 (26%)	29 (25%)
	Esketamine 84 mg	114	40 (35%)	39 (34%)	38 (33%)	36 (32%)	32 (28%)	27 (24%)	25 (22%)
	Placebo	113	33 (29%)	31 (27%)	26 (23%)	24 (21%)	21 (19%)	20 (18%)	20 (18%)
Study 3002	Esketamine	112*	54 (48%)	48 (43%)	43 (38%)	36 (32%)	34 (30%)	29 (26%)	23 (21%)
	Placebo	109	33 (30%)	28 (26%)	26 (24%)	23 (21%)	20 (18%)	19 (17%)	19 (17%)

*N is 112 after excluding 2 subjects from FA population who had no recorded post-baseline MADRS score (see Study 3002 Study Results for more details)

Source: Reviewer JMP Analysis of ADMADRS.xpt from Summary of Clinical Efficacy

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Having occurred across three short-term phase 3 studies, these consistent remission and response trends, although not statistically compared, may still indicate that there is a clinically relevant subgroup of TRD patients who greatly respond to esketamine in addition to their oral antidepressant for their depressive symptoms and daily functioning.

7.1.3. Subpopulations

See above re: responders and remitters. There was no consistent trend between Study 3001 and 3002 re: higher number of previous antidepressant trials affecting results or higher baseline MADRS scores, so higher levels of baseline treatment resistance were not a clear factor in the study results. The type of oral antidepressant used also did not appear to correlate with any shifts in efficacy trends. US subgroups were consistent with overall study trends, indicating applicability of phase 3 study results to the US population.

7.1.4. Dose and Dose-Response

Although the phase 2 PK studies indicated a more definitive dose-response trend with esketamine 56 mg versus 84 mg, Study 3001 did not confirm that trend. As dose-response information cannot be stratified from Study 3002 or 3005 due to their design, we may not have sufficient supportive evidence that esketamine 84 mg provides any additional benefit over 56 mg. However, in the combined-dose esketamine treatment arm in Study 3002 (with about 2/3rd of subjects in the group taking esketamine 84 mg), esketamine 84 mg appears to be an effective dose. (It is unclear from the study protocol what investigators used as efficacy and tolerability criteria for advancing the dose to 84 mg.) The 84-mg dose has an increased incidence of some adverse events (AEs) over 56 mg (mainly vomiting, dissociation, and sedation; see the safety review section). However, the types and rates of AEs on 84 mg are not severe enough to consider it an unsafe dose affecting benefit-risk to the point of a labeling restriction. We have requested a postmarketing commitment for a repeat fixed-dose study to gather additional data on dose response.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Studies 3001 and 3002 indicate esketamine already separates from placebo as early as Day 2, and with higher rates of responders by Day 8. This early onset of potential antidepressant response may confirm esketamine's rapid-onset profile, with the oral antidepressant in both arms not yet fully taking effect. (Reportedly oral antidepressant effects should start Week 2 and increase thereafter, although there are some disagreements on this issue in the literature, with some meta-analyses indicating response as early as end of Week 1.)¹³

¹³ Taylor MJ, et al. Early Onset of Selective Serotonin Reuptake Inhibitor Antidepressant Action: Systematic Review and Meta-Analysis. *Arch Gen Psychiatry*. 2006; 63(11):1217-1223.

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Both studies show a response curve (except for the slight bump upward on the 3rd visit) where mean MADRS total scores continue to trend downward in both arms by Day 28. Overall, it appears that esketamine provides an “add-on” booster response to the baseline oral antidepressant treatment response curve (based on the placebo arm) at all timepoints in Studies 3001 and 3002. The amount of the “add-on” response is generally consistent at all timepoints in both studies (and confirmed by a change from baseline analysis in the statistical review), which is likely the primary effect of esketamine. It is impossible to know completely from this study design if the continued improvement of the esketamine arm is partly from independent effects of esketamine simply adding onto the underlying oral antidepressant response, or a synergistic combination with the oral antidepressant leading to a stronger treatment response versus the oral antidepressant alone. In any case, the esketamine arm by study endpoint shows a numerical improvement over the placebo arm, with oral antidepressant ongoing in both arms.

It is also unclear if early response to esketamine correlates with later treatment response, or vice versa (lack of early response means later poorer response). Exploratory analyses by the statistical reviewer could not answer this question due to the study design including concomitant IN study drug and oral antidepressant in both arms.

There may be some short-term persistence of esketamine response post-induction dosing (twice weekly); in Study 3001, mean MADRS scores continued to decrease in the 2-week follow-up period after esketamine discontinuation in both arms (with oral antidepressant ongoing) but still maintained higher response in the esketamine arms.

There is also statistically significant longer-term durability of effect with maintenance dosing of esketamine versus placebo, based on the results of maintenance-of-effect study 3003. Subjects who remained on esketamine weekly or every other week relapsed less and maintained remission than those who switched to placebo, with oral antidepressant ongoing in both groups.

However, the rate of relapse (as per increasing MADRS scores or clinically significant event) after maintenance esketamine discontinuation was more rapid (within two to four weeks) in the placebo arm relative to the esketamine arm than that seen in other oral antidepressant maintenance-of-effect studies, even with an oral antidepressant still ongoing. This faster relapse rate may indicate that esketamine’s effects are not as persistent post-discontinuation with more infrequent dosing, or after a longer period of treatment. The clinical relevance of this more rapid rate of relapse in the trial is not completely clear (the rate is a comparative rate of decline between arms; however, the absolute percentage of subjects relapsing early in the study was still low). Additional clinician vigilance for signs of depressive relapse may be warranted soon after stopping maintenance esketamine treatment in patients (although no clear trends in this regard were seen at least based on AEs: there were ten subjects (6.6%) with

depression or anxiety-related AEs still on esketamine + oral antidepressant versus six subjects (4.2%) switched to placebo + oral antidepressant up to 30 days post-randomization in 3003).

Overall, the response properties seen in the phase 3 esketamine studies support durability (and brief persistence post-induction dosing) of efficacy of esketamine in combination with oral antidepressant treatment for the treatment of TRD after 4 weeks of twice weekly IN esketamine dosing, and then stepping down to optimization and maintenance dosing. There is some evidence for an early rapid-onset response based on MADRS total score reduction for esketamine versus placebo groups at Day 2 which largely continued at most timepoints and at Day 28; however, the onset of response ($\geq 50\%$ MADRS reduction at Day 2 sustained through to Day 28) secondary endpoint was not statistically significant and did not fully confirm the longer-term clinical significance of this early effect in the study population. Still, an early antidepressant response, even with variable sustained response, could have potential clinical ramifications in real-world treatment settings where acute depressive crises require urgent intervention and alleviation of distress.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Some potential postmarket considerations are as follows:

- Esketamine in clinical practice is likely to still be used with or without oral antidepressant, or as add-on to a pre-existing oral antidepressant in real-life clinical practice. There may be concerns about insurance coverage or pharmacy restrictions for the use of esketamine monotherapy (which would not be a labeled indication of use as yet, due to how the clinical trials were conducted).
- Dose-response for 84 mg over 56 mg is still unclear from the phase 2 and 3 studies.
- The drug is likely to be used with varying off-label frequency in dosing, as recommended by clinicians, compared to labeling recommendations (as little as monthly, and possibly more frequently than twice weekly if REMS restrictions are adjusted in the future). Patients may also have to miss doses due to limited or lack of esketamine-certified clinic access during travel or illness or other delays.
- Patients who receive esketamine will have a wider range of comorbidities than studied in the clinical trials: both psychiatric (anxiety, substance abuse, bipolar, personality disorders, dementia, active suicidality) and physical (cardiovascular issues). In particular, the effects of esketamine on depression that occurs with psychosis (such as MDD with psychotic features, or schizoaffective disorder) needs to be better characterized, given esketamine's psychotogenic effects.
- Patients who take esketamine may take concomitant medications that can potentially interact with the drug, particularly sedative-hypnotics which are common in patients

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with psychiatric conditions.

- Esketamine will likely still be used clinically in an elderly population, despite (b) (4) the lack of a positive geriatric efficacy study. A limitation of use is unnecessary though, as there still may be individual geriatric patients who respond to esketamine, and the safety profile showed no unusual concerns in that population.
- In clinical practice, esketamine may possibly be used in limited cases in older adolescents but our iPSP agreed with a pediatric study waiver for now and no labeled indication for use. The IND for MDD with imminent suicidal risk will include requirements for a pediatric study.
- Overall, the US subgroup in the clinical studies had efficacy trends in line with the phase 3 study results, so the phase 3 study results are likely still applicable to the US population.
- Given the human factor study concerns (difficulty getting accurate dosing with existing packaging and instructions, single-container packaging, spray technique), we should follow-up on postmarketing human factor issues that arise, both already identified and any new ones. Instructions for use should be made clear to patients.
- We may have to consider the following interventions to mitigate future risks and inform future recommendations on safe use during the postmarket period:
 - Postmarketing commitment study for esketamine as monotherapy for TRD and fixed-dose data to reassess dose response
 - Labeling to address medical warnings for BP, bladder, cognition, liver, etc.
 - Pharmacovigilance/REMS for adverse reaction tracking (such as cardiovascular comorbidities, long-term cognition and bladder concerns, drug interactions especially with sedative-hypnotics, etc.)
 - REMS for substance abuse risk (office setting administration only)
 - Monitoring or flagging prescribers who use esketamine more frequently than indicated for abuse or diversion concerns, or observe in postmarketing data whether increased use is clinically necessary in a subset of patients and adjust our REMS program accordingly
 - Ongoing postmarket tracking and data on dosing and access concerns (rural areas, people going on vacation to areas without clinics or missing doses for various reasons, nonadherence due to restricted access, etc.)
 - Future studies for other psychiatric indications (particularly other forms of depression such as bipolar depression, psychotic depression, schizoaffective disorder, etc.). SI reduction is currently being studied for esketamine.

7.2.2. Other Relevant Benefits

Other pertinent practical and clinical benefits of esketamine relative to other existing therapies for TRD include:

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- Intranasal dosing (easier than IV or IM for ketamine, less invasive than procedural treatments)
- Different mechanism of action (may provide additive or different benefit to existing antidepressants, different side effect profile)
- Infrequent dosing (twice weekly initially but can be as infrequent eventually as every other week, less frequent office visits than ECT or TMS)
- Fewer drug interactions than most oral antidepressants
- No need for respiratory monitoring/general anesthesia (as with ECT) or surgical intervention (VNS), no use of exogenous electrical impulses (ECT, TMS, VNS).
- *Patient Preference Study Results:*

A patient preference study conducted by the Applicant surveyed 159 subjects with TRD enrolled in the esketamine clinical trials (from Studies 3004 and 3008 in the US, UK, Canada, and Australia) and 297 patients in the general population (via online screening panel) with TRD. The survey asked subjects to make a series of choices between pairs of depression treatments on what types of symptoms, degree of efficacy, and adverse reactions they would consider acceptable and/or preferable. These choices were quantified as maximum acceptable risk (MAR) when the degree of acceptable risk for a given issue (i.e., memory problems, bladder issues, etc.) matched the degree of mood improvement (either 30-point drop in MADRS, 20-point, or 10-point). Clinical trial respondents were older, more male, completed higher education levels, had longer depression histories, and rated depression less severe than the panel respondents.

There were three distinct types of responses noted:

1. “Mood-dominant” set in 35% of clinical trial respondents and 14% of panel respondents who preferred the medication improving mood in all 8 choice questions, regardless of other issues
2. “Risk/sensation/time-dominant” set in 6% of clinical trial respondents and 14% of panel respondents who selected the alternative with the better level of a given attribute (long-term risk, short-term sensations, post-dose symptoms, time to efficacy) each time
3. “Trade-off” set in 54% of clinical trial respondents and 64% of panel respondents who were willing to accept tradeoffs for benefit and risk with each treatment.

For the “trade-off” respondents, a preference weight analysis was conducted for given medication attributes to determine MAR:

- The MAR for cognitive and bladder issues were both 5% in the clinical trial sample compared to 10% MAR in the panel sample.
- The preference for 24-hour versus 6-week onset of effect was not statistically significant in the clinical trial sample.

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- The preference for “unusual sensations, wait time, help getting home” and “none” was not statistically significant in the clinical trial sample. There was a higher weight of concern on these issues in the panel sample. The Applicant theorized that this discrepancy may reflect that after experiencing these issues firsthand in the clinical trials, those respondents were not as worried about them relative to their treatment response.
- Respondents in both groups who reported having their worst depression ever at milder MADRS scores (10, 20, 40) placed less weight on achieving mood improvement and avoiding cognitive problems than those with more severe depression at MADRS 60.
- Respondents with previous ketamine experience (13% of panel respondents) placed less weight on achieving mood improvement.

Overall, these survey results indicate that potential patients with TRD considering esketamine treatment would likely accept the issues with dissociation and waiting time and not driving home in order to obtain clinically significant improvement in their depressive symptoms, but these patients may not be as tolerant of serious issues with cognitive impairment and bladder toxicity (although these issues were described as “permanent” in the survey which would intensify concern).

- *Efficacy Relative to Other Approved Antidepressants:*

According to prior efficacy endpoint results for MADRS in other FDA-approved antidepressants, the numerical improvement for esketamine mean difference from placebo is similar, and in a population with a higher baseline MADRS score indicating more illness severity.

Table 62 Effect Sizes Relative to Other Approved Antidepressants

Indication	Antidepressant	MADRS LS Mean CFB at Primary Endpoint Range	MADRS LS Mean CFB Difference from Placebo/Active Control	Baseline MADRS Score
MDD	Vortioxetine	-13 to -20	-2.8 to -7.1	31 to 34
	Vilazodone	-9.7 to -13	-2.5 to -3.2	31 to 32
	Levomilnacipran	-14 to -17	-1.3 to -4.9	30 to 36
Adjunctive MDD	Aripiprazole	-8.5 to -8.8	-2.8 to -3.0	31 to 32
	Brexipiprazole	-7.7 to -8.5	-1.3 to -3.1	33 to 35
	Quetiapine XR	-14 to -17	-1.6 to -4.1	28 to 32
TRD	Symbyax	-8.6 to -14	n/a	23 to 30
	Fluoxetine (vs.	-1.2 to -11	-1.4 to -12	“

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Indication	Antidepressant	MADRS LS Mean CFB at Primary Endpoint Range	MADRS LS Mean CFB Difference from Placebo/Active Control	Baseline MADRS Score
	Symbyax)			
	Olanzapine (vs. Symbyax)	-2.8 to -10	-0.8 to -11	“
	Esketamine	-10.1 to -20.8	-3.2 to -4.1	37 to 38 adult, 35 geriatric

Source: Antidepressant Trials from Previously Approved NDAs

7.3. Integrated Assessment of Effectiveness

The primary efficacy endpoints for Studies 3002 and 3003 (using change in MADRS total score from baseline and time to relapse as measured by MADRS total score, respectively) were statistically significant. Study 3002 was a flexibly-dosed, randomized, parallel group, placebo-controlled trial, and Study 3003 was a randomized withdrawal placebo-controlled trial.

Typically, antidepressant development programs conduct longer-term maintenance studies (such as Study 3003) on a supplementary basis after initial drug approval with evidence derived from two short-term studies. These studies answer the important question of efficacy of a drug for longer-term maintenance treatment. But given the unique mechanism of action of esketamine (with more rapid onset but also more rapid metabolism), and the lack of information on the durability of antidepressant effect for this new drug class, we requested maintenance data with the initial NDA submission. Accordingly, Study 3003 has provided crucial evidence of effectiveness in longer-term treatment for esketamine.

All of the short-term studies also had several efficacy endpoints or analyses that were either nominally significant or numerically superior for esketamine compared to placebo and provided supportive evidence for the primary efficacy results in 3002 and 3003. The 56-mg esketamine arm in Study 3001 was nominally significant, although due to the prespecified analysis plan, this statistical comparison could not be formally tested or considered fully interpretable. The treatment response curve (based on the MADRS total score) in Study 3001 for both esketamine arms was similar to that seen in Study 3002, including signs of early differentiation from placebo at Day 2. Also, the numerical mean difference from placebo on the MADRS at endpoint in the phase 3 short-term studies were comparable to other approved antidepressants, in spite of the fact that the esketamine studies enrolled a treatment-resistant population whose mean baseline MADRS score was higher than that of any studies supporting other FDA antidepressant approvals. The mean numerical MADRS score reductions in both Studies 3001 and 3002 for the esketamine arms (and not placebo) were $\geq 50\%$ from baseline, a known index of MADRS-based

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clinical response in MDD per research literature. The percentage of subjects meeting criteria for maintaining remission and response, while not statistically compared, was larger in the esketamine arms of all the phase 3 parallel-group studies versus the placebo arms. These remission/response percentage results across multiple studies provide supportive evidence that there is a consistent subgroup of patients with TRD that experience a substantial improvement in clinical symptoms (as based on MADRS total scores) with esketamine combined with an oral antidepressant, and at rates higher than continuing an oral antidepressant alone.

However, there are other mixed efficacy results that raise questions as to whether the results are conclusive. Study 3001, the fixed-dose adult RCT, was not statistically significant for the 84-mg esketamine arm, the higher dose in the study. A higher number of withdrawals/dropouts occurred in that dose arm, which may have impacted its interpretability and results. The increased dropout rate did not appear to be due to higher-dose-related tolerability issues, as most of the dropouts occurred only after the initial 56-mg dose. A higher number of study withdrawals by chance, in combination with a relatively small sample size, might have prevented that study arm from being statistically significant.

Also, the geriatric Study 3005 was not statistically significant on its primary endpoint, despite the use of the same maximum dosage (84 mg) as the non-geriatric studies (although the geriatric study used a lower starting dose of 28 mg). The response curve was dissimilar to the other short-term studies, with an odd and sudden trend towards differentiation from placebo only at Day 28.

Despite being statistically significant on their primary endpoints, Study 3002 and 3003's results could have hypothetically been affected by potential expectation bias from esketamine's acute effects. Without the use of a psychoactive intranasal placebo, all of the phase 3 studies had potential unblinding concerns regarding esketamine's immediate and well-known effects of sedation, dissociation, and cardiovascular changes. Both subjects and site personnel (who had to closely monitor AEs) may have perceived which arm they were assigned to based on those effects. (The use of blinded remote raters to score the primary efficacy measure (MADRS) mitigates the concern of rater unblinding to some extent.) These changes may have been even more noticeable in a randomized withdrawal design, when all subjects became familiarized with esketamine treatment for many weeks, and then experienced either a continuation or discontinuation of the familiar effects, according to treatment assignment.

The Applicant conducted a symptom-based sensitivity analysis in Study 3003 to monitor for potential unblinding in the first 19 placebo subjects who relapsed (within 4 weeks), using pre- and post-randomization scores on the CADSS and MOAA-S. The Applicant noted the majority of those subjects did not notice a difference in dissociative symptoms per the CADSS before or after randomization, and none reported changes in sedation. When potentially affected subjects (those who exhibited CADSS and MOAA-S changes post-randomization) were excluded

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post-hoc, the relapse trends remained the same. Investigators were also instructed not to inform subjects of BP changes during treatment sessions unless clinically warranted. Our statistical reviewer conducted an analysis indicating a correlation between lack of dissociation and relapse on placebo; however, it was impossible to confirm the significance of this correlation.

Additionally on the efficacy-supportive side for Study 3003, an exploratory analysis of Study 3003 by the statistical reviewer found that even when excluding the early weeks of the maintenance phase, the relapse rate was lower in subjects receiving esketamine than placebo. There was still a nominally significant difference between the esketamine group and placebo group: the p-value (new = 0.0027, original = 0.0029) and hazard ratio (new = 0.43, original = 0.49) both decrease. While this result may still include unblinded subjects in the placebo arm, it may indicate the esketamine group is maintaining remission and response longer-term regardless, and that subjects in the placebo arm are still relapsing more frequently, even past the initial transition period to placebo of one month. However, this analysis is exploratory, and it is also impossible to differentiate what proportion of the results even in this later phase is affected or unaffected by unblinding concerns.

It is unclear if changes in the patient perception of the drug affected efficacy results in the short-term studies as well. Subgroup efficacy analyses in patients who experienced dissociative or sedation events due to their small and imbalanced sample sizes that would not be statistically meaningful or conclusive. Also, the relatively high placebo response in the phase 3 studies may argue against expectation bias solely related to esketamine's immediate effects.

Regarding the clinical meaningfulness of the above efficacy results, the MADRS is considered to be a well-established indicator of clinical response in MDD, with known ranges corresponding to illness severity and remission of symptoms. Statistically significant response results on the MADRS can likely be considered clinically meaningful, although support from functional outcome measures would have helped with this assessment. Also, there were subgroups of remitters as measured by the MADRS ≤ 12 in the esketamine treatment arms, at rates higher relative to placebo across all the short-term phase 3 studies (and also in the phase 2 parallel-group study SUI2001). Even if the remitter rates were not statistically compared, with a serious condition like TRD, the consistent presence of any subgroup who may show a strong treatment response to esketamine is a clinically meaningful factor to consider in the benefit-risk assessment to support drug approval. Despite no secondary endpoints and functional outcome measures reaching statistical significance, some of the secondary patient-reported and functional outcome measures also suggested consistent benefit and preference for esketamine over placebo across all phase 3 studies (with nearly all showing at least numerical improvement); this provides further support for the clinical meaningfulness of the efficacy findings.

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Another factor in the benefit-risk determination is the possible rapid effect of esketamine. There was a nominally significant difference between esketamine and placebo arms in Studies 3001 and 3002 on MADRS mean total score as early as Day 2, indicating a potential rapid treatment effect. The mean MADRS total score numerical difference between esketamine and placebo stayed fairly constant throughout the study to Day 28, although it was not statistically significant at every time point (Day 15 for both studies) and also not significant for the key secondary endpoint (onset of clinical response at Day 2 with sustained effect through Day 28) for either adult short-term study. (There was no similar early differentiation of esketamine from placebo in Study 3005.)

An exploratory analysis comparing esketamine's effect to the newly initiated background oral antidepressant response by our statistical reviewer indicated esketamine's effect appears to be an 'add-on' to the oral antidepressant effect that starts at Day 2 and remains fairly constant through to Day 28. Due to the study design, it isn't clear if the effect is synergistic or separate between esketamine and the oral antidepressant, but at least the response continues to improve even past Day 28 into the 2-week post-esketamine follow-up period in Study 3001 (the only study with more consistent follow-up period data). Study 3003 also subsequently confirms esketamine's ongoing effectiveness and durability even during longer-term maintenance dosing.

Overall, a potential rapid antidepressant effect may be of unique clinical benefit to someone suffering from depression (particularly in clinically acute situations requiring immediate intervention) and represents a novel effect relative to existing FDA-approved oral antidepressants. Conversely, if a patient is not responding to esketamine, that may be apparent early on based on these response curves, and a switch to alternative treatment may be initiated more quickly than a conventional oral antidepressant trial.

Summary

Overall, the studies submitted for the approval of intranasal esketamine met the evidentiary standard by providing substantial evidence of effectiveness in at least two adequate and well-controlled phase 3 studies for esketamine, but with some caveats. There is evidence of effectiveness in one adequate and well-controlled short-term parallel-group phase 3 study (Study 3002). The second adequate and well-controlled phase 3 study is a randomized withdrawal study examining time to relapse in stable remitters on esketamine; this design uses an enriched population and is not typically used as a study for initial approval of a drug intended to treat major depressive disorder. Study 3003 provides crucial evidence of esketamine's longer-term effectiveness for TRD with maintenance dosing.

There is also supportive but not fully conclusive evidence in the phase 2 and 3 esketamine program: a nominally significant effect of esketamine in the 56-mg treatment group in Study

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3001; a nominally significant improvement on MADRS total scores versus placebo as early as Day 2 in Studies 3001 and 3002; a subgroup of esketamine remitters and responders based on changes in MADRS total score consistently greater than placebo across all phase 3 studies and Study SUI2001 (but not statistically compared); MADRS mean total score distribution of response favoring esketamine over placebo in all phase 3 short-term studies (not statistically compared); nominally significant efficacy endpoints in phase 2 Study 2003 and statistical significance on the primary endpoint in Study SUI2001; numerical improvement over placebo in nearly all primary and secondary efficacy measures across all phase 3 studies; mean numerical MADRS score reductions in the esketamine arms consistent with literature-based definitions of MDD clinical response ($\leq 50\%$ reduction from baseline to endpoint) in Studies 3001 and 3002; and a numerical difference in MADRS total score change from baseline endpoint improvement comparable to those seen in other FDA-approved antidepressants and in a more seriously ill population (with a higher mean baseline MADRS total score).

In all studies, the primary efficacy measure was the MADRS, a scale frequently used to measure symptoms of depression in clinical trials and listed in the FDA Clinical Outcome Assessment Compendium. The application also includes some limited supportive evidence from additional secondary endpoints (e.g., Patient Health Questionnaire-9 Item (PHQ-9), a self-reported measure of depressive symptoms).

TRD is a life-threatening, severely impairing and, by definition, difficult-to-treat condition; in this instance, we must strongly consider the public health benefit to providing this medication without further delay to the population of patients who may improve. Therefore, we considered Study 3003, conducted in an enriched population of patients who are stable remitters and responders, to provide important information about esketamine's efficacy. Study 3003 provided statistically significant evidence of esketamine's maintenance-of-effect over placebo for this clinically pertinent study population. Despite not having two short-term studies (the conventional standard for approval), Study 3003 provided independent confirmation of the effects seen in Study 3002.

Additional practical considerations of a different time of onset and mechanism of action and side effect profile from previously approved oral antidepressants, fewer drug-drug interactions than other oral antidepressants, standardized intranasal dosing (less invasive than IV or IM) at less frequent intervals than treatments like TMS render esketamine distinctive from existing therapies for TRD, including the off-label use of ketamine.

Accordingly, there is substantial evidence of effectiveness for intranasal esketamine, in combination with a newly initiated oral antidepressant, for the treatment of TRD.

8. Review of Safety

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8.1. Safety Review Approach

The safety evaluation of the NDA for Spravato 56 and 84 mg nasal spray is based on the integrated summary of safety (ISS) which presents an analysis of safety data across the completed phase 3 studies TRD3001, TRD3002, TRD3003, TRD3004 and TRD3005, and the phase 2 study TRD2003.

Esketamine is also known as S-ketamine, the S-enantiomer of ketamine. Ketamine (as Ketalar) is currently approved as an anesthetic agent. Its main adverse reactions include increased blood pressure and heart rate. For the last couple decades, ketamine has been used off-label for multiple psychiatric disorders, including MDD, using much lower doses than for anesthetic use. Ketamine is also abused as a “club drug” because of its dissociative properties.

In addition to the labeled adverse reactions, the Division of Pharmacovigilance (DPV) has identified interstitial or ulcerative cystitis, cardiac arrest, hepatobiliary events, and cognitive impairment with chronic use (either abuse or off-label use) as safety signals from post-marketing data for ketamine (see section 8.9).

This safety review focuses primarily on issues of sedation, dissociation, cardiovascular adverse events including increased blood pressure, impaired cognition, liver injury, bladder adverse effects, and suicidal ideation or behavior.

Safety effects were ascertained through physical examination, adverse event reports, vital sign measurements, electrocardiograms, and laboratory studies. In addition, the following structured interviews and questionnaires were used to assess safety:

- Columbia-Suicide Severity Rating Scale (C-SSRS) to assess for suicidal ideation or behavior
- Clinician Administered Dissociative States Scale (CADSS) to measure dissociation
- Four-item Positive Symptom Subscale of the Brief Psychiatric Rating Scale (BPRS+) to identify psychiatric adverse events other than depression
- Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) to assess sedation
- (b) (4) to assess cognition
- Hopkins Verbal Learning Test-Revised (HVLTR) to assess verbal learning and memory.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The combined cumulative exposure to esketamine in the five completed phase 3 studies was 601 patient-years. Studies 3001, 3002 and 3005 were 4-week short-term studies which included a total of 418 subjects exposed to at least one dose of esketamine. In long-term open-label study 3004, of the 802 subjects enrolled, 364 subjects (45.4%) were treated for at least 6

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months, and 136 subjects (17.0%) were treated for at least 12 months. The composition of each safety population in the phase 3 double-blind, placebo-controlled studies (3001, 3002, and 3005), randomized withdrawal study (3003), and long-term open-label study (3004) are described in the following tables.

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Table 63 Composition of Safety Population in Double-blind, Placebo-controlled Trials 3001, 3002, and 3005

Safety Population	Number of Subjects				
	Esketamine Flexible-Dose	Esketamine 56 mg	Esketamine 84 mg	Placebo	Total
3001	.	115	116	113	346
3002	115	.	.	109	236
3005	72	.	.	65	139

Source: ISS report

Table 64 Composition of Safety Population in Randomized-Withdrawal Study 3003

Safety Population	Number of Subjects		
	Esketamine	Placebo	Total
3003	152	145	297

Source: ISS report

There were 418 esketamine-exposed subjects in studies 3001, 3002, and 3005, receiving a total of 3074 doses (see Table 65).

Table 65 Number of Subjects Receiving Specified Number of Esketamine Treatments Phase 3, Double-blind, Placebo-controlled Trials 3001, 3002, and 3005

Number of esketamine treatments:	1	2	3	4	5	6	7	8
Number of subjects	18	5	5	6	7	7	30	340

Source: Qi Chen, MD, MPH, Safety Reviewer

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Table 66 Drug Exposure and Duration in Phase 3 Randomized-Withdrawal Subjects in 3003

Number of esketamine treatments:	1 to 5	6 to 10	11 to 20	21 to 30	31 to 40	41 to 85
Number of subjects	24	45	45	25	12	5

Source: Qi Chen, MD, MPH, Safety Reviewer

Table 67 Drug Exposure and Duration in Phase 3, Open-label Subjects in 3003 and 3004

Number of esketamine treatments:	1 to 5	6 to 10	11 to 20	21 to 30	31 to 40	41 to 56
Number of subjects	146	394	465	160	164	118

Source: Qi Chen, MD, MPH, Safety Reviewer

8.2.2. Relevant Characteristics of the Safety Population

Patient demographics for studies 3001, 3002, and 3005 are presented in Section 6.1.2. Most subjects were female (66%). They were 85% white, 4% black or African American, and 1% Asian. The mean age was 46 for the non-elderly studies (3001 and 3002) and 70 for the elderly study 3005. Subjects met the inclusion criterion for having had an inadequate response to at least two antidepressants (AD) at entry into the induction phase. Patient demographics, baseline disease characteristics, and prior medication use were approximately evenly distributed between the esketamine + oral AD and intranasal placebo + AD groups. Studies 3001, 3002, and 3005 were conducted in 19 countries and 127 clinical sites. Races other than white were under-represented in these studies.

8.2.3. Adequacy of the Safety Database

A total of 1708 subjects with TRD received at least one esketamine treatment in the six completed phase 2 and 3 studies. In phase 3 studies, there were 1601 subjects exposed to esketamine, of which 479 were exposed to esketamine for at least 6 months and 178 were exposed to esketamine for at least 12 months. The safety population in the double-blind, placebo-controlled studies (3001, 3002, and 3005) included 705 patients. The safety population in the maintenance phase of the randomized withdrawal study (3003) numbered 297 subjects; an additional 627 were exposed to esketamine in the induction and optimization phases. The safety population in the open-label study (3004) included 802 patients.

The size of the safety database appears adequate to draw meaningful conclusions from the

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study results. Uncommon adverse reactions (1 to 2% or less) resulting from sustained exposure over time may not be accurately represented.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were several deficiencies in the identification, description, and classification of adverse events:

1. Some adverse events that occurred during trials were treatment-emergent sequelae of pre-existing conditions; the Applicant treated them as unchanged pre-existing conditions.
2. Some adverse events were not reported because they were considered, with insufficient evidence, to be part of a diagnosis or syndrome.
3. During the review process, we found some adverse event PT terms (AEDECOD) reported in narratives for serious adverse events that were not included in ADAE data sets. After investigation, the Applicant reported that the cause of the problem was that information in the Council for International Organization of Medical Sciences (COIMS) report forms was not bridged into the ADAE data sets. The Applicant resubmitted the ADAE data sets after adding the PT terms, and the updated ADAE data sets were consistent with the narratives. However, serious adverse event flags were not coded with the added PT terms.
4. Adverse event narratives were not written by investigators in direct contact with patients, so they may not provide genuine clinical context to the events.

Some of these deficiencies were corrected, and it is unlikely that they led to a dramatically different picture of clinical safety; however, they may have led to some degree of underestimation of the incidence of adverse events with both drug and placebo.

Categorization of Adverse Events

The Applicant coded adverse events by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Treatment-emergent adverse events (TEAEs) were defined as AEs that either commenced following nasal spray administration of study drug (i.e., esketamine or placebo) or were present prior to nasal spray but increased in frequency or severity following drug administration, regardless of causality. However, as noted in Section 8.3.1, the Applicant misclassified some AEs as being unchanged pre-existing conditions when they should have been coded as treatment-emergent sequelae of pre-existing conditions. The number and percentage of subjects with any TEAEs, drug-related TEAEs as determined by the Applicant, TEAEs by severity (mild, moderate, and severe), serious

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TEAEs, AEs leading to discontinuation, and AEs leading to death were summarized by treatment group. Causality of AEs were reported as “related” or “not related” to study drug.

After evaluation of the Applicant’s translation of verbatim terms to preferred terms, we requested the Applicant make the following changes before resubmitting the ADAE datasets:

FDA-Requested Action	Verbatim term	Original preferred term
add SYNCOPE	FAINT DUE TO ORTOSTATIC HYPOTONIE	Orthostatic hypotension
change to ABDOMINAL DISCOMFORT	ABDOMINAL CRAMPING DUE TO REMOVAL OF IUD	Abdominal pain
change to DYSTONIA	DYSTONIA IN LEFT HAND	Writer's cramp
change to EPIGASTRIC DISCOMFORT	BURNING SENSATION EPIGASTRIUM	Burning sensation

Source: Qi Chen, MD, MPH, Safety Reviewer

To capture complex phenomena, like dissociation, the applicant grouped similar PTs for adverse event analyses. We supplemented the Applicant’s groupings with additional terms, as displayed below:

	Applicant grouped	We added
Dissociation	dissociation; depersonalization/derealization disorder; derealization; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change	dysgeusia; dysmetropsia; feeling abnormal; feeling drunk; hyperaesthesia; hypersensitivity; illusion; metamorphopsia; oral hyperaesthesia; pharyngeal hypoesthesia; photopsia; photosensitivity reaction; synaesthesia; altered visual depth perception; confusional state; delirium; hypogeusia; pain threshold decreased; dysgeusia; dysmetropsia; feeling abnormal; feeling drunk; hyperesthesia; hypersensitivity; illusion; metamorphopsia; oral hyperesthesia; pharyngeal hypoesthesia; photopsia; photosensitivity reaction; synesthesia; altered visual depth perception; confusional state; delirium; hypogeusia; pain threshold decreased
Vertigo	vertigo; vertigo positional	

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Dizziness	dizziness; dizziness postural; procedural dizziness; dizziness exertional	
Sedation	sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor	loss of consciousness
Blood pressure increased	blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis	blood pressure fluctuation
Lower urinary symptoms		bladder discomfort; bladder dysfunction; bladder irritation; bladder pain; dysuria; lower urinary tract symptoms; micturition urgency; nocturia; pollakiuria; polyuria; urinary hesitation; urinary incontinence; urinary retention; urinary sediment abnormal; urinary sediment present; urinary tract discomfort; urinary tract infection; urinary tract infection bacterial; urine analysis abnormal; urine flow decreased; urine leukocyte esterase positive; urine odor abnormal; urine output decreased; suprapubic pain
Interstitial or ulcerative cystitis suggestive		bladder discomfort; bladder dysfunction; bladder irritation; bladder pain; dysuria; lower urinary tract symptoms; micturition urgency; nocturia; pollakiuria; polyuria; urinary sediment abnormal; urinary sediment present; urinary tract discomfort; urinary tract infection; urinary tract infection bacterial; urine analysis abnormal; urine leukocyte esterase positive; urine odour abnormal; suprapubic pain; cystitis
Dysarthria	dysarthria; speech disorder; slow speech; dysphonia	
Lethargy	lethargy; fatigue; listless	asthenia
Anxiety	anticipatory anxiety, anxiety disorder, generalized anxiety disorder, agitation, fear, nervousness, tension, panic attack, panic disorder, panic reaction, feeling jittery, irritability, psychogenic tremor, anxiety	fear of death, restlessness, morbid thoughts
Sexual dysfunction		ejaculation delayed, erectile dysfunction, libido decreased, loss of

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		libido, male orgasmic disorder, orgasm abnormal, sexual dysfunction
Headache	sinus headache, headache	tension headache, procedural headache, migraine
Tachycardia	sinus tachycardia, heart rate increased, extrasystole, tachycardia	ventricular extrasystoles, atrial fibrillation, supraventricular extrasystoles
Suicidal ideation or behavior		suicide attempt, intentional self-injury, suicidal ideation, suicidal behavior
Nasal discomfort	nasal crusting, nasal dryness, nasal pruritus, nasal discomfort	
pollakiuria	pollakiuria; micturition disorder	
dysgeusia	dysgeusia; hypogeusia	
hypoesthesia	hypoesthesia; hypoesthesia oral; hypoesthesia teeth; pharyngeal hypoesthesia; intranasal hypoesthesia	

Source: Qi Chen, MD, MPH, Safety Reviewer

8.3.2. Routine Clinical Tests

The schedule for collection of routine clinical tests is presented in the Appendices (Section 13.1). The scheduling of clinical tests appears adequate to support the clinical safety review.

8.4. Safety Results

8.4.1. Deaths

Through March 4, 2018 (the 120-Day Safety Update cutoff date), there were a total of six deaths reported in subjects treated with esketamine + oral AD: two in randomized, placebo-controlled studies in phase 2 and 3 of development; two in open-label, long-term study 3004; and two in the ongoing long-term open-label safety study 3008. No deaths were reported in the oral AD + placebo group. (See Section 8.2.3 for the total number of subjects exposed.) I reviewed the narrative summaries for each death. Among the six deaths, three were caused by non-depression-related accidents or acute illnesses, and three were completed suicides. In the suicide cases, only one occurred in a placebo-controlled study. Overall, there were no clear drug-related trends that these deaths identified.

Patient (b) (6), a 41-year-old man, committed suicide by hanging on Day 45 during the posttreatment follow-up phase. The patient had the diagnosis of MDD for 7 years and had no past history of suicidal behavior. His MADRS score was 32 as baseline, 7 at Day 25 when he received last dose of esketamine, 7 on Day 32 (the first follow-up visit), and 21 on Day 39 (when

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no suicidal ideation or behavior was reported). His C-SSRS score had been 0 during the study. On Day 39 the patient was prescribed aripiprazole 6 mg prn, perphenazine 12 mg tid, quetiapine 100mg daily, and ethyl loflazepate 1 mg daily for irritability, anxiety, and insomnia.

Reviewer's comment: The patient's MADRS score decreased from 32 to 7 during esketamine treatment and increased to 21 at 14 days after discontinuation of esketamine. A MADRS score of 21 would indicate relatively mild depression but represented a substantial change from 7 days earlier. Possibly, the patient's depression continued to deteriorate rapidly over the subsequent 6 days. No alternative cause was identified for his worsening depressive symptoms. Suicide was likely related to relapse of MDD after drug discontinuation. Conceivably, the relapse and its rapidity could represent a rebound effect from esketamine discontinuation, but it would require the observation of several additional similar cases to reasonably make that inference. It is also possible that the antipsychotics initiated on Day 39 could have caused akathisia, which has a risk of suicide.

Patient (b) (6), a 41-year-old white man with TRD and gastritis, had a motor vehicle (motorcycle) accident on Study Day 16, 26 hours after the third and last dose of esketamine, and died on Day 55 while hospitalized for multiple injuries after the accident. The patient's MADRS score was 38 at baseline, 29 on Day 2 and Day 8, and 30 on Day 15. His CSSRS score had decreased to 0 since Day 4 from a 1 at baseline.

Reviewer's comment: The death was not likely caused by esketamine-induced sedation, which normally lasts for no more than 6 hours post-dose. The patient's MADRS and CSSRS scores had decreased from baseline, which would not support a suicidal intention of the accident, although he was still experiencing significant depression.

Patient (b) (6), a 55-year-old woman in the esketamine + oral AD (duloxetine) group, had a history of hypertension but no history of suicidal behavior. She committed suicide by suspected overdose on Day 188, 12 days after the last dose of esketamine and 1 day after the last dose of duloxetine. The subject's husband reported she received a diazepam prescription the previous day and an empty diazepam bottle was found. The family reported marital conflict for the previous 3 days and found a note in which the patient had left gifts to the children. Her MADRS score was 27 at baseline and 12, 7, and 9 on Days 28, 176, and 183, respectively. Her C-SSRS score had been 0 at all visits. An autopsy reported no obvious cause of death (cardiovascular causes or stroke were ruled out).

Reviewer's comment: There is no clear evidence to support the correlation between esketamine and this suicide. The suicide was possibly related to marital conflict.

Patient (b) (6) a 60-year-old white man with a history of hypertension and BMI 32.6 kg/m² at baseline, collapsed on Day 113; cause of death was likely due to acute respiratory

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failure and acute cardiac failure. No autopsy was performed. The patient's blood pressure, pulse rate, and pulse oximetry were within normal limits pre- and post-esketamine use during the last clinical visit on Day 108.

Reviewer's comment: The adverse reactions of increased blood pressure and heart rate normally last up to 4 hours post dose. The sudden death is not likely related to esketamine use.

Patient [REDACTED]^{(b) (6)}, a 38-year-old man with history of minimal alcohol use and no history of suicide attempts or other substance abuse disorders, committed suicide by gunshot on Day 25 of the induction phase. His MADRS scores were 34, 41, and 25 on Days 8, 15, and 22, respectively. The patient's girlfriend stated that the patient felt despair that "if this drug didn't work, then nothing will" and had shot himself because the drug "didn't get him better." His last dose of esketamine was on Day 22.

Reviewer's comments: The suicide was likely related to depression. Although the MADRS score suggested modest improvement a few days earlier, the pattern of scores suggest an ongoing pattern of rapid fluctuations between moderate and severe depression. An effect of esketamine in creating or augmenting these fluctuations cannot be ruled out, but this cannot be concluded from a single case.

Patient [REDACTED]^{(b) (6)}, a 74-year old woman with history of hypertension and hyperlipidemia, died due to myocardial infarction on Day 321 of treatment with esketamine 84 mg, 6 days after the last dose.

Reviewer's comments: The patient's age and history of hypertension and hyperlipidemia increased the risk of myocardial infarction. The effect of increased blood pressure normally lasts for less than 4 hours post-esketamine dose. The myocardial infarction was not likely related to esketamine use.

8.4.2. Serious Adverse Events

In the double-blind, placebo-controlled phase 3 studies (3001, 3002, 3005) and the randomized withdrawal study (3003), there were 24 serious adverse events (SAEs) reported across esketamine and placebo treatment groups in 16 subjects during both the double-blind and follow-up phases. SAEs were reported more in the esketamine + oral AD group than in the placebo + oral AD group. Some SAE flags were not accurately coded in the adverse event data files due to the data integrity issue mentioned in 8.3.1. The following tables were generated based on information from both the AE datasets and SAE narratives.

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Table 68 Studies 3001, 3002, and 3005: SAEs by Treatment Groups

	3001			3002		3005	
	Placebo	Esketamine		Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
		56 mg	84 mg				
N	113	115	116	109	115	65	72
N(%) of subjects with SAEs	1 (0.9%)	4 (3.5%)	3 (2.6%)	1 (0.9%)	2 (1.7%)	2 (3.1%)	3 (4.2%)
Depression	0	3	2	0	0	0	0
Suicidal ideation	1	1	2	1	0	0	1
Blood pressure 170/110, anxiety	0	0	0	0	0	0	1
Road traffic accident/death	0	0	0	0	1	0	0
Dizzy/fall, Hip fracture	0	0	0	0	0	0	1
Cerebral hemorrhage	0	0	0	0	1	0	0
Headache and nausea, BP 190/100	0	1	0	0	0	0	0
Anxiety, feeling of despair, gait disturbance	0	0	0	0	0	1	0
Dizziness/Vertigo	0	0	0	1	0	1	0

Source: Qi Chen, MD, MPH, Safety Reviewer

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Table 69 Study 3003, Maintenance Phase: SAEs by Treatment Groups

Treatment	Placebo	Esketamine
N	145	152
Percent of subjects with SAEs	1.4%	3.3%
Number of subjects with SAEs	2	5
Clavicle fracture	1	0
Depression	1	3
Suicidal ideation	0	1
Ectopic pregnancy	0	1

Source: Qi Chen, MD, MPH, Safety Reviewer

SAEs of depression and suicidal ideation were reported with higher incidence in subjects treated with esketamine than placebo in Study 3001, but not in Studies 3002 or 3005. There was no obvious difference between the esketamine and placebo groups with other SAEs. In the 3003 Maintenance Phase, worsening of depression and suicidal ideation were also reported with higher incidences in the esketamine group, which is consistent with Study 3001.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 70 Dropouts and Discontinuations due to Adverse Events in Phase 3 Short-Term Studies

	3001			3002		3005	
	Placebo	Esketamine 56 mg	Esketamine 84 mg	Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
N	113	115	116	109	115	65	72
Discontinued subjects (n)	6 (5.3%)	4 (3.5%)	19 (16.4%)	10 (9.2%)	17 (14.8%)	5 (7.7%)	10 (13.9%)
Anxiety	0	0	0	0	1	0	1
Blood pressure increase	0	0	0	0	0	0	2
Bronchitis	0	0	0	0	1	0	0
Bursitis	0	0	1	0	0	0	0
Depression	0	1	0	0	2	0	0
Disturbance in attention	0	0	1	0	0	0	0
Dizziness	0	0	1	0	0	0	0
Drug intolerance	0	0	0	0	1	0	0
Headache	0	0	0	1	1	0	0
Hip fracture	0	0	0	0	0	0	1
Insomnia	1	0	0	0	1	0	0
Mania	0	0	1	0	0	0	0
Nausea	0	0	2	0	0	0	0
Panic attack	0	0	1	0	1	0	0
Road traffic accident/death	0	0	0	0	1	0	0

Source: Douglas Warfield, PhD, Associate Director for Bioinformatics

The most common cause for discontinuation in esketamine groups was depression (three subjects). Blood pressure increase, headache, nausea and panic attack were each the cause of dropouts in two subjects in esketamine groups in these studies. The remainder of the AEs leading to discontinuation were reported in one subject.

8.4.4. Significant Adverse Events

Urinary and Bladder-Related Adverse Events and Cystitis

Postmarketing data from racemic ketamine and published literature have identified cases of interstitial cystitis or ulcerative cystitis after chronic recreational ketamine use or off-label use

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at high doses or with long-term use. No cases of interstitial or ulcerative cystitis were found in any of the esketamine studies, but numerous subjects had mild symptoms that could be associated with subclinical interstitial or ulcerative cystitis, even during the short-term studies.

Table 71 Lower Urinary Tract Symptoms Suggestive of Interstitial or Ulcerative (I/U) Cystitis in Double-Blind Phase of Studies 3001, 3002 and 3005

Study	3001			3002		3005	
	Placebo	ESK 56 mg	ESK 84 mg	Placebo	ESK 56 to 84 mg	Placebo	ESK 28 to 84 mg
N=	113	115	116	109	115	65	72
Cystitis suggestive AEs n (%)	3 (2.7%)	10 (8.7%)	5 (4.3%)	1 (0.9%)	11 (9.6%)	5 (7.7%)	6 (8.3%)
Urinary discomfort/pain (n)	0	1	1	0	7	4	1
Cystitis/UTI (n)	2	3	1	1	2	1	6
Micturition urgency (n)	0	1	2	0	0	0	0
Pollakiuria/Nocturia (n)	1	6	3	0	4	0	1
Sediment/Odor abnormal (n)	0	0	1	0	0	0	0

Source: Qi Chen, MD, MPH, Safety Reviewer

The incidence of cystitis-suggestive AEs was higher in esketamine groups compared to placebo groups in studies 3001, 3002 and 3005. The most commonly reported I/U cystitis-suggestive lower urinary tract adverse events in subjects treated with esketamine relative to placebo were urinary frequency (pollakiuria/nocturia) and dysuria (urinary discomfort/pain). Most (67%) of the lower urinary tract AEs were mild. Only two (4%) were severe; both were urinary frequency in the esketamine group. No dose effect was observed on the severity of the urinary AEs. Around 76% of the AEs were resolved or resolving. No dose effect was observed in the outcome of the AEs.

In the long term (>1 year) open-label study (3004), cystitis-suggestive AEs were reported in 137 (19%) subjects. Most of the AEs (90%) resolved during treatment. Only one subject required dose reduction due to urinary symptoms. There were 14 AEs (including 6 UTIs) that did not resolve. The following table shows the ratio of number of subjects reporting urinary AEs to the total number of treatments (exposures) in Studies 3001, 3002, 3005, and 3004.

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Table 72 Reports of Urinary AEs versus Esketamine Exposure in Studies 3001, 3002, 3005, and 3004

Study	3001			3002		3005		3004
	Placebo	Esketamine		Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg	Esketamine (open label) 28 to 84 mg
		56 mg	84 mg					
Exposures	866	886	812	864	877	494	531	19218
Subjects with cystitis-suggestive urinary symptoms (n)	3	10	5	1	11	5	6	137
Rate per 1000 exposures	3.5	11.3	6.2	1.2	12.5	10.1	11.3	7.1

Source: Qi Chen, MD, MPH, Safety Reviewer

The incidence of interstitial or ulcerative cystitis-suggestive symptoms could be confounded by urinary tract infection symptoms in AE reports. However, the notably higher incidences of urinary frequency and dysuria in esketamine-treated subjects suggest adverse effects of esketamine on the urinary tract. The rate of subjects developing urinary AEs over more than 1 year of ongoing treatment was 7.1 per 1000 exposures in Study 3004—a lower incidence than the rate in short-term studies 3001, 3002, and 3005. On the other hand, esketamine was administered with lower frequency (twice weekly or weekly for 4 to 8 weeks, then every other week) in Study 3004 as compared to twice weekly in Studies 3001, 3002, and 3005. The longer treatment interval may have allowed the urinary tract to recover between treatments from the effects of esketamine.

In the long-term, randomized withdrawal study (3003), the incidence of lower urinary tract symptoms was 5% (7 cases) both in esketamine and placebo groups during the double-blind phase. However, fewer subjects who reported cystitis-suggestive AEs in the induction and/or optimization phases were assigned to esketamine than to placebo in the maintenance phase (7 vs. 14, respectively). The higher rate of reported urinary AEs during esketamine treatment in the induction and optimization phases among subjects who were assigned to placebo at baseline may have confounded the relative occurrence of urinary AEs for esketamine vs. placebo in the 3003 Maintenance Phase. The reduction in incidence of cystitis-suggestive symptoms in the Maintenance Phase compared to the pre-randomization period was greater in the group assigned to placebo (Table 73).

Table 73 Number of Subjects with Lower Urinary Tract Symptoms, 3003 Maintenance Phase

		Esketamine	Placebo
N of total subjects=		152	145
Subjects with cystitis-suggestive symptoms (n=)		7	7
Reports of	Bladder discomfort	0	1
	Dysuria	1	0
	Lower urinary tract symptoms	0	2
	Pollakiuria	1	1
	Urinary sediment abnormal	1	0
	Urinary tract infection	4	4
	Urine output decreased	0	1

Overall, a drug-related signal for urinary and bladder-related adverse events was seen in the esketamine studies (both short-term and long-term), but with no apparent cases of interstitial or ulcerative cystitis or cancer. We recommend follow-up of these issues with the ongoing multiyear Study 3008 (which we are requiring full completion of as a postmarketing requirement) and with ongoing REMS data collection and pharmacovigilance-related surveillance and reporting (such as FAERS). A warning related to this signal will be included in labeling.

8.4.5 Treatment-Emergent Adverse Events and Adverse Reactions

The most commonly reported adverse events were dissociation, dizziness/vertigo, nausea, vomiting, sedation, paresthesia, hypoesthesia, and blood pressure increase in Studies 3001, 3002, and 3005. The distribution of common adverse events was similar across age groups. However, the common AEs in the esketamine groups were less frequently reported in subjects ≥ 65 years old than in subjects < 65 years old. Adverse events occurring in $>2\%$ of esketamine-treated subjects, and more frequently than placebo-treated subjects, are presented in Table 74 for subjects < 65 years-old and Table 75 for subjects ≥ 65 -years-old.

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Table 74 Adverse Events Occurring in >2% and More than Placebo, by Treatment Group, in Studies 3001 and 3002 (Subjects <65 years old)

Adverse Events	3001			3002	
	Placebo	Esketamine 56 mg	Esketamine 84 mg	Placebo	Esketamine 56 to 84 mg
	N=113 n= (%)	N=115 n= (%)	N=116 n= (%)	N=109 n= (%)	N=115 n= (%)
Dissociation	22 (19.5%)	53 (46.1%)	54 (46.6%)	20 (18.3%)	60 (52.2%)
Dizziness	11 (9.7%)	38 (33.0%)	32 (27.6%)	7 (6.4%)	32 (27.8%)
Nausea	12 (10.6%)	32 (27.8%)	37 (31.9%)	7 (6.4%)	31 (27.0%)
Headache	20 (17.7%)	23 (20.0%)	24 (20.7%)	20 (18.3%)	21 (18.3%)
Sedation	13 (11.5%)	29 (25.2%)	29 (25.0%)	9 (8.3%)	22 (19.1%)
Anxiety	9 (8.0%)	15 (13.0%)	13 (11.2%)	8 (7.3%)	18 (15.7%)
Vertigo	2 (1.8%)	24 (20.9%)	24 (20.7%)	4 (3.7%)	30 (26.1%)
Paresthesia	3 (2.7%)	19 (16.5%)	11 (9.5%)	1 (0.9%)	14 (12.2%)
Hypoesthesia oral	2 (1.8%)	16 (13.9%)	12 (10.3%)	1 (0.9%)	9 (7.8%)
Hypoesthesia (not including oral)	2 (1.8%)	14 (12.2%)	17 (14.7%)	1 (0.9%)	8 (7.0%)
Blood pressure increased	5 (4.4%)	11 (9.6%)	14 (12.1%)	1 (0.9%)	12 (10.4%)
Vomiting	2 (1.8%)	7 (6.1%)	14 (12.1%)	2 (1.8%)	11 (9.6%)
Cystitis-suggestive adverse events	3 (2.7%)	5 (4.3%)	10 (8.7%)	1 (0.9%)	11 (9.6%)
Dry mouth	4 (3.5%)	5 (4.3%)	5 (4.3%)	3 (2.8%)	9 (7.8%)
Throat irritation	4 (3.5%)	5 (4.3%)	8 (6.9%)	5 (4.6%)	8 (7.0%)
Hyperhidrosis	2 (1.8%)	4 (3.5%)	5 (4.3%)	3 (2.8%)	5 (4.3%)
Dysarthria	0	7 (6.1%)	4 (3.4%)	0	4 (3.5%)
Constipation	1 (0.9%)	5 (4.3%)	3 (2.6%)	2 (1.8%)	3 (2.6%)

Source: Qi Chen, MD, MPH, Safety Reviewer

Table 75 Adverse Events Occurring in >2% and More than Placebo, by Treatment Group, in Study 3005 (Subjects ≥65 years old)

Adverse Events	Placebo	Esketamine
	N=65 n (%)	N=72 n (%)
Dizziness	5 (7.7%)	17 (23.6%)
Dissociation	6 (9.2%)	15 (20.8%)
Nausea	3 (4.6%)	13 (18.1%)
Lethargy	5 (7.7%)	10 (13.9%)
Blood pressure increased	4 (6.2%)	10 (13.9%)
Headache	2 (3.1%)	10 (13.9%)
Vertigo	2 (3.1%)	8 (11.1%)
Cystitis suggestive	5 (7.7%)	6 (8.3%)
Hypoesthesia oral	0 (0%)	5 (6.9%)
Vomiting	1 (3.1%)	5 (6.9%)
Hypoesthesia	1 (1.5%)	4 (5.6%)
Paraesthesia	2 (3.1%)	4 (5.6%)
Insomnia	3 (4.6%)	4 (5.6%)
Dysphoria	0	4 (5.6%)
Diarrhea	1 (1.5%)	3 (4.2%)
Hyperhidrosis	1 (1.5%)	3 (4.2%)
Nasal mucosal disorder	1 (1.5%)	3 (4.2%)
Nasal discomfort	0 (0%)	2 (2.8%)
Rhinorrhea	0	2 (2.8%)
Nasal congestion	1 (1.5%)	2 (2.8%)
Cough	0 (0%)	2 (2.8%)
Malaise	0	2 (2.8%)
Fall	0	2 (2.8%)
Respiratory rate increased	0	2 (2.8%)
Electrocardiogram ST segment depression	0	2 (2.8%)
Hangover	1 (1.5%)	2 (2.8%)

Source: Qi Chen, MD, MPH, Safety Reviewer

Table 76 shows that the most common adverse events in the 3003 Maintenance Phase were the same as in Studies 3001, 3002, and 3005 (except for nasal discomfort; see section 8.5.5).

Most AE incidents were reported as frequently in the placebo group as in the esketamine group, which provides little evidence of withdrawal effects. Arthralgia and abdominal pain had higher incidences in the placebo than the esketamine group, but the difference was too small

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to clearly suggest a causal relationship to esketamine withdrawal. The incidence of depression was higher in the placebo group than in esketamine group, which corresponds to the higher relapses in placebo groups.

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Table 76 Adverse Events >2% by Treatment Group in Study 3003 Maintenance Phase, n(%).

Adverse Events	Placebo	Esketamine
	N=145	N=152
Dissociation	12 (8.3%)	75 (49.3%)
Sedation	4 (2.8%)	41 (27.0%)
Dizziness	11 (6.9%)	39 (25.7%)
Vertigo	8 (5.5%)	39 (25.7%)
Headache	14 (9.7%)	29 (19.1%)
Nausea	1 (0.7%)	25 (16.4%)
Hypoesthesia, oral	0 (0.0%)	22 (13.2%)
Nasal discomfort	7 (4.8%)	17 (11.2%)
Anxiety	7 (4.8%)	13 (8.6%)
Blood pressure increased	5 (3.4%)	13 (8.6%)
Viral upper respiratory tract infection	12 (8.3%)	11 (7.2%)
Paresthesia	0 (0.0%)	11 (7.2%)
Vomiting	1 (0.7%)	110 (6.6%)
Hypoesthesia	0 (0.0%)	9 (5.9%)
Paresthesia, oral	1 (0.7%)	8 (5.3%)
Throat irritation	1 (0.7%)	8 (5.3%)
Cystitis suggestive adverse events	7 (4.8%)	8 (5.3%)
Diarrhea	4 (2.8%)	6 (3.9%)
Rhinalgia	3 (2.1%)	6 (3.9%)
Oropharyngeal pain	2 (1.4%)	6 (3.9%)
Upper-airway cough syndrome	1 (0.7%)	6 (3.9%)
Euphoric mood	0 (0.0%)	6 (3.9%)
Depression	7 (4.8%)	5 (3.3%)
Cough	4 (2.8%)	5 (3.3%)
Lethargy	4 (2.8%)	5 (3.3%)
Spinal pain	3 (2.1%)	5 (3.3%)
Back pain	1 (0.7%)	5 (3.3%)
Nasal congestion	2 (1.4%)	4 (2.6%)
Upper respiratory tract infection	2 (1.4%)	4 (2.6%)
Bradyphrenia	1 (0.7%)	4 (2.6%)
Derealization	0 (0.0%)	4 (2.6%)
Arthralgia	5 (3.4%)	2 (1.3%)
Abdominal pain	3 (2.1%)	0 (0.0%)

Source: Qi Chen, MD, MPH, Safety Reviewer

8.4.5. Laboratory Findings

Esketamine treatment had little apparent effect on laboratory study findings in phase 3 trials—either in terms of average values or the incidence of outliers—compared to placebo or baseline values. Notably, in view of reports of liver injury associated with intravenous ketamine, intranasal esketamine was associated with an average reduction in liver enzymes relative to baseline and placebo; however, the magnitude of change was small and not clinically meaningful.

Table 77 Changes in Liver Enzymes Relative to Baseline and Placebo

Study	3001			3002			3005		
	Geometric Mean Effect (% change)								
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Alkaline Phosphatase	(2.3)	(3.5)	(1.1)	(3.9)	(5.5)	(2.3)	(4.5)	(6.5)	(2.6)
ALT	(2.8)	(6.4)	1.0	(5.5)	(9.8)	(1.1)	(4.3)	(9.1)	0.8
AST	(2.5)	(5.2)	0.3	(3.8)	(7.3)	(0.3)	(2.9)	(6.4)	0.7
GGT	(5.0)	(7.9)	(2.0)	(6.2)	(9.8)	(2.4)	(6.5)	(10.7)	(2.2)

Values in parentheses are negative numbers, indicating a reduction in values.

Source: Marc Stone, MD, Deputy Director for Safety

Although we noted a higher rate of urinary-tract-related AEs on drug versus placebo, there was no increase in abnormalities on urinalysis on drug relative to placebo.

The effect of esketamine on thyroid function, specifically thyroid stimulating hormone, was not evaluated in the phase 3 studies either by comparison with baseline or to placebo. (Per the nonclinical team, there are no known thyrotoxic issues with ketamine or esketamine from animal data.) The only studies that collected TSH levels that could be evaluated for esketamine effect were:

Study 1011: This study measured TSH in all 24 subjects before and 60 hours after a single, 28-mg intranasal dose of esketamine. Using a repeated-measures mixed-effects model, the random effects mean (REM) baseline value was 2.21 mU/L (95% CI 1.63 to 2.78). After esketamine, the REM was 2.96 mU/L (95% CI 2.35 to 3.56). The REM difference, 0.75 mU/L, was highly statistically significant ($p < 0.0005$). The geometric REM increase was 35.3% (95% CI 13.4% to 57.1%).

Study 1014: This study also measured TSH in all 32 subjects before and 60 hours after a single, 28-mg intranasal dose of esketamine. Using a repeated-measures mixed-effects model, the REM baseline value was 2.22 mU/L (95% CI 1.64 to 2.81). After esketamine the REM was 3.10

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mU/L (95% CI 2.42 to 3.79). The REM difference, 0.88 mU/L, was highly statistically significant ($p=0.0005$). The geometric REM increase was 36.9% (95% CI 19.0% to 54.7%).

Study 1016: This study measured TSH in all 8 subjects before and 7 days after a single dose, either 20 mg intravenously or 50 mg orally. Using a repeated-measures mixed-effects model, the REM baseline value was 1.78 mU/L (95% CI 1.21 to 2.34). After esketamine the REM was 2.11 mU/L (95% CI 1.50 to 2.72). The REM difference, 0.33 mU/L, was not statistically significant ($p=0.1$). The geometric REM increase was 24.7% (95% CI 2.9% to 46.5%) and was statistically significant ($p=0.01$).

The results for 1011 and 1014 were extremely similar and, as the studies were conducted under nearly identical protocols but different patient populations, must be considered a strongly reproducible finding despite the small sample size. Pooling the two samples provides an estimated geometric REM increase of 36.1% with narrower 95% confidence intervals (22.3% to 50%). The lesser effect seen in Study 1016 makes sense because TSH was measured much later after dosing; it may also reflect the differences in dosage and mode of administration of esketamine.

It is possible that this effect may accumulate over time with repeated dosing. It would seem advisable to explore this as a post-marketing requirement.

8.4.6. Vital Signs

8.4.6.1. Blood Pressure

Blood pressure was measured pre- and post-dose at 40 minutes, 60 minutes, and 90 minutes. The average peak increase in esketamine-treated subjects relative to baseline and placebo was 8 mmHg in systolic blood pressure (SBP) and 5 mmHg in diastolic blood pressure (DBP). The proportion of subjects younger than 65 years with markedly increased BP on at least one occasion (defined as an increase of SBP of ≥ 20 mmHg to ≥ 180 mmHg or DBP ≥ 15 mmHg to ≥ 105 mmHg) was approximately 10% with esketamine compared to 2% with placebo. There were few increases of this magnitude in subjects 65 years or older in Study 3005. However, lesser increases, such as to a SBP of 160, were more likely in the esketamine group. Of the subjects with markedly increased BP, about 80% had BP $< 140/90$ at pre-dose (see Table 78 and Figures 37 and 38).

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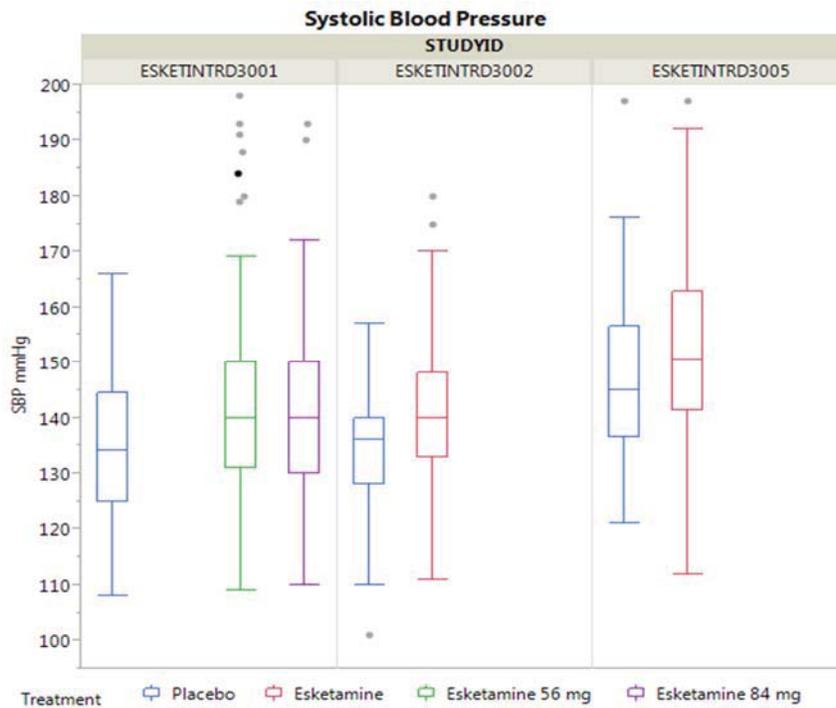
Table 78 Post-Dose Maximal Blood Pressure Changes in Esketamine- and Placebo-treated Patients in Studies 3001, 3002, and 3005

Study	3001			3002		3005	
Treatment	Placebo	ESK 56 mg	ESK 84 mg	Placebo	ESK 56 to 84 mg	Placebo	ESK 28 to 84 mg
n=	113	116	115	109	115	65	72
SBP (mmHg)							
Mean change ± SD	12 ± 10	20 ± 14	20 ± 13	9 ± 8	18 ± 12	15 ± 11	23 ± 16
SBP ≥180 and increase ≥ 20 n (%)	0	6 (5.2%)	2 (1.7%)	0	1 (0.9%)	1 (1.6%)	2 (2.8%)
DBP (mmHg)							
Mean Change ± SD	10 ± 8	15 ± 8	14 ± 8	7 ± 5	12 ± 8	10 ± 7	12 ± 7
DBP ≥ 105 and increase ≥ 15 n (%)	2 (1.8%)	8 (7.0%)	10 (8.7%)	0	10(8.8%)	1(1.6%)	0

Source: Qi Chen, MD, MPH, Safety Reviewer

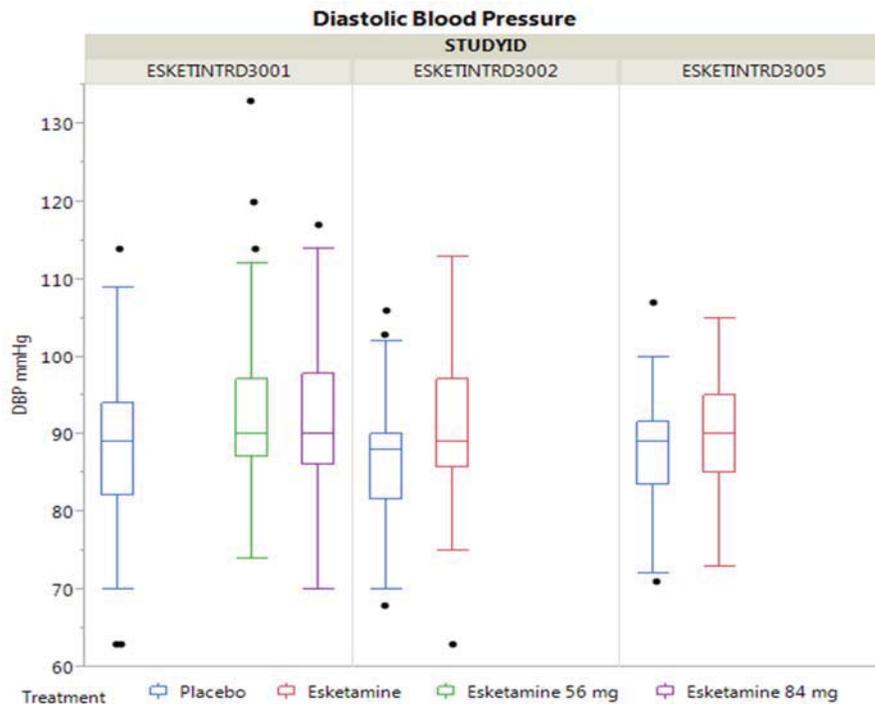
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Figure 37 Post-Dose Maximal Systolic Blood Pressure Changes in Esketamine- and Placebo-treated Patients in Studies 3001, 3002, and 3005.



Source: Qi Chen, MD, MPH, Safety Reviewer

Figure 38 Post-Dose Maximal Diastolic Blood Pressure Changes in Esketamine- and Placebo-treated Patients in Studies 3001, 3002, and 3005.



Source: Qi Chen, MD, MPH, Safety Reviewer

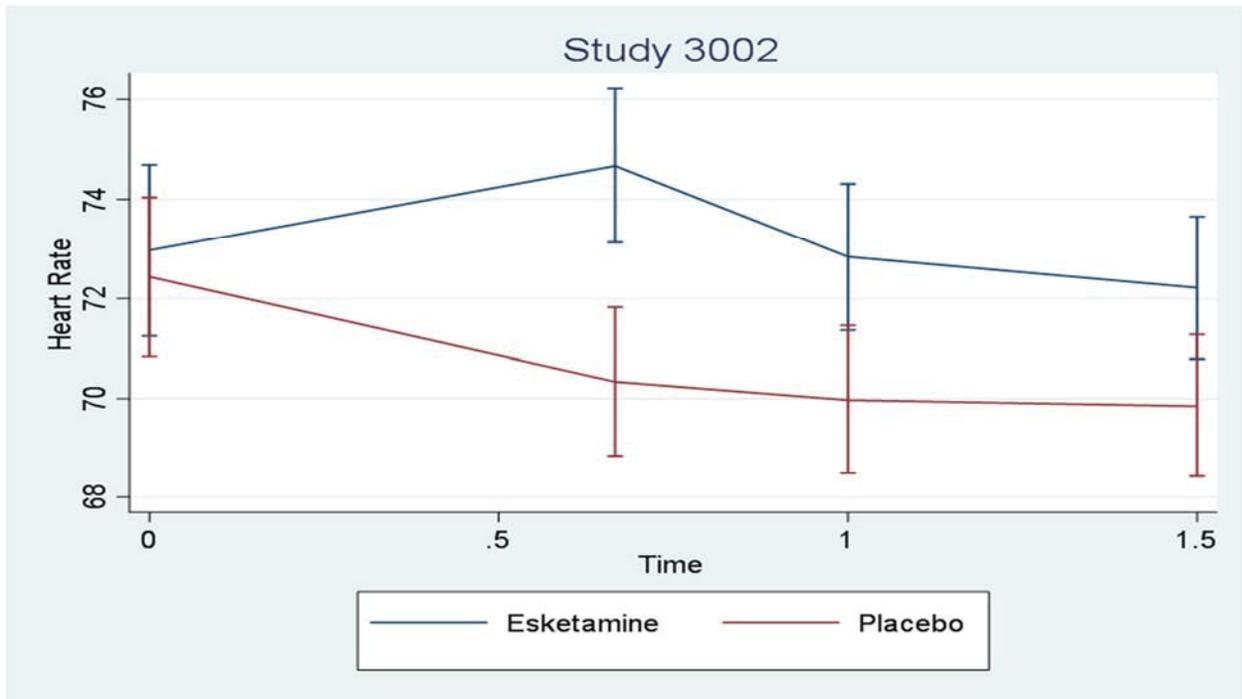
For most subjects, the maximal SBP was observed at 40 minutes. Data from clinical pharmacology Study 1013 showed blood pressure effects last for about 4 hours and closely follow esketamine plasma levels.

8.4.6.1. Heart Rate

In most phase 1 and 2 studies, esketamine treatment was associated with increases in heart rate. The random effects mean difference at 40 minutes in Study 3001 was 0.7 bpm and not statistically significant ($p=0.49$); the average overall post treatment difference was less (0.5 bpm) but statistically significant ($p=0.02$), suggesting the presence of a small effect. In Study 3002, an increase in heart rate relative to placebo (random effects mean 4.7 bpm) was observed at 40 minutes and was strongly statistically significant (see Figure 39). In Study 3005 the random effect mean difference at 40 minutes was 1.6 bpm ($p<0.00005$). Given that the time pattern of heart-rate changes seen in Study 3002 and phase 1 and 2 studies matched the time pattern of changes in blood pressure and the esketamine pharmacokinetic profile, it is likely that esketamine does cause an increase in heart rate in some patients. The absence of a stronger observed effect in Study 3001 may have been due to statistical noise. The smaller effect seen in 3005 relative to 3002 is consistent with the lesser sensitivity to esketamine seen

in elderly subjects in terms of both efficacy and incidence of sedation and other adverse reactions.

Figure 39 Heart Rate Increase in Study 3002



Source: Marc Stone MD, Deputy Director for Safety

8.4.7. Electrocardiograms (ECGs)

8.4.8. QT

In a thorough QT study, intranasal esketamine treatment (84 mg dosage) was associated with a maximum heart-rate-adjusted reduction in QT interval relative to placebo of about 6 milliseconds at maximum effect, returning to baseline in 3-4 hours. No effects on PR or QRS intervals were found. The principal concern in thorough QT studies is significant QT prolongation; this has been ruled out by this study. A reduction in QT interval of this magnitude is benign with no known adverse outcomes.

8.4.9. Immunogenicity

There were no esketamine-related signals for immunogenicity or hypersensitivity-related issues. None of the hypersensitivity-suggestive adverse events (rash, choking sensation, hyperactivity, laryngospasm, and urticaria, etc.) required drug discontinuation—indicating the reaction was not a hypersensitivity reaction. Table 79 and Table 80 show incidences of

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hypersensitivity-suggestive adverse events in Studies 3001, 3002, 3005, and the 3003 maintenance phase.

Table 79 Hypersensitivity-Suggestive Adverse Events in Studies 3001, 3002, and 3005

Study	3001			3002		3005	
Treatment	Placebo	Esketamine 56mg	Esketamine 84mg	Placebo	Esketamine 56 to 84 mg	Placebo	28 to 84 mg
N	113	115	116	109	115	65	72
Rash	2	2	1	3	1	0	0

Source: Qi Chen, MD, MPH, Safety Reviewer

Most rashes were mild and did not result in drug discontinuation, indicating these AEs were likely not major hypersensitivity reactions.

Table 80 Hypersensitivity-Suggestive Adverse Events in Randomized Withdrawal Study 3003 Maintenance Phase

	Placebo	Esketamine
N	145	152
Rash	0	2
Choking sensation	0	1

Source: Qi Chen, MD, MPH, Safety Reviewer

The choking sensation listed in Table 80 was described as mild and lasted for approximately 30 minutes. It was consistent with discomfort from inhalation of the medication and unlikely to have been a hypersensitivity reaction.

In the Induction and Optimization Phase in Study 3003, there were three reports of rash, and one report each for bronchial hyperreactivity, choking sensation, and laryngospasm. In the open-label study (3004), there were 21 reports of rash, one allergic bronchitis.

Laryngospasm events have been reported as adverse events in the ketamine label. In phase 3 esketamine studies, most of these adverse events (including laryngospasm) were mild and none of the esketamine-treated subjects required dose reduction.

Although no esketamine-related hypersensitivity signals were noted during the clinical trials, a general warning to avoid the drug if one has a prior history of reactions will still be included in labeling.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Sedation

Sedation was one of the most common effects associated with esketamine treatment in all phase 2 and 3 studies. Sedation was evaluated using the Modified Observer's Alertness/Sedation scale (MOAA/S) at pre-dose and 15, 30, 45, 60, 75, and 90 minutes post-dose. In the phase 3 studies, subjects with sedation were monitored every 5 to 15 minutes until the sedation resolved.

MOAA/s Scale

MOAA/s score	Description
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Respond only after mild prodding or shaking
1	Respond only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Table 81 Number of Subjects Who Experienced Sedation At Least Once in Studies 3001, 3002, and 3005

Study	3001			3002		3005	
Treatment	Placebo	Esketamine 56 mg 84 mg		Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
n*= Any sedation (score 0-4)	112	114	114	107	114	63	72
n= (%)	12 (10.7%)	57 (50.0%)	69 (60.5%)	11 (10.3%)	66 (57.9%)	12 (19.0%)	35 (48.6%)
Severe sedation (score 0-2)							
n=	0	3 (2.6%)	3 (2.6%)	0	1 (0.8%)	0	0

*Number of subjects who were evaluated by MOAA/s scale

Source: Qi Chen, MD, MPH, Safety Reviewer

There was a substantially higher incidence of sedation in esketamine-treated patients (49 to 61%) than in placebo-treated patients (10% to 19%). In Study 3001, the incidence of sedation

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was slightly higher in the esketamine 84-mg group than in the esketamine 56-mg group, suggesting a possible dose effect (see **Table 81**).

In the randomized controlled Studies 3001, 3002, 3003 (maintenance phase), and 3005, there were 11 subjects who experienced severe sedation (MOAA/S score 0 to 2). Some subjects experienced severe sedation on more than one visit. All visits with severe sedation were with esketamine treatment and occurred in subjects <65 years old.

In Studies 3001, 3002, 3003, and 3005, there were two subjects who experienced sedation with a MOAA/s score of 0. One subject was transferred to the emergency room. The other subject had this level of sedation at five different visits with onset 15 to 30 minutes after receiving esketamine; these episodes lasted between 15 and 35 minutes (see Table 82). It is unclear why the investigator continued to repeat dosing in this subject.

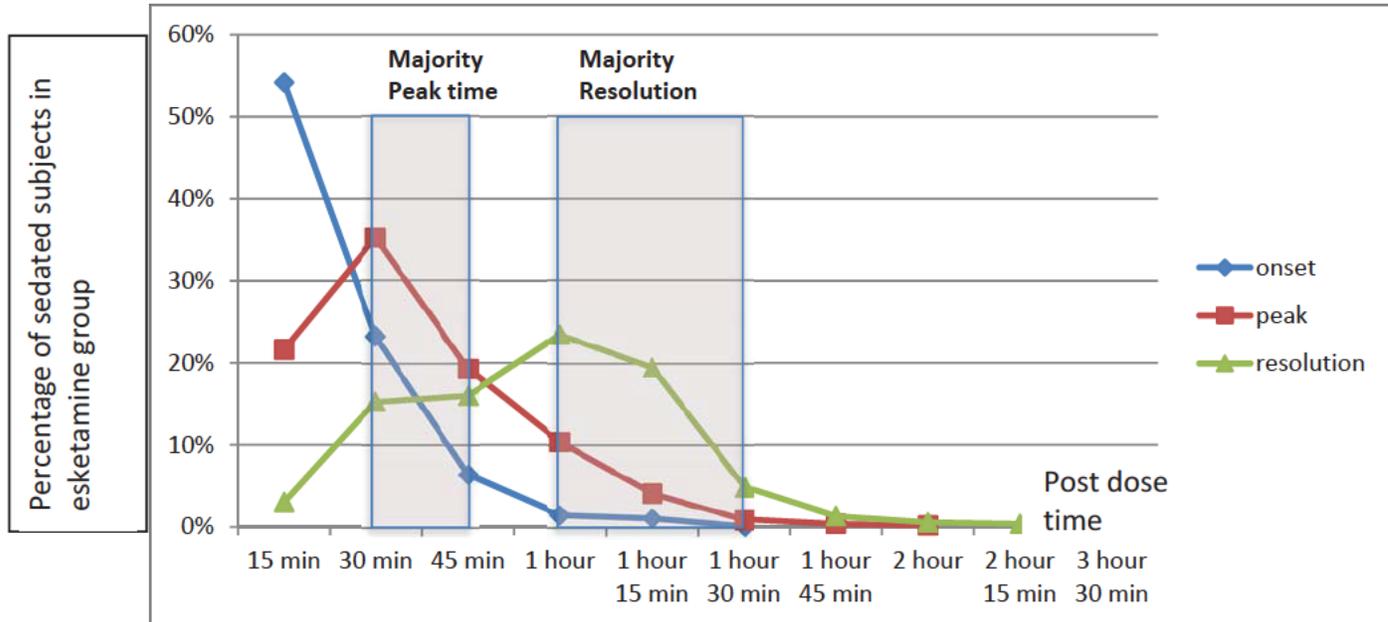
Table 82 Two Esketamine-treated Subjects Who Experienced Sedation with a MOAA/s score of 0 in Phase 3 Studies

STUDY	Subject ID	Study Day (phase)	Start time of LOC	End time of LOC	Disposition
3003	(b) (6)	22 (Induction)	1 hour 15 min	1 hour 30 min	transferred to ER
3003		4 (Induction)	15 min	35 min	observed
		8 (Induction)	15 min	50 min	observed
		18 (Induction)	30 min	45 min	observed
		22 (Induction)	20 min	35 min	observed
		25 (Induction)	20 min	45 min	observed

Source: Qi Chen, MD, MPH, Safety Reviewer

Figure 40 shows all subjects who experienced sedation after esketamine treatment in Studies 3001, 3002, and 3003 (subjects < 65) by time of onset, peak sedation, and time of resolution. The onset of sedation was usually shortly after esketamine administration, typically peaked at 30 to 45 minutes post dose and resolved by 60 to 90 minutes post dose. However, some subjects had much later onset, peak, and resolution times. Among all the esketamine-treated subjects who experienced sedation in these studies, about 18% peaked after 45 minutes and about 3% resolved after 90 minutes. The latest onset, peak, and resolution times were 90 minutes, 120 minutes, and 210 minutes, respectively. This indicates that some patients may have later onset of sedation and need longer observation times.

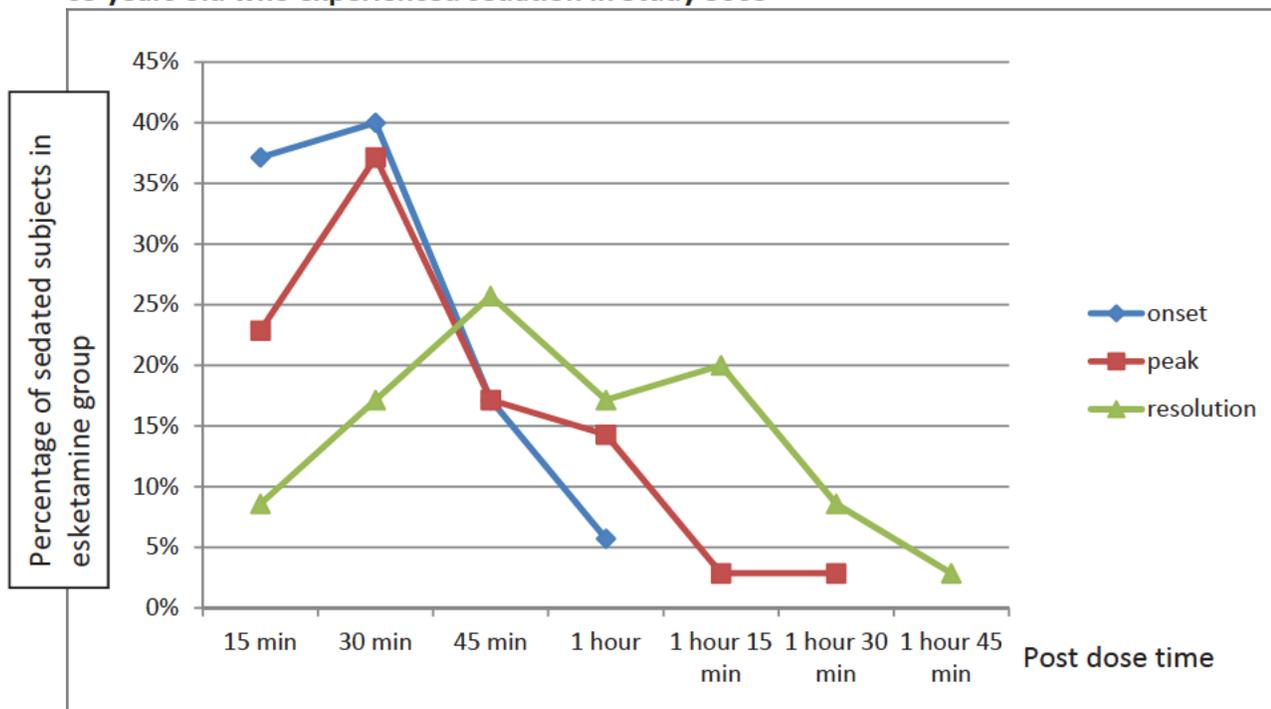
Figure 40 Time of Onset, Peak, and Resolution Time by Percentage of Esketamine-treated Subjects <65-years-old who Experienced Sedation in Studies 3001, 3002, and 3003.



Source: Qi Chen, MD, MPH, Safety Reviewer

Among all subjects age 65 years and older, the majority of subjects experienced sedation between 30 to 45 minutes. Sedation began at 60 minutes for around 6% of subjects who experienced sedation after receiving esketamine. The latest onset, peak, and resolution time for elderly subjects was 60 minutes, 90 minutes, and 105 minutes, respectively. (Figure 41) Compared to subjects <65 years old, sedation was not as severe in subjects ≥65 years old (minimum score=3) and was shorter in duration.

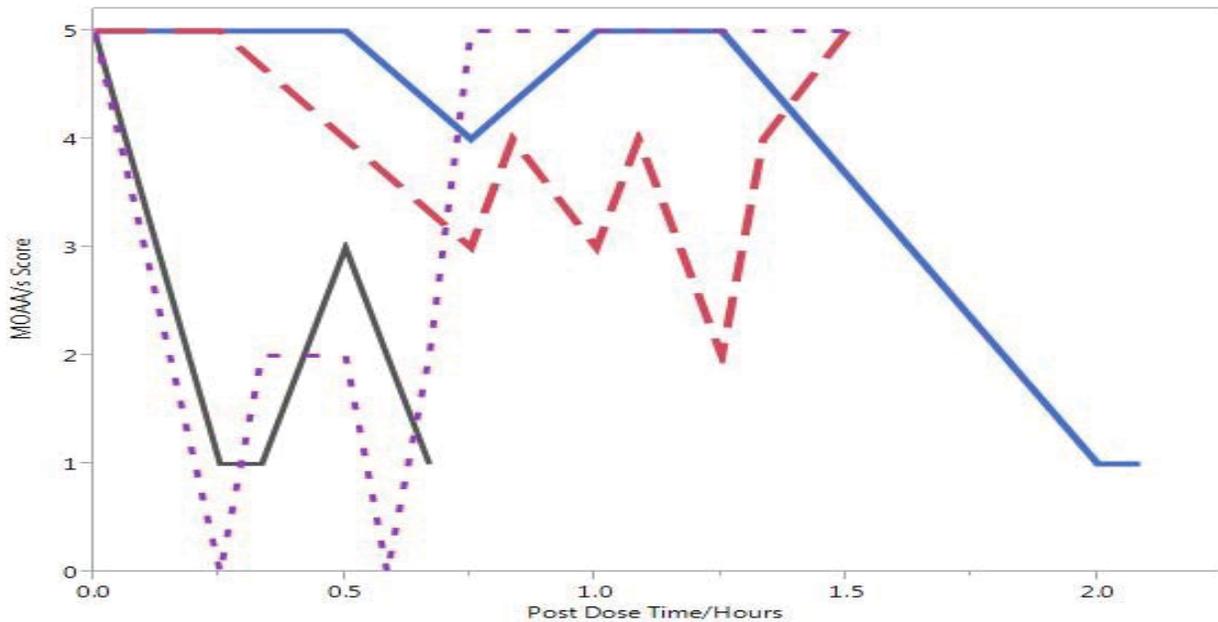
Figure 41 Time of Onset, Peak and Resolution by Percentage of Esketamine-treated Subjects \geq 65 years old who experienced sedation in Study 3005



Source: Qi Chen, MD, MPH, Safety Reviewer

In several subjects, severe sedation showed markedly fluctuating patterns. Figure 42 shows extreme cases in four subjects, demonstrating severity of sedation by MOAA/S score and post-dose time. Each line represents a subject.

Figure 42 Subjects with Fluctuating Sedation Scores



Source: Qi Chen, MD, MPH, Safety Reviewer

The severity of sedation, time of onset, time of peak sedation, and time of resolution varied across visits in some subjects. It appears that the experience of previous visits cannot accurately predict future onset, peak, or resolution time—or degree of severity.

In the short-term Studies (3001, 3002, and 3005), 10 subjects out of 418 (2.4%) in the esketamine group (compared with 0/287 placebo subjects) reported vomiting and sedation (by MOAA/s) on the same day. Sedation severity was 3 to 4 for these subjects. No pulmonary aspiration cases were reported in the clinical studies.

In Studies 3001 and 3002, 281 out of 563 (50%) subjects had concomitant sedative or hypnotic drug use although they were not supposed to have taken these drugs in the 12 hours preceding their study treatment. In a mixed-model analysis, concomitant sedative drugs did not significantly affect sedation as measured by MOAA/s score. The average difference in MOAA/s score post-treatment between esketamine and placebo subjects who did not have concomitant sedatives was 0.59 points; for subjects with sedatives the difference was 0.63 points ($p=0.76$).

Little data on sedation were collected after 1.5 hours in the phase 3 studies; however, sedation was monitored for an extended period in the phase 1 Study 1005. In this study, sedation was assessed using the Karolinska sleepiness scale at regular intervals through 6 hours post-dose. Although most subjects reported that they were “alert” by 6 hours, there were subjects who felt “sleepy” around 4 to 6 hours post-dose in both placebo and esketamine groups. (Six

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subjects (25%) on esketamine reported somnolence AEs ranging from between 1.6 to 20 hours, with an average duration of 6.5 hours.)

Because of the fluctuating pattern of sedation and the potential severity of sedation events, patients will need to be monitored following administration of esketamine until sedation resolves or until they have passed the period of greatest risk for sedation. In the clinical development program, sedation resolved within 2 hours of dosing (with rare exceptions). Thus, it seems reasonable to monitor patients for 2 hours following administration of esketamine to mitigate the risk of adverse events associated with excessive sedation (e.g., falls, motor vehicle accidents).

8.5.2. Dissociation

Dissociation was described as feeling “spacey” or a sensation of “floating”, and patients experiencing dissociation described visual disturbances, trouble speaking, confusion, numbness, feelings of dizziness/faintness, distortion of time and space, illusions, derealization, and depersonalization. Dissociation was evaluated at pre-dose and 40 and 90 minutes post-dose using the Clinician-Administered Dissociative States Scale (CADSS) questionnaire, which has 27 items scored from 0 (not at all) to 4 (extremely) and component scores for amnesia, depersonalization, and derealization. The normal range for CADSS questionnaire was defined as 0 to 4.

Table 83 shows the incidence of dissociation was 60 to 79% of esketamine-treated patients versus 9 to 23% of placebo-treated patients in the three short term studies (3001, 3002, and 3005).

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Table 83 CADSS Median Score and Incidence of Increases in Score >4 Post-dose in Studies 3001, 3002 and 3005.

Study	3001			3002		3005	
Treatment	Placebo	Esketamine 56 mg	Esketamine 84 mg	Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
N=	113	113	116	109	114	65	72
Median (25%, 75%)	0 (0, 1)	6 (2, 14)	8 (3, 16)	0 (0, 1)	9.5 (3, 17)	0 (0, 2)	8.5 (4.5, 15)
Dissociation change >4 n= (%)	10 (9%)	68 (60%)	83 (72%)	16 (15%)	80 (70%)	15 (23%)	57 (79%)

Source: Qi Chen, MD, MPH, Safety Reviewer

Repeated-measures mixed-model analyses of Studies 3001, 3002, 3003, 3004, and 3005—and a repeated-measures mixed-model analysis for dose-effect in Study 3001—showed the following:

1. Significant difference: For the initial treatment in Studies 3001, 3002, and 3005, the average dissociation score in the esketamine group was significantly higher than in the placebo group, with an average increase relative to placebo of 5.8 at 40 minutes and 0.7 at 90 minutes.
2. Attenuation with repeated treatment: The CADSS score at 40 minutes averaged 5.8 points higher on esketamine than placebo after the initial treatment. This difference decreased significantly with subsequent treatments for the first 4 weeks, averaging 2.4 points more than placebo at 40 min at the end of this period. Subjects who continued into the randomized withdrawal study (3003) did not show further reduction in this difference. This plateau effect was also suggested by the results of the open-label extension study (3004) where CADSS scores did not decrease over time.
3. Dose effect: Study 3001 demonstrated a significant dose-effect at 40 minutes, with the average increase for subjects on 84 mg 1.3 points greater than for subjects on 56 mg. No dose effect on dissociation was observed at 90 minutes.

As with sedation, we have recommended a 2-hour observation period for safe resolution of most dissociative symptoms and not driving afterwards. This is being instituted as a REMS goal and requirement.

8.5.3. Impaired Cognition

Impaired cognition has been reported in ketamine post-marketing experience. The evidence suggests that ketamine may have stronger negative effects on specific cognitive domains, such as immediate/delayed recall, which may be dose-dependent. In the esketamine clinical trials, cognition was evaluated by the (b) (4) and the Hopkins Verbal Learning Test-Revised (HVLTR). The tests were measured at Day 1, Day 28, and Week 2 of Follow-Up for the short-term studies, and for 3003, at Day 1 and Day 28 (Open-Label Phase), then Week 16 of Optimization Phase, then Week 32, 44, 56, 68, 80, 92, and End Point of Maintenance Phase. For the long-term, open-label Study 3004, the tests were measured at Week 20, Week 32, Week 44, and End Point. No significant negative effect was found in the esketamine treatment group in Studies 3001, 3002, 3003, and 3005. In Study 3004, in subjects of 65 years and above, there was some evidence of slowed reaction time (RT) pronounced at week 44 of optimization and maintenance phase, with some improvement at the end of the phase; however, there was high intra-individual variability in RT, with large increases as well as large decreased over time within subjects. Without a comparison arm, it is difficult to distinguish drug effect from other reasons for slowed reaction time.

We have recommended longer-term monitoring of this issue in the ongoing multiyear Study 3008 (and have required completion of the full study as a postmarketing requirement). Ongoing REMS data collection and pharmacovigilance-related surveillance and reporting (such as FAERS) will also continue to monitor longer-term concerns with cognition and neurotoxicity.

8.5.4. Suicidal Ideation and Behavior

Treatment-emergent suicidal ideation was assessed using both adverse event reports and the Columbia-Suicide Severity Rating Scale (C-SSRS). For adverse events, AEs coded with preferred terms "Suicide attempt," "Intentional self-injury," "Suicidal ideation," and "Suicidal behavior" were included in our analyses of suicidal ideation and behavior events; the results are summarized in Table 84.

1	Wish to be Dead
2	Non-Specific Suicidal Thought
3	Suicidal Ideation-No Intent
4	Ideation with Intent, No Plan
5	Ideation with Plan/Intent
6	Preparatory Acts/Behavior
7	Aborted Attempt
8	Interrupted Attempt
9	Actual Attempt
10	Suicide

Table 84 Subjects with AEs Related to Suicidal Ideation or Behavior (SI/B) During Double-Blind Study Phases

Study	3001			3002		3005	
Treatment	Placebo	Esketamine		Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
		56 mg	84 mg				
n=	113	115	113	109	112	65	71
Subjects with SI/B (n=)	1	2	2	1	0	0	1

Source: Qi Chen, MD, MPH, Safety Reviewer

The odds ratio for suicide-related AEs was calculated using exact logistic regression stratified by study. Although the odds ratio (1.52) was suggestive of a higher risk with esketamine treatment, this was not statistically significant ($p=0.71$, 95% confidence interval 0.24 to 16.3).

Results for the C-SSRS are summarized in **Table 85**.

Table 85 Subjects with Suicidal Ideation or Behavior as Measured by C-SSRS

Study	3001			3002		3005	
Treatment	Placebo	Esketamine		Placebo	Esketamine 56 to 84 mg	Placebo	Esketamine 28 to 84 mg
		56 mg	84 mg				
N=	113	115	113	109	112	65	71
Suicidal Ideation or Worse (Score >0)							
n=	40	29	37	24	23	20	20
Significant Suicidal Ideation or Suicidal Behavior (Score ≥4)							
n=	0	2	1	0	0	0	1

Source: Qi Chen, MD, MPH, Safety Reviewer

The odds ratio for suicidal ideation (0.82) was suggestive of a lower risk with esketamine treatment but not statistically significant ($p=0.26$, 95% confidence interval 0.57 to 1.16). Suicidal behavior was reported in four esketamine-treated subjects and no placebo subjects (median unbiased estimate odds ratio 3.17) but, again, was not statistically significant ($p=0.30$, 95% confidence interval 0.39 to infinity).

We also examined suicidal ideation and behavior (SI/B) cases that occurred post-randomization in Study 3003, to make sure there was no rebound relationship to esketamine discontinuation

during maintenance treatment. There were four SI/B cases that occurred post-randomization during the maintenance phase.

Study	Subject ID	Study Day (Maintenance Phase)	Treatment Arm	Event
3003	(b) (6)	259	Esketamine	Intentional self-injury
3003	(b) (6)	45	Esketamine	Intentional self-injury
3003	(b) (6)	170	Placebo	Suicidal ideation
3003	(b) (6)	9	Esketamine	Suicidal ideation

Only one of these cases occurred after switching to placebo, and 170 days after esketamine discontinuation, so a relationship to rebound SI/B post-discontinuation from maintenance treatment is unlikely according to this study. We also examined depression and anxiety-related AEs up to 30 days post-randomization. There were 10 subjects with AEs on esketamine versus 6 on placebo, so again, there appears to be no clear relationship to stopping esketamine treatment and the re-emergence of depression and anxiety AEs after discontinuing maintenance treatment.

Based on the all of the above information, there does not appear to be significant evidence for a drug-related (or drug withdrawal-related) signal in the esketamine phase 3 studies for suicidal ideation and behavior.

8.5.5. Nasal Tolerability and the Sense of Smell

In the short-term phase 3 studies, the incidence of nasal discomfort or intolerability adverse events was low and not significantly higher in esketamine than placebo. In the long-term randomized withdrawal study (3003), nasal discomfort was reported with 17 subjects (11.2%) in the esketamine group compared to 7 subjects (4.8%) in the placebo group. Nasal discomfort resolved in all subjects and did not require any change in treatment regimen.

The smell test results for both the UPSIT and the Smell Threshold Test Scores' expert review did not identify any differences between esketamine-treated subjects and placebo-treated subjects in the three short-term phase 3 studies. There was no significant impact on the sense of smell with long-term intermittent dosing in the relapse prevention study.

8.6. Safety Analyses by Demographic Subgroups

The Applicant submitted subgroup analyses by age (18 to 44, 45 to 64, 65 to 74, and ≥75 years for Studies 3004 and 3005), sex (female and male), and race (white, black/African-American, "other") on AEs. There were no clinically meaningful safety differences between strata for any demographic variable.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Human Factors Validation Study

The Human Factors (HF) validation study did not demonstrate that the user interface supports the safe and effective use of this product. Of concern were errors and confusion observed regarding the strength and dosing for this product. The Applicant proposes the product be supplied in a carton containing one 28-mg nasal spray device (28 mg total dose), a carton containing two 28-mg nasal spray devices (56 mg total dose), and a carton containing three 28-mg nasal spray devices (84 mg total dose). Based on the HF data submitted, confusion occurred between the proposed packages regarding strength and dosing, and the proposed packaging may contribute to product-selection medication errors and wrong-dose errors. In the HF validation study, healthcare providers cited confusion regarding how much drug is available per spray, how much drug is available per device, and how many devices should be administered to achieve the correct dose. It was not clear to all study participants that the number of devices per carton is dose specific. Thus, it may be appropriate, considering the findings from the HF validation study, that the Applicant consider marketing a single packaging configuration of one device in one carton, with further label and labeling improvements to increase clarity and minimize the risk for medication errors.

8.7.2. Driving Studies

The effect of intranasal esketamine on driving performance was assessed by an on-road driving test using the standard deviation of lateral position as the primary end-point. The results from two individual studies (1006 and 1019) demonstrated that the driving performance after 84 mg intranasal esketamine was not different from placebo 6 hours post-dose or later (i.e., 8 and 18 hours), provided the subject had met other requirements for discharge. Two subjects from Study 1006 discontinued the driving test due to persistent and worsening adverse events. The first subject had pressure behind the eyes and paresthesia of the hands and feet. The second subject had headache with light sensitivity and anxiety. (Please refer to the clinical pharmacology review for more details.) No information on the driving performance between 0 to 6 hours post-dose was available.

Neither driving study included elderly subjects (≥ 60 years), and the median age was approximately 25 to 35 years. Elderly subjects have a relatively higher exposure to esketamine as compared to younger adults receiving the same dose and may have pre-existing difficulties operating a motor vehicle (due to age-related factors) but also exhibited less sedation when they were treated with esketamine. Thus, it is unclear whether the results can be generalized to elderly subjects.

Patients with moderate hepatic impairment have a longer elimination half-life of esketamine as compared to those with normal hepatic function. Changes in cognitive function, upon esketamine treatment, would need to be monitored for a longer period in such patients.

Overall, we recommend in labeling that the patients should not drive on the day of intranasal esketamine dosing, but they may drive the next day.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity studies were submitted with this application.

8.8.2. Human Reproduction and Pregnancy

No new human reproduction or pregnancy data were submitted with this application.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in studies with this application.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant conducted Study 1015 to evaluate the abuse potential of esketamine and concluded that intranasal administration of esketamine in recreational drug users did not show a markedly different abuse-potential profile compared to IV administration of ketamine. However, there was a drug-liking preference for its effects relative to placebo. Patients on both esketamine (84 mg and 112 mg) and IV ketamine (0.5 mg/kg) reported drug-liking scores that were similar to each other and higher than placebo at 8 hours and 24 hours post-dose.

Table 86 Esketamine Overall Drug Liking Visual Analogue Scores (Study 1015)

Time Point	Overall Drug Liking Visual Analogue Scores (Study 54135419TRD1015)			
	Mean (SD)			
	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

Source: [Mod5.3.4.1/TRD1015/Sec5.2.1.2/Tab15](#)

Table 87 Esketamine Take Drug Again Visual Analogue Scores (Study 1015)

Table 19: Take Drug Again Visual Analogue Scores (Study 54135419TRD1015)

Time Point	Mean (SD)			
	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

Source: [Mod5.3.4.1/TRD1015/Sec5.2.1.3/Tab16](#)

The randomized withdrawal study (3003) did not show higher rates of AEs in the withdrawal (placebo) group compared to the esketamine group, although withdrawal effects were unlikely given that the dosing pre-randomization was infrequent (weekly or every other week).

Because esketamine will be administered under clinical supervision and only be distributed to certified prescribers, the possibility of overdose and abuse/misuse is less likely. Ongoing REMS monitoring and data collection will assist in tracking potential diversion, abuse, or misuse concerns with esketamine.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Adverse Events Related to Repeated Off-Label Use of Ketamine

In recent postmarket safety assessments relating to ketamine, the Division of Pharmacovigilance (DPV) has identified concerns relating to the potential risk of genitourinary, hepatobiliary, and cognitive adverse effects associated with repeated exposure to ketamine for the treatment of depression or pain. DPV prioritized these signals based upon routine surveillance of the literature; however, DPV's review of these potential risks does not address all potential safety concerns regarding ketamine. The post-market safety data do not provide a sufficient base to characterize whether such risks are specific to certain routes of administration or doses and, in many instances of off-label use examined, routes of administration were oral or parenteral. Despite these limitations, findings from the review of ketamine may be considered relevant to discussions regarding the safety of esketamine.

DPV's assessment of data within the FDA Adverse Event Reporting System (FAERS) and the published literature suggests a likely causal relationship between repeated ketamine exposure and the onset of genitourinary (e.g., cystitis) and hepatobiliary events (e.g., cholestasis, periductal fibrosis, elevated transaminases). DPV also reviewed a number of small studies (i.e., randomized controlled trials and observational studies) that suggested subanesthetic doses of ketamine may have negative short-term effects on memory and cognitive function (though it remains unclear whether or under what circumstances such effects persist over the long-term).

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Although DPV did not include patients noted to be abusing ketamine in their review, similar safety findings have been reported among patients abusing ketamine. Please refer to DPV's review for more details.

Ketamine Abuse and Associated Harms

The Division of Epidemiology II performed a review of ketamine abuse and provided the following findings:

Based on national sales distribution patterns of ketamine vials (excluding veterinary sales), ketamine utilization appears to be largely in the hospital setting. Ketamine sales increased approximately 72% from 2013 to 2017 overall and sales to clinic settings, specifically, more than doubled during this 5-year period. Numerous off-label uses of ketamine have been proposed and implemented (including for treatment-resistant depression), and recent literature suggests growth in some of these off-label uses of ketamine.

National survey data and the published literature indicate that ketamine abuse is relatively uncommon in the general population, with a reported lifetime prevalence of 1.3% among persons age 12 years and older—which is lower than that for other hallucinogens such as ecstasy and LSD. Among 12th graders, the annual prevalence of ketamine use has declined from 2.5% in 2000 to 1.2% in 2017. Exposure calls to U.S. poison centers involving ketamine abuse or misuse also declined slightly from 2013 to 2017 (176 calls in 2013 to 116 calls in 2017), despite the growth in non-veterinary ketamine sales. Single-substance exposure calls involving ketamine abuse or misuse were most commonly associated with minor or moderate health effects, and there were no deaths identified among these calls. In a representative sample of approximately 60 U.S. emergency departments (ED), there were 44 ketamine-related ED cases in 2016-2017, corresponding to an estimated 669 visits nationally. Of the 44 ketamine-related ED cases, 35 (81.5%) were classified as associated with ketamine abuse. Only six (17.1%) of these cases resulted in hospitalization. From 2015 to 2017, FAERS received 17 reports of death involving ketamine abuse. Of note, only one of these reports listed ketamine as the only suspected drug, and the drug-event causal association has not been assessed for any of these FAERS cases.

Overall, this analysis suggests that ketamine abuse continues to occur but has remained relatively limited with modest associated harms. The available data are insufficient to determine the extent to which U.S. pharmaceutical ketamine for humans contributes to abuse, relative to ketamine that is smuggled into the country or diverted from veterinary settings. Nonetheless, the risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and postmarketing surveillance for esketamine, if approved.

These findings provide some reassurance in describing a lack of growth in ketamine abuse despite increased off-label use. This likely describes a worst-case scenario for esketamine given the proposed limitations on dosage forms and distribution.

8.9.2. Expectations on Safety in the Postmarket Setting

For the transient adverse effects of sedation, dissociation and increased blood pressure, subjects will be observed for at least 2 hours. Because esketamine will only be administered under supervision, abuse potential and off label use will be lowered (see Section 11 for more details on the REMS plan).

There are two potential long-term safety issues not yet fully resolved. The first is the question of whether long-term use of esketamine can result in cognitive decline. The second is the possible development of ulcerative or interstitial cystitis with long-term exposure. To better characterize these risks, FDA will require the completion of the currently ongoing 3-year prospective, open-label clinical study of patients undergoing esketamine treatment (which includes regular monitoring of cognitive function and urinary symptoms). This study includes appropriate assessments to evaluate these risks over a full 3 years.

8.9.3. Additional Safety Issues from Other Disciplines

No additional safety issues have been raised by other disciplines.

8.10. Integrated Assessment of Safety

The main adverse effects identified in the esketamine studies include sedation, dissociation, and increased blood pressure. Around 49 to 61% of patients experienced sedation and 60 to 79% of patients experienced dissociation compared to 23% or less on placebo. The average peak blood pressure increases in esketamine-treated subjects relative to baseline and placebo was 8 mmHg in systolic and 5 mmHg in diastolic. These effects generally correspond to serum esketamine levels. The majority required about 1.5 hours to resolve but there were some outliers. In clinical pharmacology studies, blood pressure effects last up to 4 hours, and sedation and dissociation up to 4 to 6 hours were observed. The latest onset time of 1.5 hours and fluctuating patterns were observed in sedation. We recommend at least 2 hours observation time post-dose to cover potential late onset and/or unexpected worsening of sedation. Hepatically impaired patients likely need to be monitored longer.

The major safety concerns with chronic or longer-term use (as identified by previous issues with ketamine) were hepatotoxicity, bladder toxicity, cognitive impairment, and unknown long-term neurotoxicity (related to nonclinical concerns with ketamine). A higher rate of urinary tract and bladder AEs was seen in the short-term studies on esketamine compared to placebo, although no cases of interstitial or ulcerative cystitis were reported, including the long-term safety studies. Although sedation and vomiting were common effects, no aspiration cases were noted in the studies. No cases of acute hepatotoxicity or clinically meaningful liver function test trends were noted. Some slowed reaction time with high intra-individual variability was noticed in elderly subjects

in a long-term open-label study, but without a comparison arm, it is difficult to distinguish drug effect from other reasons. We have requested a postmarketing requirement for a long-term safety study to better evaluate these concerns (full completion of the ongoing multiyear Study 3008 may be able to fulfill this requirement). Ongoing REMS data collection and pharmacovigilance will also continue to monitor for longer-term safety issues, particularly urinary/bladder-related and cognitive concerns.

Abuse potential is also a major identified concern, because esketamine has similar drug-liking characteristics (i.e., euphoria and dissociation) to ketamine, a known drug of abuse. This effect was confirmed in a phase 1 abuse potential study (Study 1015); subjects on esketamine endorsed similar drug-liking scores to IV ketamine and higher than placebo. Esketamine will be categorized as a Schedule III drug. The REMS will restrict esketamine distribution to registered and certified prescribers and clinical settings, in order to reduce diversion and abuse risks.

9. Advisory Committee Meeting and Other External Consultations

Questions and issues that were addressed during the Advisory Committee (AC) meeting on February 12, 2019 included:

- Main Efficacy Concerns
 - Is Study 3003, a randomized withdrawal study with an enriched population of stable remitters and responders on esketamine, an adequate and well-controlled trial that can be used as a study to support substantial evidence of effectiveness for esketamine?
 - Is there supportive evidence for approval in the other studies conducted for esketamine that were not statistically significant on their primary endpoint (i.e., Study 3001 and 3005)?
 - Are there concerns about change in perception of treatment assignment due to side effects affecting efficacy results?
- Main Safety Concerns
 - Acute (Occurring within 2 hours of administration)
 - Dissociation
 - Sedation
 - Cardiovascular (Increased Blood Pressure and Heart Rate)
 - Effects on Driving
 - Post-Acute and Long-Term
 - Suicidal Ideation and Behavior
 - Cognition (and nonclinical neurotoxicity concerns seen with ketamine)
 - Urinary Tract and Bladder Toxicity (Cystitis)

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- Liver Toxicity
- Abuse Potential
- REMS
 - Do we require a REMS plan for safety and abuse concerns?
 - Safety
 - What period of observation is recommended to minimize risks after short-term dissociation, sedation, and increased blood pressure?
 - What level of medical support and clinical monitoring and oversight is recommended?
 - Abuse
 - What methods to reduce diversion and monitor substance abuse behavior should we include?
 - What type/level of postmarketing data collection should be required to confirm and ascertain the need for an ongoing REMS?
 - What are the consequences of the proposed REMS plan regarding clinical management and patient access to esketamine? How do you balance concerns about limitation of access with potential effects on inability to access treatment and missed doses and nonadherence with abuse and diversion risks?

Patient voice concerns were taken into consideration from the open public hearing and the patient representative on the committee, such as the ongoing urgency for additional safe and effective treatments for TRD and the need to consider functional outcome measures for esketamine's effects on TRD.

The AC committee voted 14 to 2 (with 1 abstention) in favor of the benefit-risk profile as presented (including the REMS) for the approval of esketamine for the treatment of TRD. There were similar votes in favor of the efficacy and safety of esketamine being sufficiently characterized (14 to 2 with 1 abstention, and 15 to 2 for efficacy and safety respectively).

The committee noted that some parameters of the REMS still needed additional clarification, such as the definition of a medically supervised health-care setting (and the wish to avoid "esketamine mills" that only prescribe esketamine without other options for comprehensive medical/psychiatric care), any concerns about drug interactions with sedative-hypnotics or opioids or over-the-counter drugs, and the need for standardized procedures for REMS-related adverse reaction monitoring without overly restricting drug access. The committee generally agreed with the overall scope of the REMS plan and the need to mitigate the acute drug effects and the risk of abuse accordingly. They recommended ongoing safety monitoring for effects such as long-term cognitive deficits, high blood pressure, and suicidal ideation. They recommended consideration of additional studies or data to address questions on functional outcomes, suicide risk, geriatric efficacy, subgroups of treatment responsiveness, efficacy in

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depressed patients with psychosis (e.g., psychotic depression, bipolar depression, or schizoaffective disorder) or patients with more severe TRD (i.e., failing ECT), and better characterization of the novel mechanism of action and its potential relationship to rapid-acting effects. Please see the minutes and transcript for the Advisory Committee Meeting for more details.

Other external consultations (other than those already cited in this review) included the Division of Cardiorenal Products (DCRP) regarding the increased blood pressure and heart rate signal; their recommendations have been incorporated into labeling. Please see their consultation review for more details.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

- We agree for now with the inclusion of the use of an oral antidepressant with esketamine, given the design of the phase 3 clinical trials; however, a postmarketing study to determine esketamine's effectiveness for TRD as monotherapy should be considered to inform future labeling and likely clinical use of esketamine accordingly. The use of a background oral antidepressant was in part considered ethically necessary, given the potential illness severity of a study population with TRD receiving only placebo and no prior phase 3 esketamine efficacy data.
- Of note, the Applicant labeled the phase 3 studies as "active-controlled" due to the use of a background oral antidepressant in all treatment groups. Technically, the control variable being compared in these studies is the use of intranasal esketamine versus intranasal placebo, and the studies are not active-controlled; the label was corrected accordingly.
- The SI/B antidepressant boxed warning should still be included in the label, given that concomitant use of an oral antidepressant is also recommended, and the treatment indication is for depression. There were few subjects under 25 years of age so there was no basis for determining whether the effect described in the boxed warning occurs with esketamine. Esketamine has a different mechanism of action than any other oral antidepressants.
- Warnings and precautions should align with the safety issues outlined in the proposed REMS plan. We also agree with the inclusion of bladder and urinary concerns in that section, given the increased incidence of those AEs in the phase 3 studies on esketamine versus placebo. We may also need to consider whether aspiration precautions should be noted in the label (as it is included in the Ketalar label), given the potential co-occurrence of the common AEs of sedation and nausea/vomiting, although no aspiration-related adverse events were noted in the esketamine program.

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- We recommend more specific criteria on blood pressure monitoring. In the phase 2 studies, subjects with previously elevated blood pressures at baseline (i.e., above 140/90) were noted to have blood pressures that increased into clinically concerning ranges (as high as 200/130). We have added specific instructions to check blood pressure readings before and after esketamine administration and a general guideline that the drug should not be administered if the baseline reading is above 140/90. Clinicians may still ascertain benefit-risk for individual patients as per their clinical judgment. We also generally agree with the Applicant's proposed contraindications regarding patients with pre-existing cardiovascular, cerebrovascular, and other acute risk factors (i.e., aneurysms) that can be exacerbated by esketamine's effects but requested more specific data and justification.
- (b) (4)
[REDACTED] We do not recommend a limitation of use for this population given the unremarkable safety profile relative to non-geriatric adults and the possibility that individual subjects in that age group may still clinically benefit from esketamine.
- We recommend cautionary language (per DPMH and nonclinical) regarding the potential teratogenicity of esketamine based on nonclinical data and the need to use contraception if taking this drug. Information about referral to general pregnancy drug event registries will be included in the label.
- (b) (4)
[REDACTED] (b) (4) Relevant safety and pharmacokinetic information will be considered in those studies for inclusion in the label as warranted.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant has submitted a REMS proposal with ETASU which is under negotiation and discussion with our review team. Our team agrees that institution of a REMS with ETASU for esketamine if approved is warranted for several reasons:

- Safety
 - Observation period of at least 2 hours to safely manage acute dissociation, sedation, and blood pressure increases
 - Restriction of driving until the next day (and accompanied discharge home) due to residual above effects

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- On-site clinical equipment (i.e., blood pressure cuff and vital signs monitoring) to assess the above and appropriate emergency management and triage availability as clinically warranted
- Abuse Potential
 - Restrict esketamine dispensing and administration to medically supervised, REMS-certified settings via certified pharmacies
 - Disposal monitoring
- Site certification, instruction, and postmarket tracking of REMS-related adverse reactions via monitoring forms (to also determine ongoing need for REMS).

The following are the finalized goals of the REMS for esketamine:

The goal of the REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and abuse and misuse of SPRAVATO by:

- *Ensuring that SPRAVATO is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients*
- *Ensuring pharmacies and healthcare settings that dispense SPRAVATO are certified*
- *Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring*
- *Enrollment of all patients in a registry to further characterize the risks and support safe use.*

Please refer to the DRISK review for more details on the REMS plan.

12. Postmarketing Requirements and Commitments

- The NDA-submitted esketamine studies, due to their design (inclusion of a concomitant oral antidepressant), did not provide sufficient data to demonstrate the efficacy of esketamine as monotherapy; this remains an important clinical question given the likelihood that patients and clinicians will want to use esketamine as monotherapy. We also as yet do not have sufficient dose-response data to answer whether esketamine 84 mg provides any additional clinical benefit over 56 mg. Based on the results of the fixed-dose Study 3001, the higher dose has a higher incidence of vomiting and increased blood pressure and heart rate over the lower dose, but no other clear dose-related adverse effects.

We will recommend a post-marketing commitment study for esketamine as monotherapy for the indication of treatment of TRD. The short-term study should be a 4-week

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randomized placebo-controlled trial and should utilize the same TRD inclusion criteria as the phase 3 trials and use MADRS as an outcome measure. A fixed-dose arm will also be recommended in the short-term study to ascertain whether there is a dose response for the 84-mg dose of esketamine versus 56 mg. (We decided that a placebo-controlled trial was ethically feasible this time due to the notable early placebo arm response in the phase 3 studies in a TRD population, where oral antidepressant was unlikely to have taken effect yet. We felt that subject safety would not be compromised with the high level of monitoring (e.g., at least twice weekly visits) and provisions for immediate clinical triage to be planned for this clinical trial.)

- There are three safety issues that we believe merit further study post-marketing:

1) Cognitive effects. There is evidence of deleterious effects on cognition with long-term use or abuse of racemic ketamine. This was not seen in the esketamine development program. In short-term controlled studies, esketamine treatment was associated with modest improvements in cognition relative to placebo. This may have been the result of improvements in depression and this could have obscured adverse effects in the short run. It is possible that adverse effects could slowly accumulate over time.

2) Chronic or severe cystitis. This has been seen with ketamine but was not observed in the esketamine clinical development program. This could be due to differences in dosage and administration but there was good evidence of less severe adverse effects on the bladder with esketamine use. It is possible that with long-term use these effects could cumulatively lead to more serious consequences. It is also possible that a small subgroup of patients may be unusually sensitive to the bladder effects of esketamine. If severe interstitial or ulcerative cystitis were occurring, it would likely be reported in FAERS. It may not, however, be possible to distinguish, solely from FAERS reports, a chronic cumulative effect to which many patients may be susceptible from a more acute sensitivity present in a small subgroup. A long-term prospective study with routine collection of bladder symptom information and urinalyses could provide useful information. This may not justify a study by itself but would increase the value of performing or extending a long-term study conducted for other purposes.

A currently ongoing study, Study 3008, would be adequate for these purposes if subjects were followed for the nominal three-year observation period. The protocol provides, however, for the study to terminate when esketamine becomes commercially available. We propose that this study be continued post-marketing to allow all subjects to remain in the study for at least three years.

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3) Effects on thyroid function. Single-dose studies in Phase 1 showed a clear effect of esketamine on levels of thyroid-stimulating hormone. It is not clear whether this increase is a result of direct stimulation of TSH or indirectly through reducing production of thyroxine or the effect of thyroxine. It is also not known whether the increase in TSH has cumulative effects on thyroid function over time.

We propose that the Applicant obtain a full panel of thyroid function tests (TSH, Free T3 and Free T4) before every treatment in a group of esketamine-naïve subjects who are beginning treatment who will be following the labeled dosage intervals (twice weekly, weekly and biweekly) for several months. The exact number of subjects and length of observation can be discussed with the Applicant.

13. Appendices

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13.1. Study Visit Tables

13.1.1. Study 3001

TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Double-blind Induction Phase)

Visit number	Screening/ Prospective Observational Phase			Double-blind Induction Phase										EW ^b
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Screening/Administrative														
Informed consent (ICF)	X													
Medical history, psychiatric history, demographics, employment status	X													
MINI	X													
MGH-ATRQ	X													
Site Independent Qualification Assessment	X													
Height	X													
Inclusion/exclusion criteria	X			X										
Prestudy therapy	X													
Preplanned surgery/procedures	X													
STOP-Bang questionnaire (including assessment of BMI and neck circumference)	X													
MGH-Female RLHQ: Module I	X													

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IDS-C ₃₀	X													
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4				—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Study Drug														
Randomization				X										
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine)				X									X ⁱ	X
Practice session for use of intranasal device				X ^c										
Intranasal esketamine or placebo				X		X	X	X	X	X	X	X		
Drug accountability (intranasal study)				X		X	X	X	X	X	X	X		X
Drug accountability (oral antidepressant study)				X									X	X
Dispense subject diary for oral antidepressant				X										
Review subject diary and update (if applicable)						X	X	X	X	X	X	X	X	X
Oral antidepressant compliance check							X		X		X		X	X
Return of subject diary if not entering follow up phase													X	
Safety Assessments (Clinician)														

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Physical examination	X			X									X	X
Nasal examination ^c	X			X									X	X
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4				—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Vital signs: blood pressure, pulse, respiratory rate, temperature ^{c,q}	X			X		X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate				X		X	X	X	X	X	X	X		
Weight	X			X									X	X
12-lead ECG ^{r,q}	X			X			X		X			X		X
C-SSRS: Baseline/Screening version	X													
C-SSRS: Since last visit version ^q		X	X	X ^r		X	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry ^{g,q}	X			X		X	X	X	X	X	X	X		
BPRS+ ^{h,q}				X		X	X	X	X	X	X	X		
CADSS ^{h,q}				X		X	X	X	X	X	X	X		
CGADR ⁱ				X		X	X	X	X	X	X	X		
PWC-20												X		X
Safety Assessments (Subject-completed)														
Nasal symptom questionnaire ^k				X		X		X		X		X		
BPIC-SS ^c				X					X				X	X
Assessment of Sense of Smell														
UPSIT ^{c,o}		X							X				X	X

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Smell Threshold Test ^{c, o}		X											X	X
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4				—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Efficacy Assessments (Clinician)														
MADRS (7-day recall; performed by independent, remote raters)	X	X ^p	X ^p	X ^d			X ^p		X ^p		X ^p		X ^p	X
MADRS (24-hr recall; performed by independent, remote raters)					X									
CGI-S ^c	X			X		X	X		X		X		X	X
Subject-completed Assessments														
PAQ	X	X	X											
PHQ-9 ^c	X			X					X				X	X
SDS ^c	X			X					X				X	X
GAD-7 ^c	X			X									X	X
EQ-5D-5L ^c	X			X					X				X	X
Cognition Testing														
Practice sessions for computerized test battery		X												
Computerized test battery and HVLT-R				X									X	X
Clinical Laboratory Assessments														
TSH, HbA1c	X													
Lipid panel (fasting)		X												
Hematology, chemistry ^c	X			X									X	X

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Urine drug screen ^c	X			X					X			X		
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4				—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Alcohol breath test	X			X										
Urinalysis ^c	X			X					X				X	X
Serum pregnancy test	X													
Urine pregnancy test ^c				X					X				X	X
Pharmacokinetics														
Blood collection ^l						X					X			
Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations														
Blood sample collection (protein) ^{c, m}	X			X			X					X		X
Blood sample collection (DNA) ^{c, m}	X											X		X
Blood sample collection (RNA) ^{c, m}	X			X			X					X		X
Ongoing Subject Review														
Concomitant therapy	<i>Ongoing</i>													
Adverse events	<i>Ongoing</i>													
Other														
Menstrual cycle tracking (start date of last menstrual period prior to study visit)				X ⁿ									X ⁿ	

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Footnotes:

Abbreviations: BMI, body mass index; BPIC-SS, Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+, 4-item positive symptom subscale of the Brief Psychiatric Rating Scale; C, clinic visit; CADSS, Clinician Administered Dissociative States Scale; CGADR, Clinical Global Assessment of Discharge Readiness; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia Suicide Severity Rating Scale; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 dimension- 5-level; EW, early withdrawal; GAD-7, Generalized Anxiety Disorder, 7-item scale; HbA1c test, glycated hemoglobin test; HVLT-R, Hopkins Verbal Learning Test-Revised; IDS-C₃₀, Inventory of Depressive Symptomatology Clinician-rated, 30-item scale; MADRS, Montgomery-Asberg Depression Rating Scale; MGH-ATRQ, Massachusetts General Hospital - Antidepressant Treatment History Questionnaire; MGH-Female RLHQ, Massachusetts General Hospital - Female Reproductive Lifecycle and Hormones Questionnaire; MINI, Mini-International Neuropsychiatric Interview; MOAA/S, Modified Observer’s Assessment of Alertness/Sedation; PAQ, Patient Adherence Questionnaire; PHQ-9, Patient Health Questionnaire – 9; PWC-20, Physician Withdrawal Checklist, 20-item scale; RNA, ribonucleic acid; SDS, Sheehan Disability Scale; STOP-Bang, Snoring, Tired, Observed Apnea, High Blood Pressure, Body mass index, Age, Neck Size, Gender (a questionnaire); TSH, thyroid-stimulating hormone

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

- a) An additional, optional period of up to 3 weeks is permitted to taper and discontinue current antidepressant treatment(s) after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind induction phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).
- b) If a subject withdraws before the end of the double-blind induction phase (ie, before completing Visit 2.10/Day 28) for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- c) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study- related procedures during a clinic visit.
- d) Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be considered as the subject’s baseline MADRS for the double-blind induction phase. For all other subjects, the baseline MADRS for the double-blind induction phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.
- e) Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.2.1 for guidance for blood pressure monitoring on intranasal dosing days.
- f) Twelve-lead ECG will be performed predose and at t=1 hour postdose at Visit 2.1. Twelve-lead ECG will be performed at t=1 hour postdose only (ie, no predose ECG required) at Visits 2.4, 2.6, and 2.9. A time window of ±15 minutes is permitted.
- g) The MOAA/S will not be performed at Visit 1.1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose (please refer to Section 9.7 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.7 for further guidance on timing of pulse oximetry assessments).

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- h) The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
- i) CGADR to be performed at 1 hour and 1.5 hour postdose; if the response is not “Yes” at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
- j) Performed only if the subject is not continuing into Study ESKETINTRD3003.
- k) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- l) PK blood collection will be performed at t=40 minutes and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray).
- m) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) Only applicable to women with a menstrual cycle.
- o) If the subject has significant nasal congestion on the day of a scheduled assessment, the site should consider postponing the smell test assessment(s) to the next scheduled clinic visit.
- p) The MADRS should be administered no more than 2 days prior to the subject’s targeted (not actual) clinic visit date (except Visit 2.10, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- q) If intranasal dosing is postponed (but occurs within visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual intranasal dosing day.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

Visit number	Follow-up Phase												
	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13
Weeks after last intranasal dose	1	2	4	6	8	10	12	14	16	18	20	22	24
Visit window for clinic visit or remote assessments only (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit (C) or remote assessments only (RA)	RA ^T	C	RA ^T	RA ^T	RA ^T	RA ^T	C	RA ^T	C				
Oral antidepressant compliance ^a													
Oral antidepressant compliance check		X											
Drug accountability													

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Drug accountability (oral antidepressant study medication)		X					X ^e						
Return of subject diary		X											
Safety Assessments (Clinician-completed)													
Physical examination		X											X
Nasal examination		X											
Vital signs: Blood pressure, pulse, respiratory rate, temperature		X											X
12-lead ECG		X											
C-SSRS: Since last visit version		X					X						X
PWC-20	X ^c	X											
Safety Assessments (Subject-completed)													
BPIC-SS		X											
Efficacy Assessments (Clinician-completed)													
MADRS (performed by independent, remote raters)		X											X
CGI-S		X					X						X
Efficacy Assessments (Subject-completed)													
PHQ-9		X	X		X		X		X		X		X
SDS		X	X		X		X		X		X		X
GAD-7		X	X		X		X		X		X		X
EQ-5D-5L		X	X		X		X		X		X		X
Visit number	Follow-up Phase												
	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13
Weeks after last intranasal dose	1	2	4	6	8	10	12	14	16	18	20	22	24
Visit window for clinic visit or remote assessments only (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit (C) or remote assessments only (RA)	RA ^f	C	RA ^f	RA ^f	RA ^f	RA ^f	C	RA ^f	C				
Cognition testing													
Computerized test battery and HVLt-R		X											
Medical Resource Utilization													
HRUQ ^b		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments													

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Hematology, chemistry		X												
Urinalysis		X												
Serum pregnancy test		X												
Urine pregnancy test							X							X
Biomarker and Expression (RNA) Evaluations														
Blood sample collection (protein) ^d		X												
Blood sample collection (RNA) ^d		X												
Ongoing Subject Review														
Concomitant therapy	<i>Ongoing</i>													
Adverse events	<i>Ongoing</i>													

Note: No intranasal study medication will be administered during the follow-up phase.

- a) In order to better assess potential withdrawal symptoms from intranasal study medication, the oral antidepressant medication should be continued for at least the first 2 weeks of the follow-up phase unless determined to be not clinically appropriate.
- b) For the HRUQ, a clinician-completed assessment may be required (based on subject-responses).
- c) Performed by telephone by qualified site staff.
- d) It is preferred that subjects adhere to a low fat diet the day of sample collection.
- e) For any remaining oral antidepressant study medication.
- f) At each "Remote Assessment " visit, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

13.1.2. Study 3002

TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Double-blind Induction Phase)

Study 3002	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Visit number														

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Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
				1 (baseline)	2	4	8	11	15	18	22	25	28	
Study day	—	—	—	(baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Screening/Administrative														
Informed consent (ICF)	X													
Medical history, psychiatric history, demographics, employment status	X													
MINI	X													
MGH-ATRQ	X													
Site Independent Qualification Assessment	X													
Height	X													
Inclusion/exclusion criteria	X			X										
Prestudy therapy	X													
Preplanned surgery/procedures	X													
STOP-Bang questionnaire (including assessment of BMI and neck circumference)	X													
MGH-Female RLHQ: Module I	X													
IDS-C ₃₀	X													
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3^a	2.1^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW^b
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—

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Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Study Drug														
Randomization				X										
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X									X ⁱ	X
Practice session for use of intranasal device				X ^c										
Intranasal esketamine or placebo				X		X	X	X	X	X	X	X		
Drug accountability (intranasal study)				X		X	X	X	X	X	X	X		X
Drug accountability (oral antidepressant study medication)				X									X	X
Dispense subject diary for oral antidepressant				X										
Review subject diary and update (if applicable)						X	X	X	X	X	X	X	X	X
Oral antidepressant compliance check							X		X		X		X	X
Return of subject diary if not entering follow-up phase													X	
Safety Assessments (Clinician)														
Physical examination	X			X									X	X
Nasal examination ^c	X			X									X	X

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Spravato (Esketamine)

Visit number	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Vital signs: blood pressure, pulse, respiratory rate, temperature ^{c,q}	X			X		X	X	X	X	X	X	X	X	X
Vital signs (postdose): blood pressure, pulse, respiratory rate				X		X	X	X	X	X	X	X		
Weight	X			X									X	X
12-lead ECG ^{f,q}	X			X			X		X			X		X
C-SSRS: Baseline/Screening version	X													
C-SSRS: Since last visit version ^q		X	X	X ^r		X	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry ^{g,q}	X			X		X	X	X	X	X	X	X		
BPRS+ ^{h,q}				X		X	X	X	X	X	X	X		
CADSS ^{h,q}				X		X	X	X	X	X	X	X		
CGADR ⁱ				X		X	X	X	X	X	X	X		
PWC-20												X		X
Safety Assessments (Subject-completed)														
Nasal symptom questionnaire ^k				X		X		X		X		X		
BPIC-SS ^c				X					X				X	X
Assessment of Sense of Smell														
UPSIT ^{c,o}		X							X				X	X
Smell Threshold Test ^{c,o}		X											X	X

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Spravato (Esketamine)

Visit number	Screening/ Prospective Observational Phase			Double-blind Induction Phase											
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW ^b	
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4				—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW	
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—	
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C	
Efficacy Assessments (Clinician)															
MADRS (7-day recall; performed by independent, remote raters)	X	X ^p	X ^p	X ^d			X ^p		X ^p		X ^p		X ^p	X	
MADRS (24-hr recall; performed by independent, remote raters)					X										
CGI-S ^c	X			X		X	X	X	X		X		X	X	
Subject-completed Assessments															
PAQ	X	X	X												
PHQ-9 ^c	X			X					X				X	X	
SDS ^c	X			X					X				X	X	
GAD-7 ^c	X			X									X	X	
EQ-5D-5L ^c	X			X					X				X	X	
Cognition Testing															
Practice sessions for computerized test battery		X													
Computerized test battery and HVLt-R				X									X	X	
Clinical Laboratory Assessments															
TSH, HbA1c	X														
Lipid panel (fasting)		X													

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Hematology, chemistry ^c	X			X									X	X
Urine drug screen ^c	X			X				X				X		
	Screening/ Prospective Observational Phase			Double-blind Induction Phase										
Visit number	1.1	1.2	1.3^a	2.1^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	EW^b
Week	Week 1	End of Week 2	End of Week 4	1			2		3		4			—
Study day	—	—	—	1 (baseline)	2	4	8	11	15	18	22	25	28	EW
Clinic visit window (in days)	—	±2	±2	—	—	±1	±1	±1	±1	±1	±1	±1	±1	—
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	RM	C	C	C	C	C	C	C	C	C
Alcohol breath test	X			X										
Urinalysis ^c	X			X					X				X	X
Serum pregnancy test	X													
Urine pregnancy test ^c				X					X				X	X
Pharmacokinetics														
Blood collection ^l						X					X			
Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations														
Blood sample collection (protein) ^{c, m}	X			X			X					X		X
Blood sample collection (DNA) ^{c, m}	X											X		X
Blood sample collection (RNA) ^{c, m}	X			X			X					X		X
Ongoing Subject Review														
Concomitant therapy	Ongoing													
Adverse events	Ongoing													
Other														

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Menstrual cycle tracking (start date of last menstrual period prior to study visit)				X ⁿ									X ⁿ	
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Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

- a) An additional, optional period of up to 3 weeks is permitted to taper and discontinue current antidepressant treatment(s) after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind induction phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).
- b) If a subject withdraws before the end of the double-blind induction phase (ie, before completing Visit 2.10/Day 28) for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- c) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- d) Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be considered as the subject's baseline MADRS for the double-blind induction phase. For all other subjects, the baseline MADRS for the double-blind induction phase will be the MADRS performed at the end of Week4 of the screening/prospective observational phase.
- e) Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.2.1 for guidance for blood pressure monitoring on intranasal dosing days.
- f) Twelve-lead ECG will be performed predose and at t=1 hour postdose at Visit 2.1. Twelve-lead ECG will be performed at t=1 hour postdose only (ie, no predose ECG required) at Visits 2.4, 2.6, and 2.9. A time window of ±15 minutes is permitted.
- g) The MOAA/S will not be performed at Visit 1.1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose (please refer to Section 9.7 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.7 for further guidance on timing of pulse oximetry assessments).
- h) The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
- i) CGADR to be performed at 1 hour and 1.5 hour postdose; if the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.

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- j) Performed only if the subject is not continuing into Study ESKETINTRD3003.
- k) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- l) PK blood collection will be performed at t=40 minutes and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray).
- m) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) Only applicable to women with a menstrual cycle.
- o) If the subject has significant nasal congestion on the day of a scheduled assessment, the site should consider postponing the smell test assessment(s) to the next scheduled clinic visit.
- p) The MADRS should be administered no more than 2 days prior to the subject's targeted (not actual) clinic visit date (except Visit 2.10, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- q) If intranasal dosing is postponed (but occurs within visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual intranasal dosing day.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

Visit number	Follow-up Phase												
	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13
Weeks after last intranasal dose	1	2	4	6	8	10	12	14	16	18	20	22	24
Visit window for clinic visit or remote assessments only (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit (C) or remote assessments only (RA)	RA [†]	C	RA [†]	RA [†]	RA [†]	RA [†]	C	RA [†]	C				
Oral antidepressant compliance^a													
Oral antidepressant compliance check		X											
Drug accountability													
Drug accountability (oral antidepressant study medication)		X					X ^e						
Return of subject diary		X											
Safety Assessments (Clinician-completed)													
Physical examination		X											X

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Nasal examination		X											
Vital signs: Blood pressure, pulse, respiratory rate, temperature		X											X
12-lead ECG		X											
C-SSRS: Since last visit version		X					X						X
PWC-20	X ^c	X											
Safety Assessments (Subject-completed)													
BPIC-SS		X											
Efficacy Assessments (Clinician-completed)													
MADRS (performed by independent, remote raters)		X											X
CGI-S		X					X						X
Efficacy Assessments (Subject-completed)													
PHQ-9		X	X		X		X		X		X		X
SDS		X	X		X		X		X		X		X
GAD-7		X	X		X		X		X		X		X
EQ-5D-5L		X	X		X		X		X		X		X
Visit number	Follow-up Phase												
	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13
Weeks after last intranasal dose	1	2	4	6	8	10	12	14	16	18	20	22	24
Visit window for clinic visit or remote assessments only (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit (C) or remote assessments only (RA)	RA ^f	C	RA ^f	RA ^f	RA ^f	RA ^f	C	RA ^f	C				
Cognition testing													
Computerized test battery and HVLT-R		X											
Medical Resource Utilization													
HRUQ ^b		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments													
Hematology, chemistry		X											
Urinalysis		X											

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Serum pregnancy test		X											
Urine pregnancy test							X						X
Biomarker and Expression (RNA) Evaluations													
Blood sample collection (protein) ^d		X											
Blood sample collection (RNA) ^d		X											
Ongoing Subject Review													
Concomitant therapy	Ongoing												
Adverse events	Ongoing												

Note: No intranasal study medication will be administered during the follow-up phase.

- In order to better assess potential withdrawal symptoms from intranasal study medication, the oral antidepressant medication should be continued for at least the first 2 weeks of the follow-up phase unless determined to be not clinically appropriate.
- For the HRUQ, a clinician-completed assessment may be required (based on subject-responses).
- Performed by telephone by qualified site staff.
- It is preferred that subjects adhere to a low fat diet the day of sample collection.
- For any remaining oral antidepressant study medication.
- At each "Remote Assessment " visit, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

13.1.3. Study 3003

TIME AND EVENTS SCHEDULE (Screening/Prospective Observational and Open-Label Induction Phase)

Visit number	Screening/Prospective Observational Phase			Open-label Induction Phase								
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		
Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1

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Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
Screening/Administrative												
Informed consent (ICF)	X											
Medical history, psychiatric history, demographics, employment status	X											
MINI	X											
MGH-ATRQ	X											
Site Independent Qualification Assessment	X											
Height	X											
Inclusion/exclusion criteria	X			X								
Prestudy therapy	X											
Preplanned surgery/procedures	X											
STOP-Bang questionnaire (including assessment of BMI and neck circumference)	X											
MGH-Female RLHQ: Module I	X											
IDS-C ₃₀	X											
Study Drug												
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X								X ^m
Practice session for use of intranasal device				X ^c								
Intranasal esketamine				X	X	X	X	X	X	X	X	
Drug accountability (intranasal study)				X	X	X	X	X	X	X	X	
Drug accountability (oral antidepressant study medication)				X								X
Dispense subject diary for oral				X								
Review subject diary and update (if applicable)					X	X	X	X	X	X	X	X

	Screening/Prospective Observational Phase			Open-label Induction Phase								
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		

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Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
Oral antidepressant compliance check						X		X		X		X
Collect/return of subject diary												X
Safety Assessments (Site-completed)												
Physical examination	X			X								X
Nasal examination ^c	X			X								X
Vital signs: blood pressure, pulse, respiratory rate, temperature ^{c,p}	X			X	X	X	X	X	X	X	X	
Vital signs (postdose): blood pressure, pulse, respiratory rate ^d				X	X	X	X	X	X	X	X	
Weight	X			X								X
12-lead ECG ^{e,p}	X			X		X		X			X	
C-SSRS: Baseline/Screening version	X											
C-SSRS: Since last visit version ^p		X	X	X ^r	X	X	X	X	X	X	X	X
MOAA/S and pulse oximetry ^{f,p}	X			X	X	X	X	X	X	X	X	
BPRS+ ^{B,p}				X	X	X	X	X	X	X	X	
CADSS ^{B,p}				X	X	X	X	X	X	X	X	
CGADR ^h				X	X	X	X	X	X	X	X	
PWC-20 ⁱ											X	
Safety Assessments (Subject-completed)												
Nasal symptom questionnaire ^j				X	X		X		X		X	
BPIC-SS ^c				X				X				X
Assessment of Sense of Smell												
UPSIT ^{c,o}		X						X				X
Smell Threshold Test ^{c,o}		X										X
Efficacy Assessments (Clinician)												
MADRS (7-day recall; performed by independent, remote raters)	X	X ^q	X ^q	X ^{k,q}		X ^{c,q}		X ^{c,q}		X ^{c,q}		X ^{c,q}
CGI-S ^c	X			X	X	X	X	X	X	X	X	X
	Screening/Prospective Observational Phase			Open-label Induction Phase								

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Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9 ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4		
Study day	—	—	—	1 (baseline)	4	8	11	15	18	22	25	28
Clinic visit window (in days)	—	±2	±2	—	±1	±1	±1	±1	±1	±1	±1	±1
Clinic visit (C) or remote MADRS interview only (RM)	C	C	C	C	C	C	C	C	C	C	C	C
Subject-completed Assessments												
PAQ	X	X	X									
PHQ-9 ^c	X			X				X				X
SDS ^c	X			X				X				X
GAD-7 ^c	X			X								X
EQ-5D-5L ^c	X			X				X				X
Cognition Testing												
Practice session for computerized cognitive battery		X										
Computerized cognitive battery and HVLt-R				X								X
Clinical Laboratory Assessments												
TSH, HbA1c	X											
Lipid panel (fasting)		X										
Hematology, chemistry ^c	X			X								X
Urine drug screen ^c	X			X				X			X	
Alcohol breath test	X			X								
Urinalysis ^c	X			X				X				X
Serum pregnancy test	X											
Urine pregnancy test ^c				X				X				X
Biomarkers												
Blood sample collection (protein) ^{c,l}	X			X		X						X
Blood sample collection (RNA) ^{c,l}	X			X		X						X
Blood sample collection (DNA) ^{c,l}	X											X
Ongoing Subject Review												
Concomitant therapy	<i>Ongoing</i>											
Adverse events	<i>Ongoing</i>											
Other												

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Menstrual cycle tracking (start date of last menstrual period prior to study visit)				X									X
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Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore, postdose time points are referenced from this.

- a) An additional, optional period of up to 3 weeks is permitted to taper and discontinue all current medication(s) being used for depression after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. Subjects who do not require a taper and are thus eligible to immediately proceed to the open-label induction phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other (if not occurring the same day, the antidepressant treatment regimen should be continued and discontinued prior to Visit 2.1).
- b) If a subject withdraws before the end of the open-label induction phase (ie, before completing Visit 2.9/Day 28) for reasons other than withdrawal of consent, an Early Withdrawal Visit (refer to Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase) should be conducted, followed by the follow-up phase. If the Early Withdrawal Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- c) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- d) Postdose vital signs will be performed at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.1 for guidance for blood pressure monitoring on intranasal dosing days.
- e) Twelve-lead ECG will be performed predose and at t = 1 hour postdose at Visit 2.1. Thereafter, 12-lead ECG will be performed at t = 1 hour postdose only (ie, no predose ECG is required) at Visits 2.3, 2.5, and 2.8. A time window of ± 15 minutes will be permitted.
- f) The MOAA/S will not be performed at Visit 1.1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t = +1.5 hours postdose (please refer to Section 9.4 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t = 1.5 hours postdose (please refer to Section 9.4 for further guidance on timing of pulse oximetry assessments).
- g) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- h) CGADR will be performed at 1 hour and 1.5 hours postdose; if the response is not "Yes" at 1.5 hour postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
- i) PWC-20 will be performed only if the subject is not continuing into the optimization phase.
- j) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- k) Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be considered as the subject's baseline MADRS for the open-label induction phase. For all other subjects, the baseline MADRS for the open-label induction phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.
- l) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- m) Additional 2-week supply of the oral antidepressant medication only for subjects entering the follow-up phase.
- n) At Week 1 of the screening/prospective observational phase, the start date of the last menstrual period prior to study visit is captured as part of the MGH-FRLHQ: Module I. Thereafter, menstrual cycle tracking is only applicable to women with a menstrual cycle and is documented separately.
- o) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT, Smell Threshold Test, or both (as applicable) to the next scheduled clinic visit.
- p) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: vital signs (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS.

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- q) The MADRS should be administered no more than 2 days prior to the subject's targeted (not actual) clinic visit date (except Visit 2.9, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.

TIME AND EVENTS SCHEDULE (Optimization Phase)

Phase	Optimization Phase ^a												
Visit Number	3.1 ^b	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13 ^c
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit ^d	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
Study Procedures													
Administrative													
ICF (transferred-entry subjects only)	X												
Inclusion/exclusion criteria (transferred-entry subjects only)	X												
Efficacy Assessments (Clinician)													
MADRS (7-day recall): independent remote rater Permitted window: -3 days		X	X	X	X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X
Subject-completed Assessments													
PHQ-9 ^f			X		X		X		X		X		X
SDS ^f					X				X				X
GAD-7 ^f					X		X		X				X
EQ-5D-5L ^f			X		X		X		X		X		X
Study Drug													
Intranasal treatment session		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
Adjustment of intranasal treatment session frequency (if applicable)					X				X				
Dispensing oral antidepressant (open-label)	X				X				X				X ⁿ
Dispense subject diary for oral antidepressant	X												
Oral antidepressant compliance check, including review of subject diary		X	X	X	X		X		X		X		X
Collect/return of subject diary													X

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Spravato (Esketamine)

Drug accountability (intranasal study medication) ^f		X	X	X	X	X	X	X	X	X	X	X	
Drug accountability (oral antidepressant)					X				X				X
Safety Assessments (Site-completed)													
Physical examination, nasal examination, weight					X				X				X
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature ^{f,q}		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	X
Phase													
	Optimization Phase^a												
Visit Number	3.1^b	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13^c
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit^d	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
Study Procedures													
Vital signs (postdose): blood pressure, pulse, and respiratory rate only ^g		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
12-lead ECG ^{h,q}		X			X	X ^e		X ^e	X	X ^e		X ^e	
C-SSRS (since last visit version) ^q		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
MOAA/S and pulse oximetry ^{j,q}		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
BPRS+ and CADSS ^{j,q}		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
CGADR ^k		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^e	
PWC-20 (only for subjects not entering maintenance phase)													X
Safety Assessments (Subject)													
Nasal symptom questionnaire ^l		X	X	X	X	X ^e	X	X ^e	X	X ^e	X	X ^c	
BPIC-SS		X			X				X				X
Assessment of Sense of Smell													
UPSIT ^{f,p}									X				
Smell Threshold Test ^p													X
Cognitive Testing													
Computerized cognitive battery and HVLT-R ^f													X
Clinical Laboratory Tests^f													
Hematology and chemistry					X				X				X
Urinalysis					X				X				X
Urine drug screen					X				X				X

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Spravato (Esketamine)

Alcohol breath test					X				X				X
Urine pregnancy test					X				X				X
Medical Resource Utilization													
HRUQ			X		X		X		X		X		X
Biomarkers													
Blood sample collection (protein) ^{f,m}					X								X
Blood sample collection (RNA) ^{f,m}					X								X
Blood sample collection (DNA) ^{f,m}					X								X
Phase	Optimization Phase ^a												
Visit Number	3.1 ^b	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	3.10	3.11	3.12	3.13 ^c
Week	4	5	6	7	8	9	10	11	12	13	14	15	16
Day	28	32	39	46	53	60	67	74	81	88	95	102	109
Clinic (C) or remote MADRS only (RM) visit ^d	C	C	C	C	C	C or RM	C	C or RM	C	C or RM	C	C or RM	C
Study Procedures													
Ongoing Subject Review and Other													
Menstrual cycle tracking (start date of last menstrual period prior to study visit)					X				X				X
Concomitant therapy	<i>Ongoing</i>												
Adverse events	<i>Ongoing</i>												

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray.

- If a subject withdraws before the end of the optimization phase for reasons other than withdrawal of consent, or is not eligible to continue into the maintenance phase, an Early Withdrawal Visit (Refer to Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and follow up phase) should be conducted. If the Early Withdrawal Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- Results for all assessments performed on Day 28 of the induction phase for direct-entry subjects (Visit 2.9) and transferred-entry subjects (Visit 2.10 of Study ESKETINTRD3001 or ESKETINTRD3002) will serve as the baseline values for the optimization phase and will not be repeated as part of Visit 3.1. The Day 28 visit should coincide with Day 28 (Visit 3.1) for this study. All transferred-entry subjects must meet all of the transferred-entry subject-specific inclusion criteria and none of the exclusion criteria in order to be enrolled.
- Visit 3.13 (Week 16) serves as the last visit for the optimization phase and will also be the first visit (Visit 4.1; Week 16) of the maintenance phase for subjects who qualify to continue. Results for all assessments performed at this visit will also serve as baseline for the maintenance phase and will be completed before randomization to double-blind intranasal study drug.
- Clinic visits (visit window ± 3 days) will be conducted for all intranasal treatment sessions (weekly or every other week); otherwise only a remote MADRS (visit window: -3 days) will be conducted.

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Spravato (Esketamine)

- e) Performed only at clinic visits for intranasal treatment sessions (omitted if remote MADRS only).
- f) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- g) Postdose vital signs will be performed at t = +40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.1 for guidance for blood pressure monitoring on intranasal dosing days.
- h) The 12-lead electrocardiogram will be performed at 1 hour postdose. A time window of ± 15 minutes is permitted.
- i) The MOAA/S will be performed every 15 minutes from predose to t = 1.5 hours postdose (please refer to Section 9.4 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t = 1.5 hours postdose (please refer to Section 9.4 for further guidance on timing of pulse oximetry assessments).
- j) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- k) The CGADR will be performed at 1 hour and 1.5 hours postdose; if the response is not “Yes” at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
- l) The nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- m) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) Additional 2-week supply of the oral antidepressant medication only for subjects entering the follow-up phase.
- o) Only applicable to women with a menstrual cycle.
- p) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT or Smell Threshold Test (as applicable) to the next scheduled clinic visit.
- q) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: vital signs (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS.
- r) Drug accountability for intranasal study medication should be performed weekly during Weeks 5 through 8 (inclusive) and then weekly or every other week from Weeks 9 through 15 (inclusive).

TIME AND EVENTS SCHEDULE (Maintenance Phase)

Phase	Maintenance Phase									
Visit Number ^{a,b}	4.1 ^c	4.2	4.3	4.4	4.5	4.6 to 4.X				
						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2	Every 4	Every 8	Every 12
Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit ^a	C	C/RM	C	C/RM	C	C/RM	C	C	C	C
Study Procedures										
Study Drug ^d										

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Spravato (Esketamine)

Randomization: Primary (subjects in stable remission after treatment with intranasal esketamine and an oral	X ^e									
Randomization: Secondary (subjects with stable response after treatment with intranasal esketamine and an oral	X ^e									
Intranasal treatment session (esketamine or placebo)	X	X ^f	X	X ^f	X	X ^f	X ^f			
Adjustment of intranasal treatment session frequency (if applicable)	X				X			X		
Dispensing oral antidepressant (open-label)	X				X			X		
Dispense subject diary for oral antidepressant	X									
Oral antidepressant compliance check, including review of subject	X		X		X		X			
Drug accountability for intranasal study medication	X	X ^f	X	X ^f	X	X ^f				
Drug accountability for oral antidepressant					X			X		
Efficacy Assessments (Clinician)										
MADRS (7-day recall) ^h – independent, remote rater		X	X	X	X	X				
CGI-S			X		X	X ^f				
Subject-completed Assessments										
PHQ-9 ⁱ			X		X		X			
SDS ⁱ					X			X		
GAD-7 ⁱ					X			X		
EQ-5D-5L ⁱ			X		X		X			
Phase										
Visit Number^{a,b}	Maintenance Phase									
	4.1^c	4.2	4.3	4.4	4.5	4.6 to 4.X				
						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2	Every 4	Every 8	Every 12
Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit^a	C	C/RM	C	C/RM	C	C/RM	C	C	C	C

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Spravato (Esketamine)

Safety Assessments (Site-completed)										
Physical examination, nasal examination, and weight					X			X		
Vital signs (predose): blood pressure, pulse, respiratory rate, and temperature ^s		X ^f	X	X ^f	X	X ^f				
Vital signs (postdose): blood pressure, pulse, and respiratory rate only ^j	X	X ^f	X	X ^f	X	X ^f				
12-lead ECG ^{k,s}	X		X					X		
C-SSRS (since last visit version) ^s		X ^f	X	X ^f	X	X ^f				
MOAA/S and pulse oximetry ^{l,s}	X	X ^f	X	X ^f	X	X ^f				
BPRS+ and CADSS ^{m,s}	X	X ^f	X	X ^f	X	X ^f				
CGADR ⁿ	X	X ^f	X	X ^f	X	X ^f				
PWC-20 (performed at last clinic visit of this phase)										
Safety Assessments (Subject)										
Nasal symptom questionnaire ^o	X		X		X			X		
BPIC-SS					X			X		
Clinical Laboratory Testsⁱ										
Hematology and chemistry					X			X		
Urinalysis (to be performed at same visit as BPIC-SS)					X			X		
Urine drug screen					X			X		
Alcohol breath test					X			X		
Urine pregnancy test					X			X		
Assessment of Sense of Smell										
UPSIT ^f					X				X	
Smell Threshold Test ^f										X
Cognition Testing^e										
Computerized cognitive battery and HVLt-R										X
Phase	Maintenance Phase									
Visit Number ^{a,b}	4.1 ^c	4.2	4.3	4.4	4.5	4.6 to 4.X				
						Study Procedure Frequency From Week 20 Through End of Phase				
Week	16	17	18	19	20	Every week	Every 2	Every 4	Every 8	Every 12

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Spravato (Esketamine)

Day	109	116	123	130	137	Every 7 days	Every 14 days	Every 28 days	Every 56 days	Every 84 days
Clinic (C) or Remote MADRS only (RM) visit ^a	C	C/RM	C	C/RM	C	C/RM	C	C	C	C
Medical Resource Utilization										
HRUQ			X		X		X			
Biomarkers										
Blood sample collection (protein) ^{i,p}					X					
Blood sample collection (RNA) ^{i,p}					X					
Blood sample collection (DNA) ^{i,p}					X					
Ongoing Subject Review and Other										
Menstrual cycle tracking (start date of last menstrual period prior to study visit)					X			X		
Concomitant therapy	<i>Ongoing</i>									
Adverse events	<i>Ongoing</i>									

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray.

- Visits (clinic or remote contacts) will be conducted weekly during the maintenance phase. Clinic visits (visit window: ± 3 days) will be conducted for all intranasal treatment sessions (weekly or every other week); otherwise only a remote visit for MADRS (visit window: -3 days) will be conducted. Due to the variable duration of this phase, following Visit 4.5 visit numbers will continue sequentially (eg, 4.6, 4.7, etc) until the subject completes the phase. The frequency of study procedures from Week 20 to the end of the phase is provided within the respective column (ie, every week, 2 weeks, 4 weeks, 8 weeks, and 12 weeks).
- If a subject withdraws before the end of the maintenance phase for reasons other than withdrawal of consent, an Early Withdrawal Visit should be conducted. A subject meeting relapse criteria is not considered to be an early withdrawal subject; for relapse subjects, and those subjects remaining relapse-free at the time of study termination, an End of Maintenance Phase Visit should be conducted. If the End of Maintenance Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. Refer to the Time and Events Schedule: Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase.
- Visit 3.13 (Week 16) serves as the last visit for the optimization phase and will also be the first visit (Visit 4.1; Week 16) of the maintenance phase for subjects who qualify to continue. Results for all assessments performed at this Visit 3.13 of the optimization phase will also serve as baseline for the maintenance phase and will be completed before randomization to double-blind intranasal study drug. Duplicate assessments are not required.
- Transferred-entry subjects who achieve stable remission or stable response in the optimization phase after treatment with an oral antidepressant plus intranasal placebo will continue to receive the same treatment in order to maintain the blinding for the ongoing short-term studies.
- Performed prior to intranasal dose administration.
- Performed only at clinic visits for intranasal treatment sessions (omit if remote contact visit).

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- g) At the last clinic visit of this phase, an additional 2-week supply of the oral antidepressant medication is provided only for subjects entering the follow-up phase.
- h) The last MADRS assessment performed prior to the first intranasal treatment session of the maintenance phase will be the baseline value for this phase.
- i) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- j) Postdose vital signs will be performed at t = +40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.1 for guidance for blood pressure monitoring on intranasal dosing days.
- k) At clinic visits for intranasal treatment sessions, the 12-lead electrocardiogram will be performed at 1 hour postdose. A time window of ± 15 minutes is permitted.
- l) The MOAA/S will be performed every 15 minutes from predose to t = 1.5 hours postdose (please refer to Section 9.4 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.4 for further guidance on timing of pulse oximetry assessments).
- m) The BPRS+ and CADSS will be performed predose and at 40 minutes and 1.5 hours postdose.
- n) The CGADR will be performed at 1 hour and 1.5 hours postdose; if the response is not “Yes” at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated.
- o) At clinic visits for intranasal treatment sessions, the nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- p) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- q) Only applicable to women with a menstrual cycle.
- r) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT or Smell Threshold Test (as applicable) to the next scheduled clinic visit.
- s) If a subject has started a scheduled clinic visit in which an intranasal treatment session is planned, but then a predose observation (eg, blood pressure results) prompts the site staff to postpone the intranasal treatment session within the visit window, then all time points (including predose) of the footnoted assessments must be repeated on the actual intranasal treatment session day, as follows: vital signs (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS.

TIME AND EVENTS SCHEDULE (Early Withdrawal/End of Maintenance Phase Visit and Follow-up Phase)

Phase	Early Withdrawal//End of Maintenance Phase ^a	Follow-up Phase ^b	
Visit Number	EW/EMP	5.1	5.2
Weeks After Last Clinic Visit	-	1	2
Clinic (C) or Remote Assessments Only (RA) Visit	C	RA ^f	C
Study Procedures			
Study Drug			
Drug accountability (oral antidepressant study medication)	X		X
Dispensing of additional supply of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)	X		
Oral antidepressant compliance check	X		X

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Spravato (Esketamine)

Collect/return of subject diary	X		
Safety Assessments (Site-Completed)			
Physical examination	X		X
Nasal examination	X		X
Vital signs: blood pressure, pulse, respiratory rate, temperature	X		X
12-lead electrocardiogram	X		X
C-SSRS: Since last visit version	X		X
PWC-20	X	X	X
Safety Assessments (Subject-Completed) ^c			
BPIC-SS	X		X
Efficacy Assessments (Clinician-Completed)			
MADRS (independent, remote blinded rater)	X	X	X
CGI-S	X		X
Efficacy Assessments (Subject-Completed) ^c			
PHQ-9	X		X
SDS	X		X
GAD-7	X		X
EQ-5D-5L	X		X
Assessment of Sense of Smell			
UPSIT ^e	X		
Smell Threshold Test ^e	X		
Cognition testing			
Computerized cognitive battery and HVLt-R	X		X
Phase	Early Withdrawal//End of Maintenance Phase ^a	Follow-up Phase ^b	
Visit Number	EW/EMP	5.1	5.2
Weeks After Last Clinic Visit	-	1	2
Clinic (C) or Remote Assessments Only (RA) Visit	C	RA^f	C
Medical Resource Utilization			
HRUQ	X		X
Clinical Laboratory Assessments			
Hematology and chemistry	X		X
Urinalysis	X		X

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Serum pregnancy test	X		X
Biomarkers			
Blood sample collection (protein)	X		X
Blood sample collection (RNA)	X		X
Blood sample collection (DNA)	X		
Other Assessments			
Menstrual cycle tracking (start date of last menstrual period prior to study visit) ^d			X
Concomitant therapy	X		<i>Ongoing</i>
Adverse events	X		<i>Ongoing</i>

- a) If a subject withdraws before the end of the induction, optimization, or maintenance phase for reasons other than withdrawal of consent, or has completed the induction or optimization phase but is not eligible to continue to the next treatment phase, an Early Withdrawal Visit should be conducted followed by the follow-up phase. If the Early Withdrawal Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required. A subject meeting relapse criteria is not considered to be an early withdrawal subject; for these subjects, and subjects currently in the maintenance phase at the time the study is terminated, will conduct an End of Maintenance Phase Visit. For those subjects who relapse in the Maintenance phase, if clinically indicated based on investigator's judgment, after completing the end of maintenance visit, the subject may proceed to the open-label safety extension study, 54135419TRD3008, without completing the follow up phase. Similarly, when the study is stopped, subjects in the Induction phase who are responders, after completing the early withdrawal visit, if clinically indicated based on the investigator's judgment, may proceed to the 54135419TRD3008 study, without completing the follow up phase.
- b) Visit window will be ± 3 days.
- c) Subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- d) Only applicable to women with a menstrual cycle.
- e) If the subject has significant nasal congestion on the day of a scheduled assessment of sense of smell, then the site should consider postponing the UPSIT and Smell Threshold Test to the next scheduled clinic visit.
- f) At the "Remote Assessment" visit, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

13.1.4. Study 3005

TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Double-blind Induction Phase)

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4			
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW

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Spravato (Esketamine)

Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Screening/Administrative													
Informed consent (ICF)	X												
Medical history, psychiatric history, demographics, and employment status	X												
MINI	X												
MMSE	X												
MGH-ATRQ	X												
Site Independent Qualification Assessment	X												
Height	X												
Inclusion/exclusion criteria	X			X									
Prestudy therapy	X												
Preplanned surgery/procedures	X												
STOP Bang questionnaire (including assessment of BMI and neck circumference)	X												
IDS-C ₃₀	X												
Study Drug													
Randomization				X									
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X								X ⁿ	X
Practice session for use of intranasal device ^d				X									
Intranasal esketamine or placebo ^o				X	X	X	X	X	X	X	X		
Drug accountability (intranasal study medication)				X	X	X	X	X	X	X	X		X
Phase													
	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
Visit number	1.1	1.2	1.3^a	2.1^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW^b
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4			
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C

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Spravato (Esketamine)

Drug accountability (oral antidepressant study medication)				X								X	X
Dispense subject diary for oral antidepressant				X									
Review subject diary and update (if applicable)					X	X	X	X	X	X	X	X	X
Oral antidepressant compliance check						X		X		X		X	X
Return of subject diary if not entering follow up phase												X	

Safety Assessments (Clinician)

Physical examination	X			X								X	X
Nasal examination ^d	X			X								X	X
Vital signs: blood pressure, pulse, respiratory rate, temperature ^{d,o}	X			X	X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate ^{e,o}				X	X	X	X	X	X	X	X		
Weight	X			X								X	X
12-lead ECG ^{f,o}	X			X	X	X	X	X	X	X	X		X
C-SSRS: Baseline/Screening version	X												
C-SSRS: Since last visit version ^{d,o}		X	X	y ^r	X	X	X	X	X	X	X	X	X
MOAA/S ^{g,o}				X	X	X	X	X	X	X	X		
Pulse oximetry ^{g,o}	X			X	X	X	X	X	X	X	X		
BPRS ^{h,o}				X	X	X	X	X	X	X	X		
CADSS ^{h,o}				X	X	X	X	X	X	X	X		
CGADR ⁱ				X	X	X	X	X	X	X	X		
PWC-20												v ^j	X

Safety Assessments (Subject-completed)

Nasal symptom questionnaire ^k				X	X		X	X		X			
BPIC-SS ^d				X			X					X	X

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number													
Week	Week 1	End of Week 2	End of Week 4	1		2		3		4			
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-

Clinical Review

Jean Kim MD, MA; Qi Chen MD, MPH

NDA 211243

Spravato (Esketamine)

Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Assessment of Sense of Smell													
UPSIT ^{d,p}		X										X	X
Efficacy Assessments (Clinician)													
MADRS (performed by independent, remote raters)	X	X ^q	X ^q	X ^{c,q}		X ^{d,q}		X ^{d,q}		X ^{d,q}		X ^q	X
CGI-S ^d	X			X	X	X	X	X	X	X	X	X	X
Efficacy Assessments (Subject-completed)													
PAQ	X	X	X										
EQ-5D-5L ^d	X			X				X				X	X
Cognition Testing⁵													
Practice sessions for computerized test battery		X											
Computerized test battery and HVLTR				X ^d								X	X
Clinical Laboratory Assessments													
TSH, HbA1c	X												
Lipid panel (fasting)		X											
Hematology, chemistry ^d	X			X								X	X
Urine drug screen ^d	X			X				X			X		
Alcohol breath test	X			X									
Urinalysis ^d	X			X				X				X	X
Pharmacokinetics													
Blood collection ^l										X			
Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations													
Blood sample collection (protein) ^{m,d}	X			X		X						X	X
Blood sample collection (DNA) ^{m,d}	X											X	X
Blood sample collection (RNA) ^{m,d}	X			X		X						X	X

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Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number	Week 1	End of Week 2	End of Week 4	1		2		3		4			
Week				1 (baseline)	4	8	11	15	18	22	25	28	EW
Study day	-	-	-	(baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Ongoing Subject Review													
Concomitant Therapy	Ongoing												
Adverse Events	Ongoing												

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore postdose time points are referenced from this.

- An additional, optional period of up to 3 weeks is permitted to taper and discontinue current antidepressant treatment(s) after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind induction phase can have Visits 1.3 and 2.1 occur on the same day or within 1 week of each other (if not occurring on the same day, the antidepressant treatment regimen should be continued after visit 1.3. and then discontinued prior to Visit 2.1).
- If a subject withdraws before the end of the double-blind induction phase (ie, before completing Visit 2.9/Day 28) for reasons other than withdrawal of consent, and an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be the subject's baseline MADRS for the double-blind induction phase. For all other subjects, the baseline MADRS for the double-blind induction phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.
- Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- Postdose vital signs will be measured at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.2.1 for guidance on blood pressure monitoring on dosing days.
- Twelve-lead ECG will be performed predose and at t=1 hour postdose at Visit 2.1. Twelve-lead ECG will be performed at t=1 hour postdose (no predose) at Visits 2.2 through 2.8. A time window of ±15 minutes is permitted.
- The MOAA/S will not be performed at Visit 1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose (please refer to Section 9.6 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.6 for further guidance regarding on timing of pulse oximetry assessments).
- The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.

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- i) CGADR to be performed at 1 hour and 1.5 hours postdose; if the response is not “Yes” at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
- j) PWC-20 to be performed predose on all subjects.
- k) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- l) PK blood collection will be performed at t=40 minutes and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray).
- m) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) Only subjects entering the follow-up phase will be provided with a 2-week supply of oral antidepressant.
- o) If intranasal dosing is postponed (but occurs within visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual intranasal dosing day.
- p) If on the day of the scheduled smell test assessments the subject has significant nasal congestion, the site should consider postponing to the next scheduled visit.
- q) The MADRS should be administered no more than 2 days prior to the subject’s targeted (not actual) clinic visit date (except Visit 2.9, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.
- s) Testing can precede Visit 2.1.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

Visit Number	Follow-up Phase	
	3.1	3.2
Weeks after last intranasal dose	1	2
Visit window for clinic visit or remote assessments only (days)	±3	±3
Clinical visit (C) or remote assessments only (RA)	RA ^e	C
Oral antidepressant compliance^a		
Oral antidepressant compliance check		X
Return of subject diary		X
Safety assessments (Clinician-completed)		
Physical examination		X
Nasal examination		X
Vital signs: Blood pressure, pulse, respiratory rate, temperature		X
12-lead ECG		X
C-SSRS: Since last visit version		X

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PWC-20	X ^b	X
Safety assessments (Subject-completed)		
BPIC-SS		X
Efficacy assessments (Clinician-completed)		
MADRS (performed by independent, remote raters) ^c	X	X
CGI-S		X
Efficacy assessments (Subject-completed)		
EQ-5D-5L		X
Cognition testing		
Computerized test battery and HVLIT-R		X
Clinical laboratory assessments		
Hematology, chemistry		X
Urinalysis		X
Biomarker and Expression (RNA) evaluations		
Blood sample collection (protein) ^d		X
Blood sample collection (RNA) ^d		X
Study Drug		
Drug Accountability		X
	Follow-up Phase	
Visit Number	3.1	3.2
Weeks after last intranasal dose	1	2
Visit window for clinic visit or remote assessments only (days)	±3	±3
Clinical visit (C) or remote assessments only (RA)	RA ^e	C
Ongoing subject review		
Concomitant therapy	Ongoing	
Adverse events	Ongoing	

Note: No intranasal study medication will be administered during this phase.

- a) In order to better assess potential withdrawal symptoms from intranasal study medication, the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase, unless determined to be not clinically appropriate.

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- b) Performed by telephone by qualified site staff.
- c) MADRS will be performed by an independent remote rater. At Visit 3.1 (Week-1 of follow-up) the subject will have the MADRS assessment with a remote rater visit, in addition to a follow-up call from the site.
- d) It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- e) For the Remote Assessment (RA) Visit 3.1, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

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13.2. **References**

See footnotes.

13.3. **Financial Disclosures**

See next page.

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Covered Clinical Study (Name and/or Number): 3001, 3002, 3003, 3005, 2003

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)																		
Total number of investigators identified: <u>see table</u>																				
<table border="1"> <thead> <tr> <th>Study No.</th> <th>Number of Principal Investigators</th> <th>Number of Subinvestigators</th> </tr> </thead> <tbody> <tr> <td>ESKETINTRD3001</td> <td>100</td> <td>322</td> </tr> <tr> <td>ESKETINTRD3002</td> <td>46</td> <td>139</td> </tr> <tr> <td>ESKETINTRD3003</td> <td>292</td> <td>710</td> </tr> <tr> <td>ESKETINTRD3005</td> <td>56</td> <td>205</td> </tr> <tr> <td>ESKETINTRD2003</td> <td>26</td> <td>145</td> </tr> </tbody> </table>			Study No.	Number of Principal Investigators	Number of Subinvestigators	ESKETINTRD3001	100	322	ESKETINTRD3002	46	139	ESKETINTRD3003	292	710	ESKETINTRD3005	56	205	ESKETINTRD2003	26	145
Study No.	Number of Principal Investigators	Number of Subinvestigators																		
ESKETINTRD3001	100	322																		
ESKETINTRD3002	46	139																		
ESKETINTRD3003	292	710																		
ESKETINTRD3005	56	205																		
ESKETINTRD2003	26	145																		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 2 total (1 in 3001 and 1 in 3002)																				
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>																				
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>3</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>																				
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)																		
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)																		
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>see table</u>																				

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<u>above</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

On face, the Applicant has adequately provided financial disclosure information for this development program.

There were 2 primary investigators who provided financial disclosures:

- (b) (6) who participated in Study 3001 ((b) (6) enrolled), 3002 (b) (6) enrolled) and 3003; he reported being a (b) (6) receiving over \$25,000.
- (b) (6) who participated in Study 3001 and 3003 (b) (6) enrolled); he reported being a (b) (6) receiving over \$25,000.

There was one subinvestigator who participated in Study 2003, (b) (6), who received over \$25,000 as a Janssen consultant (not for esketamine).

The forms noted that the Applicant did due diligence to monitor for any potential conflicts of interest and did not find any with the study results involved. Also, the number of subjects involved at these investigators' sites was very small and unlikely to affect the overall study results in any substantially biased manner.

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APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEAN S KIM
03/04/2019 07:16:01 PM

QI N CHEN
03/04/2019 07:48:14 PM

MARC B STONE
03/04/2019 08:22:33 PM

TIFFANY R FARCHIONE
03/04/2019 08:23:46 PM