CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Joint Supervisory Review for Regulatory Action

Date	(electronic stamp)
From	Bernard Fischer, MD (Cross-Discipline Team Lead) Tiffany R Farchione, MD (Acting Director) *Division of Psychiatry Products* *Office of Drug Evaluation-I* *Office of New Drugs* *Center for Drug Evaluation and Research*
Subject	Joint Supervisory Review
NDA #	NDA 211243
Applicant	Janssen Pharmaceuticals
Date of Submission	September 4, 2018
PDUFA Goal Date	March 4, 2019
Proprietary Name	Spravato
Established or Proper Name	Esketamine
Dosage Form(s)	Nasal spray
Applicant Proposed Indication(s)/Population(s)	Treatment of treatment-resistant depression
Action:	*Approval*
Approved Indication(s)/Population(s)	*Treatment of treatment-resistant depression in adults*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jean Kim
Statistical Review	Andrew Potter; Peiling Yang (TL)
Pharmacology Toxicology Review	Shiny Mathew; Ikram Elayan (TL)
OPQ Review	ATL - David Claffey Drug Substance – Rohit Tiwari Drug Product – Stephanie Emory Process & Facilities – Christina Capacci-Dianiel Microbiology – Johnathan Burgos Environmental – James Laurenson CDRH – Kathleen Fitzgerald RBPM – Teshara Bouie
Clinical Pharmacology Review	OCP: Xiaolei Pan; Luning (Ada) Zhuang (TL) Pharmacometrics: Kevin Krudys; Atul Bhattaram
OPDP	Domenic D'Alessandro; Aline Moukhtara (TL)
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ATL=Application Technical Lead
CDRH=Center for Devices and Radiological Health
CSS=Controlled Substance Staff
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatrics and Maternal Health
DRISK=Division of Risk Management
OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
PLT=Patient Labeling Team

1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

Treatment-resistant depression is a severe form of major depressive disorder for which there are limited effective treatment options. Even when treatment is effective, it can be weeks before symptoms improve. This new drug application is for the drug-device combination of esketamine for intranasal administration with a nasal spray device indicated for the treatment of treatment-resistant depression (TRD). The primary evidence in support of approval comes from two positive adequate and well-controlled studies: Study 3002, a randomized, double-blind, parallel-group, controlled, short-term (4-week), flexible-dose acute treatment study; and Study 3003, a randomized, double-blind, controlled, withdrawal study. The statutory requirement for substantial evidence for IN esketamine 56 mg and 84 mg in conjunction with an oral antidepressant for the treatment of TRD is met with the positive results from these two studies. Substantial evidence was not provided for the 28-mg dose or for patients ≥ 65 years of age. We also considered the additional supportive data from Studies 2003, 3001, and SUI2001. The overall pattern of results further supports the conclusion that substantial evidence of effectiveness has been provided. The data to support this approval derives from studies in which esketamine was administered in conjunction with a newly initiated oral antidepressant. The effectiveness of esketamine as monotherapy for TRD is unknown; we have obtained a post-marketing commitment from the Applicant to evaluate this.

This development program received Breakthrough Therapy Designation based on preliminary evidence that esketamine could provide an advantage over existing therapy for TRD. Based on literature and anecdotal reports of rapid antidepressant action with off-label ketamine use, as well as phase 2 data from this program, there was an expectation that esketamine would provide rapid relief of depressive symptoms. Indeed, the Applicant designed Study 3002 to test this hypothesis by including onset of clinical response (>50% reduction in Montgomery Åsberg Depression Rating Scale (MADRS) score) as the first pre-specified secondary endpoint. Although response at Day 2 was not demonstrated, the drug-placebo difference in MADRS change from baseline is evident at Day 2 and remains fairly consistent through Day 28. Patients in both treatment groups continue to improve, but there is no further separation between groups.

As esketamine is the first drug in a new class of antidepressants, it is important to put its treatment effect into perspective. The ability to detect even a nominally significant treatment difference by Day 2 sets this drug apart from other antidepressants. Also of note, the treatment effects observed in the esketamine clinical studies were of similar magnitude to the effects for drugs approved to treat MDD, either as monotherapy or adjunctive treatment, based on studies in which the MADRS was the primary endpoint. The observed treatment differences in this study were in that range; however, for oral antidepressants, clinical studies to support approval are typically at least 6 weeks. The esketamine studies were only 4 weeks, demonstrating similar treatment effects in a shorter period of time. Taken together, the data suggest that an effect should be noticeable to patients early in the course of treatment. However, one should not expect early clinical response. Given how impaired patients were at baseline, even a nearly 10-point change on the MADRS at Day 2 still leaves patients with moderate to severe symptoms. The label will include advice to evaluate the patient for evidence of benefit after 4 weeks to determine need for continued treatment. This is important given that an

effect should be observable by that time; if not, continued treatment is likely not justified.

The safety database is adequate, meeting ICH E1 criteria for exposure. Adverse events were appropriately monitored, with specific assessments for adverse events of special interest. The adverse events of greatest concern in the clinical development program were sedation, dissociation, and increases in blood pressure. These events are monitorable, and most occurred within the first 2 hours following drug administration. This application will be approved with a Risk Evaluation and Mitigation Strategy (REMS). Among the key elements of the REMS, esketamine administration will occur only in certain healthcare settings where the patient can be monitored for 2 hours after administration, the drug will not be dispensed directly to patients, and patients will be enrolled in a registry to better characterize the risks associated with esketamine administration.

The label will also include antidepressant class language in the Boxed Warning for suicidal thoughts and behaviors. Additional risks identified in the clinical studies have been appropriately addressed in labeling. There will be two post-marketing requirements: 1) a long-term (3-year) open-label safety study and 2) an evaluation esketamine's effect on thyroid function using banked samples obtained during the double-blind clinical studies. The open-label study is ongoing and includes assessments for cognitive function and urinary tract adverse events.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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.
Current Treatment Options	• The only FDA-approved oral medication for TRD is a fixed-dose combination of fluoxetine and olanzapine. Devices used to treat TRD include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulator (VNS) implantation.	Available treatments have significant adverse reactions: weight gain and extrapyramidal symptoms (combination olanzapine and fluoxetine); risks of general anesthesia and memory loss (ECT); surgical intervention and infection (VNS). TMS has fewer risks relative to these other interventions, but may be less effective. Additional treatment options are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two positive adequate and well-controlled studies: Study 3002, a randomized, double-blind, parallel-group, placebo-controlled, short-term (4-week), flexible-dose treatment study; and Study 3003, a double-blind, placebo-controlled, randomized withdrawal study. • Supportive evidence from Studies 2003 and 3001 in TRD, and SUI2001 in a related indication. • Exploratory analyses suggest onset of effect as early as Day 2 (relative to placebo), but there is no statistical difference in response rate between esketamine and placebo at Day 2. • Observed treatment effect in phase 3 studies is similar to that observed in other approved antidepressants. • Effectiveness in geriatric population not demonstrated in dedicated study, but no basis to believe there is a specific age limit for efficacy.	The statutory requirement for substantial evidence of effectiveness for IN esketamine 56 mg and 84 mg in conjunction with an oral antidepressant for the treatment of TRD is met with the positive results from these two studies. Substantial evidence was not provided for the 28-mg dose or for patients ≥ 65 years of age.
Risk and Risk Management	• Post-Dose Safety (Acute): The adverse events of greatest concern in the clinical development program were sedation, dissociation, and increases in blood pressure. The time course of these events closely follows the pharmacokinetic profile of esketamine, and their incidence was dose-related. Nausea/vomiting were common and dose-related. Although sedation and vomiting were common effects, no aspiration cases were reported in the studies. • Subacute/Chronic-Use Safety: The major effects of concern, based on post-marketing reports or nonclinical findings with ketamine, were hepatotoxicity, bladder toxicity, cognitive impairment, and unknown potential for long-term neurotoxicity. 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. No cases of acute hepatotoxicity or clinically meaningful liver function test trends were noted. Some short-term cognitive function changes were	• This application will be approved with a Risk Evaluation Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). The REMS goals are intended to mitigate the risks of sedation, dissociation, and abuse and misuse. • Because of the risks of sedation and dissociation, patients will require at least 2 hours of observation in clinically supervised settings • 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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	noted on Cogstate 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. • Deaths and Serious Adverse Events (SAEs): There were 6 deaths (all in esketamine-treated patients) and 16 SAEs (12 esketamine, 4 placebo) in the development program. Careful review of the cases did not reveal obvious causal links to esketamine and did include details that seemed to make causation unlikely. However, there was an imbalance, and the only events occurring in more than one patient were depression and suicidal ideation. Formal assessment with Columbia Suicidal Severity Rating Scale did not reveal difference between groups (odds ratio suggests decreased risk, but not significant).	supervised, registered settings. • A post-marketing requirement for a long-term safety study will allow better characterization of long-term risks. • We will include the suicidal thoughts and behaviors antidepressant class language in the Boxed Warning and Warnings & Precautions.

1. Background

The new drug application (NDA) is for the drug-device combination of esketamine for intranasal administration with a nasal spray device indicated for the treatment of treatment-resistant depression (TRD). For regulatory purposes, FDA considers patients to have TRD if they have Major Depressive Disorder (MDD) and, despite at least two trials of antidepressant treatment given at adequate doses for an adequate duration in the current episode, they have not responded to treatment.

MDD is a serious and life-threatening condition, and the leading cause of disability worldwide.[1] More than 16 million adults in the United States may experience an episode of depression in a given year,[2] and about 30 to 40% will fail to respond to first-line treatments.[3] Even when effective, onset to response with available treatments often takes several weeks. Patients have expressed concerns related to the inadequacy of available treatments, incomplete treatment response, the need for multiple drug trials, and the side effect burden of available MDD treatments.[4]

To date, only one medication has been approved for the treatment of TRD—a fixed-dose combination of fluoxetine (a selective serotonin reuptake inhibitor) and olanzapine (an atypical antipsychotic). This product, like other available antidepressants, can take several weeks to achieve a clinically meaningful treatment effect. It also carries the risks of extrapyramidal symptoms, weight gain, metabolic syndrome, and other adverse reactions linked to olanzapine, an atypical antipsychotic. Several device-related treatments (i.e., electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS)) are also approved for TRD. Treatment with ECT involves inducing a seizure under general anesthesia, and it can cause memory loss. TMS requires daily office visits to administer treatment. VNS requires surgical implantation of a stimulator device.

Esketamine is the S-enantiomer of ketamine, an anesthetic agent approved in 1970 under the brand name Ketalar (NDA 016812). The Applicant is not relying on the Agency's previous findings of safety and effectiveness for ketamine; rather, all data reviewed under this NDA are currently owned by the applicant, regardless of who sponsored the original studies. Thus, this application is considered a 505(b)(1) NDA; 505(u) also applies because the S-enantiomer is being approved for new indications in a different therapeutic class from racemic ketamine. Esketamine is approved as a general anesthetic in 17 countries, but is not approved as an antidepressant anywhere in the world. The combination product consists of a single-use nasal spray device that administers two sprays per device for a total of 28 mg of esketamine. To

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[1] https://www.who.int/news-room/fact-sheets/detail/depression. Accessed March 3, 2019.
[2] https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed March 3, 2019.
[3] 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.
[4] https://secure2.convio net/dabsa/site/SPageServer/;jsessionid=00000000.app268b?NONCE_TOKEN=68B6AC0BF8CA6ED6EA73E7D0B6B258A9&NONCE_TOKEN=8E5900F85A7E46F4D8095EE821724DA1&pagename=FDA_videos. Accessed March 3, 2019.

achieve the recommended doses of esketamine, two (56 mg) or three (84 mg) devices are required.

The esketamine development program received a Breakthrough Therapy Designation (BTD) in November 2013. The decision was based on preliminary evidence of efficacy from a phase 2a study exploring the effect of intravenous (IV) esketamine in patients with inadequate response to antidepressants, suggesting the potential for a rapid (within 24 hours) onset of effect, which was viewed as a potential substantial improvement over existing therapy for TRD, a serious or life-threatening condition.

The Division of Psychiatry Products has typically made a distinction between acute and maintenance treatment of MDD. We have generally relied on two short-term (6- to 8- week) acute treatment studies to provide substantial evidence of effectiveness for approval for the treatment of MDD. Although efficacy for maintenance treatment of MDD is important to establish, the Division has not required maintenance studies prior to approval because they are long in duration, and conducting such studies prior to approval would significantly delay the availability of new treatment options. Given the importance of maintenance treatment in depression, the Division has obtained post-marketing commitments (PMCs) to study maintenance treatment of MDD in double-blind, placebo-controlled, randomized withdrawal studies, and almost all antidepressants approved based on data from acute efficacy studies have subsequently been shown to be effective for maintenance treatment.

As an NMDA receptor antagonist, esketamine is unique among antidepressants. Its novel mechanism of action made it impossible to draw from past antidepressant experience to predict whether esketamine would demonstrate durability of effect in maintenance treatment. Thus, rather than allowing the Applicant to conduct a maintenance study as a post-marketing commitment, we reached agreement early in development that a maintenance study would be required prior to approval.

2. Product Quality

The Office of Pharmaceutical Quality review team recommends approval.

The product under review is a 28-mg strength drug/device combination product. Each device delivers two sprays; although there is some spray-to-spray variability that prevents us from concluding that (b) (4) the total esketamine dose is reliably 28 mg per device. Successful administration of each spray is indicated by one of two dots in the indicator window changing color from green to white. The device does not require priming before use (i.e., an attempt to prime will result in loss of approximately half the contents of the device). In order to provide a dose of 56 or 84 mg, two or three devices, respectively, are required.

The labeled strength is based on esketamine (b) (4). Each device contains a solution of (b) (4) esketamine hydrochloride (equivalent to 32 (4) mg of esketamine (b) (4) (b) (4) Excipients include EDTA (b) (4) citric acid monohydrate (b) (4). Sodium hydroxide (b) (4). The solution is contained within a Type (b) (4) glass vial with a rubber stopper within the nasal spray device. Each device is packaged in a blister pack.

All excipients are compendial, and the primary container and device are constructed of commonly used materials for nasal spray products. The proposed commercial formulation was used in all phase 2 and phase 3 studies. Primary stability data supported the proposed expiry of 24 months at USP controlled room temperature. The drug substance specification, analytical methods and their validation for esketamine HCl were found to be acceptable. The drug product, vials, and device were appropriately evaluated with no significant risks identified for elemental impurities and extractables/leachables. Extractable and leachable studies were performed on the primary container closure (vial, stopper) and the device components that come in contact with the solution after actuation (b) (4) The results demonstrate that leachables do not present a significant safety risk.

The drug product manufacturing facilities have experience with several similar marketed combination products and were deemed acceptable based on recent inspection history.

The claim for an exclusion from an environmental assessment was found acceptable.

3. Nonclinical Pharmacology/Toxicology

The nonclinical review team recommends approval.

The Applicant conducted a comprehensive non-clinical safety program including: safety pharmacology studies, chronic general toxicity studies in rats and dogs, reproductive toxicity studies (including embryofetal studies in rats and rabbits that were conducted using racemic ketamine, acquired from Javelin), genotoxicity studies, acute/short-term neurotoxicity studies, and carcinogenicity studies (2-year study in rats and 6-month study in transgenic mice). Given the known effects of racemic ketamine, the potential for esketamine to cause central nervous system (CNS) toxicity was carefully evaluated.

Esketamine is a noncompetitive glutamate N-methyl-D-Aspartate (NMDA) receptor antagonist. It has a higher potency at this receptor than the racemate, the R-enantiomer, or any of its metabolites. Noresketamine (M10), the major metabolite, has a 6-fold lower affinity to the NMDA receptor than esketamine. In vitro studies demonstrated that the parent and/or noresketamine have a weak affinity (<50%) for the serotonin (5HT) transporter, opioid (mu and kappa), γ-amino butyric acid (GABA), and nicotinic acetylcholine receptors (nAChRs).

Esketamine has low oral bioavailability in both humans and nonclinical species, but is quickly absorbed from the nasal cavity with a T_{max} of 5 to 30 minutes in all adult nonclinical species. It is highly lipophilic and distributes quickly to well-perfused tissues, including the brain, in mice and rats. Based on human mass balance studies using radiolabeled oral and intravenous (IV) esketamine, the major human metabolite (i.e., >10% total circulating) is noresketamine, which was quantified in all nonclinical species. There are no unique human metabolites. In rats and humans, the major excretion pathway is through the kidney.

The Agency did not request a dedicated neurotoxicity study after in utero drug administration; neuronal apoptosis is predicted to occur with esketamine exposure during pregnancy and the product label will include a warning for embryofetal toxicity as well as language in sections 8.1 (Pregnancy) and 8.2 (Lactation). Section 8.3 (Females and Males of Reproductive Potential) will

include language under the “Contraception” subheading advising pregnancy planning and prevention for females of reproductive potential.

NMDA receptor antagonists are known to cause neuronal apoptosis in the developing brain in young animals, and neuronal vacuolation and necrosis in the sexually mature adult brain (commonly referred to as Olney lesions). Several dedicated neurotoxicity studies were conducted in rats to evaluate the potential for esketamine to cause neuronal vacuolation and necrosis. The ability to detect these lesions is time-sensitive; therefore, only Good Laboratory Practice (GLP) studies with 4 to 6 hour and 3-day sacrifice time points were considered adequate to examine neuronal vacuolation and necrosis, respectively. Following single-dose administration of subcutaneous ketamine HCL to rats, neuronal vacuoles but not necrosis was observed at the highest dose. Estimating 50% of ketamine exposure to be from esketamine, the NOAEL for neuronal vacuolation is 1.6-times and 4.5 times and the NOAEL for necrosis was 10-times and 16-times, respectively, for AUC and C_{max} exposures at the maximum recommended human dose (MRHD). In a single-dose neurotoxicity study conducted with intranasal (IN) esketamine up to the maximum feasible dose, exposures up to 17-fold and 23-fold the AUC and C_{max} at the MRHD, respectively, did not produce neuronal necrosis.

The primary nonclinical reviewer (Shiny Mathew, PhD) expressed concerns about the long-term neurotoxicity evaluation conducted by the Applicant. She noted that plasma levels at the highest dose in animal studies were at or lower than the human plasma levels and did not provide multiple-fold safety margins to the human exposures. She expressed concern about the potential for neuronal apoptosis in adolescents based on literature reports describing studies with racemic ketamine in adolescent mice and monkeys, and cited the lack of additional endpoints for detecting neuronal apoptosis or markers for other neurological diseases in long-term studies. She recommended a post-marketing requirement (PMR) for chronic animal studies examining higher exposures of esketamine to evaluate the long-term neurotoxic effect of esketamine on the brain.

Dr. Mathew’s supervisor (Ikram Elyan, PhD) disagreed with this recommendation. She noted that Dr. Mathew’s concerns were based on literature reports of racemic ketamine toxicity; however, she believes that the Applicant provided adequate evidence about the safety of the doses and dosing paradigm for esketamine use as proposed in this application. Noting the different safety margins calculated from studies using ketamine and estimating esketamine exposure compared to studies using intranasal esketamine, I agree with Dr. Elyan.

Dr. Elyan also acknowledged Dr. Mathew’s reservations about the plasma levels obtained in animal studies conducted with this program and agreed that they were not optimal. She noted that the animal studies used the maximum feasible dose (low solubility and high volume limited intranasal dosing in animals). However, animals were dosed daily and clinical dosing will be no more frequent than twice weekly. Dr. Elyan concludes that the plasma levels observed in animals at steady state based on chronic daily exposures might be an exaggerated effect of what is predicted in intermittent human dosing given that the drug does not accumulate because of its short half-life. She also explains that esketamine exposure in the brain following oral dosing was approximately twice plasma exposure, and that brain exposure is anticipated to be even higher following intranasal dosing (although this was not formally evaluated). No neuronal toxicity was observed following 6 months of IN esketamine in rat general toxicity studies; brains were examined with hematoxylin and eosin staining, with more expansive sectioning (7 sections) as

recommended for evaluation of CNS lesions.[5] Dr. Elyan notes that additional staining and investigations are typically needed as a second-tier approach when there is an observed or possible neurotoxic effect in general toxicology studies; however, there do not seem to be any neuropathological findings in the general toxicology study that would warrant this second-tier approach.

Dr. Elyan's supervisor (Paul Brown, PhD) agrees with her conclusion that a chronic toxicity study is not needed as a PMR. However, he notes that alterations in the route, dose, duration of use, or intended population could warrant conduct of additional chronic toxicity studies with higher exposures.

I agree with Drs. Elyan and Brown that a PMR is not warranted. The lesions observed with racemic ketamine treatment were not observed with esketamine in a specific single-dose neurotoxicity study or in the 6-month general toxicity study. One would expect that CNS toxicity may result in cognitive findings; effects on learning were observed in the 6-month toxicity study but not the pre- and post-natal development study in rats. In humans, racemic ketamine abuse can cause long-term cognitive deficits. The effects of esketamine on cognition were formally evaluated in short-term and long-term studies in this development program (see Safety section, below) and no deleterious effects were observed. The Applicant is conducting a 3-year open-label safety study as well; we will issue a PMR to ensure that this study (which includes specific cognitive assessments) continues for the full 3 years rather than terminating with esketamine approval. We also will address the potential for long-term cognitive effects in labeling. With regard to Dr. Mathew's specific concern about adolescents, this product will only be indicated for adults. Because it will be available only through a REMS, off-label prescribing to adolescents is less likely. Any future expansion of the indicated population that might include children or adolescents will require thorough evaluation at relevant doses to address the findings reported in the ketamine literature and to provide evidence of long-term CNS safety in this population.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review team recommends approval.

The Applicant submitted data from 19 phase 1 clinical pharmacology studies (e.g., single- and multiple-ascending dose, absolute bioavailability, food effect, mass balance, drug interaction, renal and hepatic impairment, abuse potential, TQT studies, etc.), four phase 2 studies, and four phase 3 studies. The submission also contains 17 in vitro studies evaluating distribution, metabolism, protein binding, in vitro metabolic/transporter-based drug interactions, and other parameters; one report for the development of population pharmacokinetic (PopPK) models for Esketamine; and three physiologically-based pharmacokinetic (PBPK) modeling and simulation reports to assess drug-drug interaction (DDI) potential of esketamine as a "victim" or a "perpetrator."

[5] Bolon B, Garman RH, Pardo ID, Jensen K, Sills RC, Roulois A, Radovsky A, Bradley A, Andrews-Jones L, Butt M, and Gumprecht L. Toxicol Pathol. 41:1028-1048, 2013.

OCP recommends the following dosing schedule in adults:

Induction Phase: Weeks 1 to 4	Two treatment sessions per week Starting dose (Day 1): 56 mg Subsequent doses: 56 mg or 84 mg
Maintenance Phase: Weeks 5 to 8 From Week 9 onward	 56 mg or 84 mg once weekly 56 mg or 84 mg once weekly or once every other week

Following IN administration of esketamine, the time to reach peak plasma concentration (C_{max}) is approximately 20 to 40 minutes. After Cmax is reached, the decline in plasma esketamine concentrations is multiphasic, with rapid decline in the initial 2 to 4 hours, and a mean terminal half-life ($t_{½}$) ranging from 7 to 12 hours. Esketamine does not accumulate in plasma when administered intranasally twice weekly. The time course of certain post-dose adverse reactions follows a similar pattern, with sedation, dissociation, and elevated blood pressure typically occurring or peaking by 40 minutes post-dose and resolving 2 to 4 hours post dose.

Esketamine is extensively metabolized in the liver. Although no dose adjustments are necessary in patients with mild and moderate hepatic impairment, these patients may need to be monitored longer post-dose for sedation, dissociation, and increases in blood pressure. Esketamine is not recommended for patients with severe hepatic impairment.

The primary metabolic pathway of esketamine in human liver is via N-demethylation to form active metabolite noresketamine, with CYP2B6 and CYP3A4 serving as the primary enzymes responsible for metabolism and CYP2C19 and CYP2C9 contributing to a smaller extent. Esketamine has modest induction effects on CYP3A4 and CYP2B6 in vitro in human hepatocytes, but this did not translate into a clinically relevant induction of CYP3A4 and CYP2B6 probe substrates in healthy volunteers. Esketamine and its major circulating metabolites have a low inhibition potential against CYPs and UGTs, and esketamine and its active metabolite noresketamine are not substrates of transporters. The team concluded that no dose adjustments are necessary based on concomitant medications.

For subjects with mild, moderate or severe renal impairment, the Cmax, AUC_{last} and AUC_{∞} were 20 to 26%, 14 to 32% and 13 to 36% higher, respectively, compared to subjects with normal renal function. The team concluded that no dosage adjustments are necessary based on renal impairment.

Clearance and volume of distribution of intranasal esketamine were not influenced by sex, body weight, or race. The team concluded that no dose adjustments are necessary based on gender, body weight, race or ethnicity.

The mean esketamine C_{max} and AUC_{∞} values of intranasal esketamine were 21 to 67% and 18 to 38% higher in elderly subjects (≥ 65 years) compared to younger adult subjects (<55 years), respectively. Because of these PK differences, the phase 3 study in patients ≥ 65 years of age (Study 3005, see Clinical/Statistical-Efficacy below) used a modified dosing schedule (treatment initiated with 28 mg instead of 56 mg, with titration as early as the second dose). This study did

not achieve its primary endpoint, so the OCP team did not provide dosing recommendations for patients older than 65 years.

In a randomized, double blind, placebo- and positive-controlled cross-over thorough QTc study in 60 healthy subjects using both intranasal (84 mg) and intravenous infusion (0.8 mg/kg as a 40 min), treatment with esketamine did not prolong the QTc interval. A large increase (>10 bpm) in heart rate was observed in both esketamine treatment groups in this study; this effect will be described in labeling along with the effect on QT in section 12.2 (Pharmacodynamics).

5. Clinical Microbiology

The product is not designed to be sterile and had adequate microbial controls. The application was found acceptable from a microbiology perspective.

6. Clinical/Statistical-Efficacy

The clinical review team recommends approval of IN esketamine in conjunction with an oral antidepressant for the treatment of TRD adults, and we agree.

This application includes data from four phase 2 and four phase 3 efficacy studies (a fifth phase 3 study will be discussed in Safety, below). Two phase 2 studies were conducted with intravenous (IV) esketamine (ESKETIVTRD2001; hereafter Study 2001) or IV ketamine (KETIVTRD2002; hereafter Study 2002); the rest of the studies used the IN formulation. The evidence in support of esketamine's effectiveness derives primarily from the two positive phase 3 studies—the flexible-dose trial in adults younger than 65 years of age (Study 3002) and the randomized withdrawal study (Study 3003).

Study 2001 evaluated the effects of IV esketamine (0.2 and 0.4 mg/kg) in patients with suboptimal response to antidepressants (referred to as "TRD" by the Applicant, but the requirement for two failed treatments did not specify that the failures had to have occurred in the current episode). This study provided preliminary evidence of efficacy for the 0.2 mg/kg dose and suggested a rapid response to treatment; these results supported esketamine's Breakthrough Therapy Designation. This study also informed dose selection for a subsequent fixed-dose, dose-finding study of intranasal (IN) esketamine (ESKETINTRD2003; hereafter Study 2003).

Study 2002 suggested that once-weekly administration may not be sufficient to maintain antidepressant effect, thus informing the dosing frequency for subsequent studies.

In Study 2003, the Applicant investigated IN esketamine doses from 14 to 84 mg in 67 patients aged 18 to < 65 years with TRD. The results of Study 2003 suggested a dose-response relationship for esketamine, with the placebo-subtracted differences in change from baseline on the MADRS increasing with increasing dose (28 mg = -5.0, 56 mg = -7.6, 84 mg = -10.5). The improvement in the 28-mg group was not statistically significant ($p = 0.051$); therefore, the Applicant selected the 56- and 84-mg doses for further development in phase 3.

Table 1: Phase 3 Clinical Studies to Support Efficacy

Trial Identity	Trial Design	Dosage	Primary Endpoint	Treatment Duration and Follow-up	Study Population
Study 3001	Randomized, double-blind, multicenter, parallel-group, placebo-controlled study	Twice weekly Fixed-dose Intranasal esketamine 56 mg or 84 mg vs placebo	Change from Baseline (CFB) in MADRS Total Score at Week 4	4-week treatment phase, 24-week follow-up or TRD3003	Adults with TRD 18 to 64 years N=344 total 1:1:1 randomization
Study 3002	Randomized, double-blind, multicenter, parallel-group, placebo-controlled study	Twice weekly Flexible dose Intranasal esketamine 56 mg or 84 mg vs placebo	CFB in MADRS Total Score at Week 4	4-week treatment phase, 24-week follow-up or TRD3003	Adults with TRD 18 to 64 years N=224 1:1 randomization
Study 3005	Randomized, double-blind, multicenter, parallel-group, placebo-controlled study	Twice weekly Flexible dose Intranasal esketamine 28 mg, 56 mg, or 84 mg vs placebo	CFB in MADRS Total Score at Week 4	4-week treatment phase, 24-week follow-up or TRD3004	Adults with TRD ≥ 65 years N=137 1:1 randomization
Study 3003	Randomized, double-blind, multicenter, placebo-controlled withdrawal study	Continue dose (56 mg or 84 mg) from previous study or open-label treatment vs placebo	Time to relapse (hazard ratio)	Event-driven	Adults with TRD 18 to 64 years Stable responders or stable remitters after 16 weeks of esketamine treatment N=705 437 new entry 268 from 3001 or 3002

Phase 3 Studies

The phase 3 clinical studies reviewed to support the efficacy of esketamine are listed in Table 1. Additional study design details are provided in the primary clinical review. Jean Kim, MD (clinical reviewer) and Andrew Potter, PhD (statistics reviewer) conducted the efficacy portion of the clinical review. Patients in all of these studies had failed trials of at least two prior antidepressant drugs and, at study entry, had more severe symptoms on average than patients entering antidepressant studies for previously approved drugs (including patients in the studies to support the approval of olanzapine + fluoxetine for TRD). All patients in phase 3 studies initiated a new daily oral antidepressant (open-label duloxetine, escitalopram, sertraline, or venlafaxine extended-release) at the time of randomization to IN esketamine and IN placebo. To conserve space, the concurrent oral antidepressant is not listed in the table.

The esketamine clinical studies employed some innovative trial design elements to address some of the unusual features of the drug.

- Because of the purported rapid action of esketamine, it seemed feasible to design the studies such that all patients could start on a new antidepressant at the time of randomization, without compromising the ability to detect a treatment effect in the esketamine treatment group. Given that approved antidepressants typically take 6 to 8 weeks to exert their full effect, if an effect was observed as early as 24 hours post-dose and was maintained throughout the treatment period, that would support esketamine's effectiveness. The design is important as it assessed both the acute effect of esketamine in TRD and the persistent effect of continued use when added to an oral antidepressant.

- Because of esketamine's known dissociative effects, the challenge of maintaining the study blind was acknowledged early in development. To address this, the Applicant incorporated design elements in the study protocols to enhance blinding. For example, centralized, blinded, remote raters were used in all phase 3 studies. Use of a low-dose benzodiazepine comparator instead of an inert placebo was discussed; however, acknowledging that this could complicate interpretation of the study results, FDA agreed that inert IN placebo would be acceptable. The Applicant did add a bittering agent to the placebo to enhance the blind.

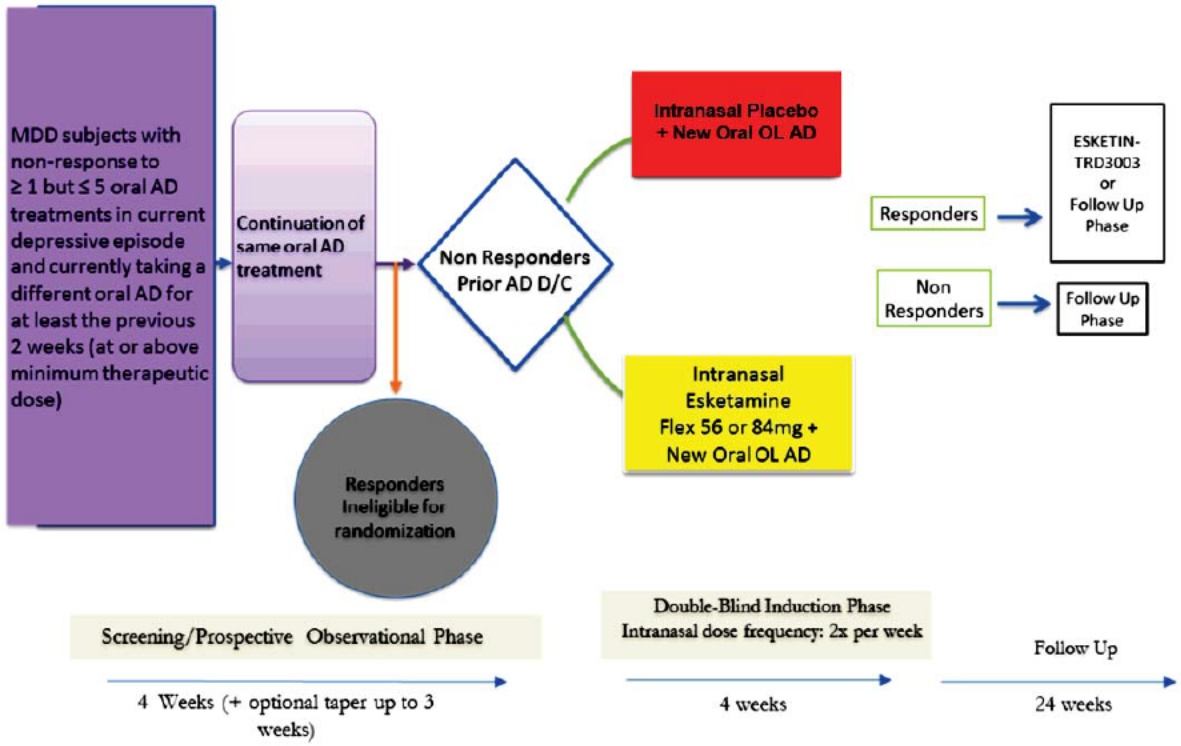
The three short-term phase 3 studies were similarly designed with the exception of fixed/flexible dosing, population age, and range of doses tested. The study schematic below (Figure 1) illustrates the design for ESKETINTRD3002 (hereafter, Study 3002). By contrast, ESKETINTRD3001 (hereafter, Study 3001) employed a fixed-dose design; ESKETIN3005 (hereafter, Study 3005) enrolled patients ≥ 65 years of age and the flexible-dose range included a 28-mg dose. The full details of these studies are described in the primary clinical review.

Across studies, demographic and baseline disease characteristics of patients randomized to esketamine and placebo nasal spray groups were similar. Of note, around 60% of patients were women, and more than 90% of patients were Caucasian. The proportion of women in the studies is not unusual given that MDD is more common in women. However, the lack of racial/ethnic diversity in the studies is striking. The Applicant did conduct phase 1 studies to explore pharmacokinetic and safety difference between Caucasian and Japanese subjects. There were no notable differences between Caucasian patients and non-Caucasian patients in the phase 3 studies, and there is no *a priori* reason to expect differences in treatment response in different

racial/ethnic groups. Nevertheless, with black patients comprising only about 5% of the patients in phase 3 studies, it is difficult to draw any meaningful conclusions.

The primary efficacy endpoint in phase 3 studies was the change from baseline to Week 4 in depressive symptoms as measured by the MADRS. The MADRS is a 10-item clinician-rated scale commonly used in antidepressant clinical studies. Scores on the MADRS range from 0 to 60, with higher scores representing more severe depression. Although there are no universally agreed upon severity cutoffs for the MADRS, scores less than 6 are generally considered "normal" (i.e., not depressed) and scores > 34 indicate severe depression.

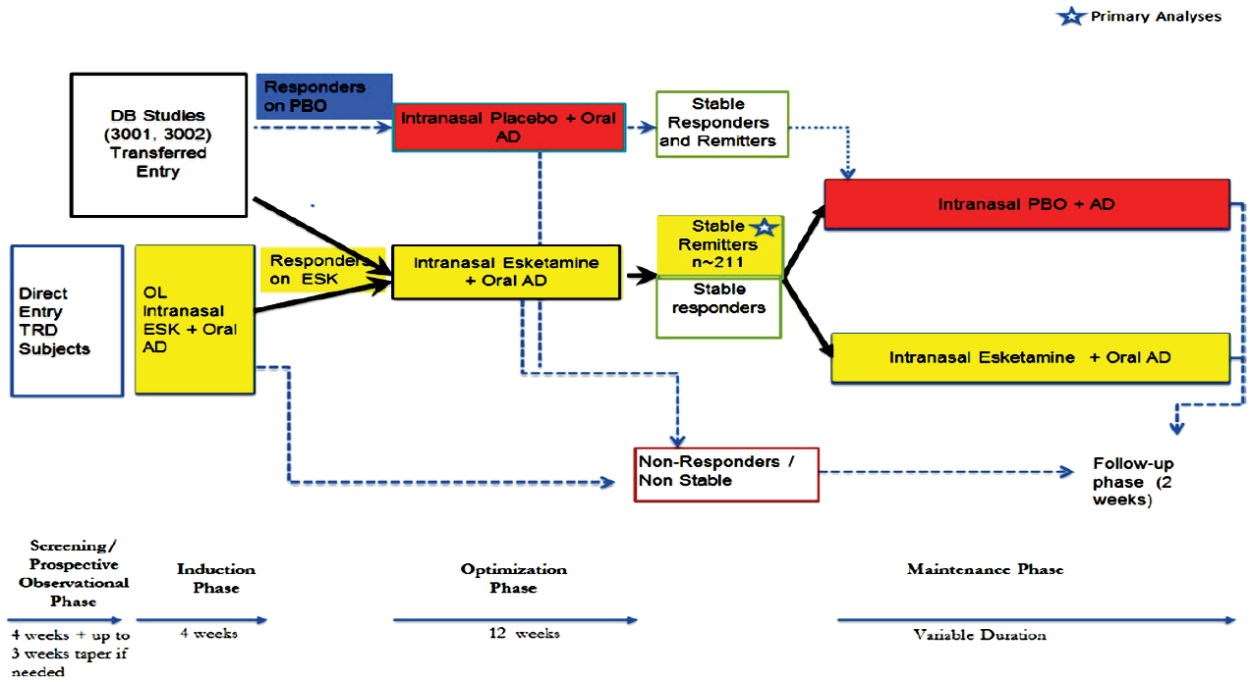
Figure 1: Schematic for Study 3002



Source: Adapted from Applicant's Clinical Study Report

At the end of each of the short-term studies patients meeting the prespecified responder definition (≥ 50% MADRS reduction from baseline) were eligible to enroll in ESKETINTRD3003 (hereafter, Study 3003), a randomized-withdrawal maintenance of effect study (Figure 2). Study 3003 enrolled responders from Studies 3001 and 3002 (i.e., adults < 65-years old) as well as direct-entry patients. The direct-entry patients received open-label, flexible-dose treatment with 56 mg or 84 mg IN esketamine twice weekly and a newly-initiated oral antidepressant for 4 weeks. As with patients entering from one of the double-blind studies, at the end of the 4-week open-label treatment period, patients with a ≥ 50% MADRS reduction from baseline (i.e., responders) were eligible for entry into Study 3003.

Figure 2: Schematic for Study 3003



Source: Adapted from Applicant's Clinical Study Report

Once enrolled in Study 3003, patients received 12 weeks of open-label treatment using the dose to which they responded in the first 4 weeks of treatment; however, the frequency of administration changed over time. During weeks 5 through 8, esketamine was administered weekly; from week 9 forward, esketamine could be administered weekly or every other week based on clinical judgement of the investigator. At the end of 12 weeks of open-label treatment (i.e., 16 total weeks of treatment), patients meeting prespecified criteria for "stable response" were randomized to continue esketamine treatment or switch to placebo. A subgroup of stable responders met prespecified criteria for "stable remission." Stable responders not meeting stable remission criteria were randomized separately from stable remitters.

- Stable Remission: MADRS total score ≤12 for at least 3 of the last 4 weeks of the optimization phase, with one excursion of a MADRS total score >12 or one missing MADRS assessments permitted at optimization week 13 or 14 only

- Stable Response: ≥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.

The population randomized to continue drug or switch to placebo in this (or any) randomized withdrawal study is an enriched population—these are individuals who have already tolerated the drug and have already experienced clinical benefit from treatment with the drug. They differ, therefore, from the patient population that would ordinarily receive a prescription for the drug and initiate treatment.

The duration of the double-blind treatment period was event-driven. The Applicant planned to continue the study until at most 84 relapses were observed in the stable remitter set with an interim analysis after 30 relapses. Based on the interim analysis, at least 59 total relapses were required to end the study. The maintenance period was to be ≥ 500 days (3 patients continuing for at least 500 days).

Phase 3 Results

Study 3002 was conducted at 39 sites worldwide with 10 sites in the United States. Subjects were randomized 1:1 to twice weekly treatment with either flexibly-dosed esketamine (56 mg or 84 mg) or placebo in conjunction with a newly-initiated daily oral antidepressant. The Applicant enrolled a total of 227 patients with 223 patients contributing data to the efficacy evaluation. The results of the primary efficacy analysis are displayed in Table 2.

The first prespecified secondary endpoint in Study 3002 was onset of clinical response by Day 2. Among esketamine-treated patients, 7.9% met the threshold for clinical response at Day 2; 4.6% of placebo-treated patients met this threshold. This difference was not statistically significant and formal hypothesis testing stopped at this point. However, considering only the drug-placebo difference in change from baseline on the MADRS, nominally significant treatment effects were observed beginning on Day 2 and consistent through the 28-day treatment period with the exception of the Day 15 assessment.

Table 2: Study 3002 MADRS Total Score at Day 28

	Placebo		Esketamine			
Dose	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean Difference (95% CI)	Two-sided p-value
56 mg – 84 mg	109	-16.84 (1.25)	114	-20.81 (1.24)	-3.98 (-7.46, -0.50)	0.0225

Source: Primary Statistical Review, Andrew Potter, PhD

The primary efficacy endpoint for Study 3003 was time to relapse in the stable remitter population; relapse during the maintenance phase was defined as a MADRS total score ≥ 22 for two consecutive assessments and/or undergoing hospitalization or another serious clinical event (as adjudicated by investigators). Stable remitters in the esketamine treatment group had a statistically significant longer time to relapse (two-sided p-value = 0.003) than patients in the placebo treatment group (HR = 0.49 esketamine/placebo; 95% confidence interval: 0.29, 0.83). The secondary efficacy endpoint in this study was time to relapse in the stable responder population. Stable responders in the esketamine treatment group had a statistically significant longer time to relapse (two-sided p-value < 0.001) than patients in the placebo treatment group (HR = 0.30 esketamine/placebo; 95% confidence interval: 0.16, 0.55).

The cumulative probability of relapse in Study 3003 increased rapidly during the first 25-30 days in the placebo arm, with 40% of placebo patients relapsing by 100 days post-randomization. The probability of relapse increased more slowly in the esketamine arm, requiring 250 post-randomization before 40% of patients relapsed. The rapidity of relapse in the placebo group was qualitatively different than what is typically observed in randomized withdrawal studies with oral

antidepressants where it can take several weeks before a difference in proportion of relapses is observed.

The primary clinical review team was concerned that unblinding (i.e., patients familiar with dissociative effects of esketamine would know if they were randomized to placebo) may have biased the study in favor of finding a treatment effect. The team conducted a number of exploratory analyses in an attempt to quantify the influence of unblinding. However, they were unable to determine conclusively whether unblinding swayed the study results. The timing of relapse in the placebo group is consistent with the Dosing and Administration language in the labeling that recommends administration of esketamine no less frequently than once every other week.

Studies 3001 and 3005 were not positive studies. Acknowledging this, the studies' results are presented below with additional comment on supportive evidence that may be gleaned from the studies.

Study 3001 was the fixed-dose study in adults younger than 65 years of age. The study was conducted at 96 sites worldwide with 42 sites in the United States. Subjects were randomized at a 1:1:1 ratio to either 56 mg esketamine, 84 mg esketamine, or placebo. The prespecified analysis plan dictated that efficacy of the 84-mg dose would be evaluated first, followed by evaluation of the 56-mg dose. However, the 84-mg dose did not separate from placebo and the testing sequence ended there.

The Applicant planned to originally enroll 234 patients with a sample size re-estimation after 50% of patients were enrolled. The maximum sample size was 348. The study was designed to have 90% power to detect a treatment difference between esketamine and placebo of 6.5 points on the MADRS at week 4. This was an ambitious target. For drugs approved to treat MDD, either as monotherapy or adjunctive treatment, based on studies in which the MADRS was the primary endpoint, treatment differences are typically closer to 3 or 4 points; the observed treatment differences in this study were in that range. Of note, the observed treatment differences in Study 3001 are also similar to those in Study 3002.

It is not clear why the treatment effect in the 84-mg group was smaller than that in the 56-mg group. In Study 2003, the fixed-dose phase 2 study results suggested that efficacy of esketamine increased with increasing dose; these results informed the design of Study 3001 and the choice to evaluate the 84-mg group first in the testing sequence.

Table 3: Study 3001 MADRS Total Score at Day 28

Endpoint	Dose	Placebo		Esketamine		LS Mean Difference (SE/ 95% CI)	One-sided p-value
		N	LS Mean (SE/ 95% CI)	N	LS Mean (SE/ 95% CI)		
Stage 1	56 mg	42	-16.83 (2.09)	37	-20.25 (2.22)	-3.42 (3.03)	0.1304
	84 mg			42	-17.12 (2.18)	-0.29 (3.00)	0.4617
Stage 2	56 mg	71	-13.39 (1.61)	78	-18.02 (1.53)	-4.63 (2.21)	0.0181
	84 mg			72	-19.07 (1.68)	-5.68 (2.30)	0.0098
Combined	56 mg	113	-14.89 (-17.41, -12.37)	115	-18.93 (-21.44, -16.42)	-4.12 (-7.66, -0.58)	0.0114
	84 mg			114	-18.22 (-20.85, -15.59)	-3.34 (-6.95, 0.27)	0.0353

Stage 1 = pre-interim analysis; Stage 2 = post-interim analysis; Combined = all patients
Source: Primary Statistical Review, Andrew Potter, PhD

Study 3005 was the flexible-dose study in patients ≥ 65 years of age. The sample size in the geriatric study was only about half of that in the successful flexible-dose study. The study included flexible doses ranging from 28 to 84 mg; the effect of esketamine in the combined dose group was not statistically superior to placebo. This study could be considered a "near miss" based on the p-value, and the magnitude of the treatment effect (3.6-point improvement on the MADRS) is in the range of effects observed in other antidepressant studies, as well as other phase 3 studies in the esketamine development program. However, examining the treatment effect over time reveals some puzzling results. Unlike the other short-term studies in the development program, there is no apparent treatment effect in the esketamine group until the final study visit.

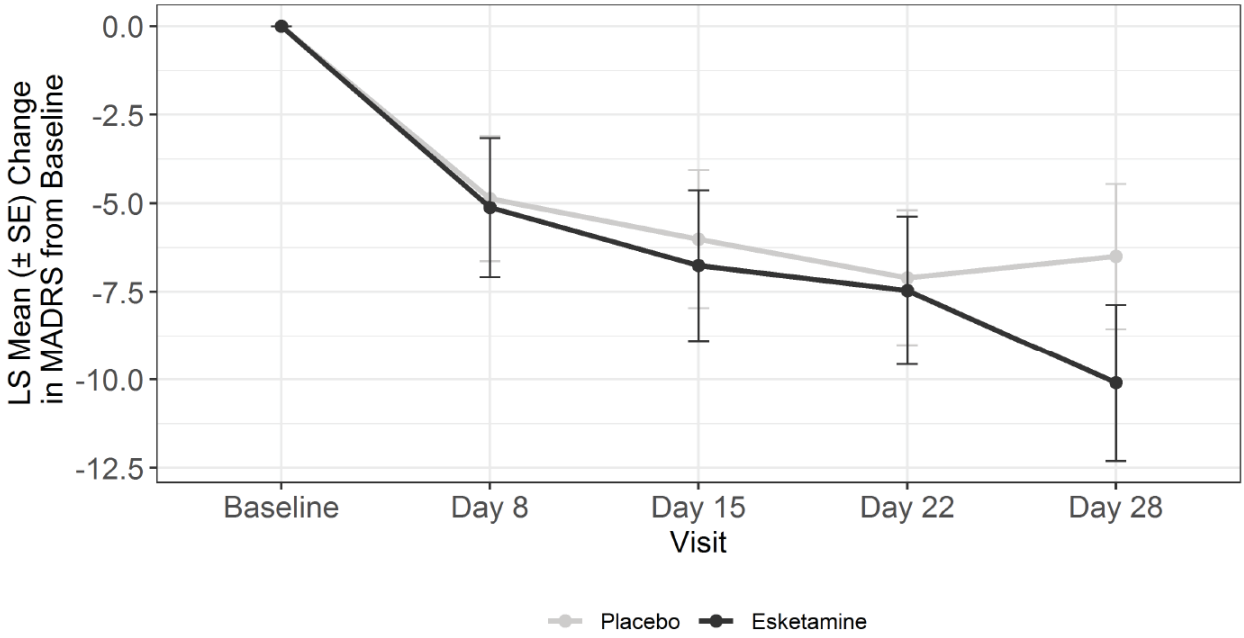
The Applicant conducted an exploratory subgroup analysis (displayed in Table 5, but not independently confirmed) that suggest patients 65- to 75-years old may be more likely to benefit from treatment with esketamine than patients older than 75 years.

Table 4: Study 3005 MADRS Total Score at Day 28

	Placebo		Esketamine		LS Mean Difference (95% CI)	One-sided p-value
Dose	N	LS Mean (95% CI)	N	LS Mean (95% CI)		
28 mg – 84 mg	65	-6.50 (-9.43, -3.57)	72	-10.09 (-13.05, -7.13)	-3.61 (-7.25, 0.02)	0.026

Source: Primary Statistical Review, Andrew Potter, PhD

Figure 3: Study 3005 MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures



Source: Primary Statistical Review, Andrew Potter, PhD

Table 5: Study 3005 MADRS Total Score for Patients 65 to 74 years and Patients ≥75 years

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

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

Source: Applicant's Advisory Committee background document, page 84

An additional study of esketamine 84 mg in patients with MDD deemed to be at imminent risk of suicide (ESKETINSUI2001; hereafter Study SUI2001) may be viewed as supportive given that the population is similar (severe MDD, though treatment resistance was not required). Data from Study SUI2001 were included in this application to provide support for the claim that esketamine acts rapidly to reduce depressive symptoms; the primary efficacy endpoint in Study SUI2001 was change from baseline (CFB) to 4 hours post-dose on the MADRS. In Study SUI2001, patients who received esketamine 84 mg experienced statistically significantly greater symptom improvement as measured by the MADRS at both 4 and 24 hours post-dose. Patients continued double-blind treatment with either twice weekly esketamine 84 mg or placebo, together with an

oral antidepressant, for a total of four weeks; however, there was no statistical difference between the two treatment groups at the end of the study.

In the primary clinical review, Dr. Kim summarizes the additional supportive evidence in the phase 2 and 3 esketamine program as follows: 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 (≤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). An additional consideration not noted by Dr. Kim, but providing further supportive evidence, is the duration of the clinical studies in the esketamine program; the magnitude of esketamine's treatment effect (relative to placebo) is similar to that observed with approved antidepressants. However, the studies supporting approval for oral antidepressants are typically 6 to 8 weeks in length; the esketamine studies are only 4 weeks.

Conclusions on the Substantial Evidence of Effectiveness

The primary evidence in support of approval comes from two adequate and well-controlled studies:

- Study 3002: a randomized, double-blind, parallel-group, controlled, short-term (4-week), flexible-dose acute treatment study
- Study 3003: a randomized, double-blind, controlled, withdrawal study

The statutory requirement for substantial evidence for IN esketamine 56 mg and 84 mg in conjunction with an oral antidepressant for the treatment of TRD is met with the positive results from these two studies. Substantial evidence was not provided for the 28-mg dose or for patients ≥ 65 years of age. We also considered the additional supportive data from Studies 2003, 3001, and SUI2001. The overall pattern of results (described in more detail above and in the primary clinical review) further supports the conclusion that substantial evidence of effectiveness has been provided.

7. Safety

The safety of esketamine was evaluated in the short-term double-blind studies relative to placebo and in a single long-term, open-label study. Because esketamine is the S-enantiomer of ketamine, special attention was paid to known adverse events associated with ketamine use as intended and with ketamine misuse and abuse. Sedation, dissociation, cognitive impairment, and suicidal

ideation and behavior were treated as adverse events of special interest; thus, the clinical studies included specific assessments for these events.

The combined cumulative exposure to esketamine in the five completed phase 3 studies was 601 patient-years. Studies 3001, 3002, and 3005 included a total of 418 subjects exposed to at least one dose of esketamine.

A total of 1708 subjects with TRD received at least one dose of esketamine in the completed phase 2 and 3 studies. In phase 3 studies, there were 1601 subjects exposed to esketamine, of which 479 were exposed for at least 6 months, and 178 were exposed for at least 12 months, satisfying the recommended extent of exposure for drugs intended for long-term treatment per ICH E1.[6] The safety population in the double-blind, placebo-controlled studies (Studies 3001, 3002, and 3005) included 705 patients. The safety population in the maintenance phase of the randomized withdrawal study (Study 3003) included 297 subjects; an additional 627 were exposed to esketamine in the induction and optimization phases. Study ESKETINTRD3004 (hereafter, Study 3004) was a long-term open-label safety study which enrolled 802 subjects. Of these, 364 subjects were treated for at least 6 months, and 136 subjects were treated for at least 12 months.

Prior to submitting the application, the Applicant provided the Division with their planned translations of verbatim adverse event (AE) terms to preferred terms. The Division reviewed their proposal and requested a number of changes to capture events potentially related to dissociation or other psychiatric AEs. The Applicant also grouped AE terms together to capture more complex phenomena (e.g., dissociation); the safety review team created additional groups for analysis (e.g., lower urinary symptoms, interstitial or ulcerative colitis suggestive). The full list of these groups and the terms included is in the primary clinical review.

Qi Chen, MD (safety reviewer) completed the safety portion of the primary clinical review under the supervision of Marc Stone, MD (Deputy Director for Safety). During the filing review, Drs. Chen and Stone noted some discrepancies in AE reporting; an information request was sent to the Applicant and these discrepancies were corrected to the extent possible. One issue that could not be resolved—case narratives for AEs were not written by investigators; rather, they were generated from AE reports. This likely resulted in loss of some context in the narratives, but it is not an unusual practice.

There were six deaths in the esketamine development program at the time of the 120-day Safety Update cutoff. Two deaths occurred in esketamine-treated patients in double-blind studies; the remaining deaths occurred in open-label studies. Dr. Chen reviewed each case narrative and was unable to identify any pattern to suggest that esketamine caused these deaths. In two cases, there is some suggestion that patients experienced a recurrence of symptoms after esketamine was discontinued; we intend to include instructions in labeling for dose adjustments if patients miss doses and experience worsening depression.

[6] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf. Accessed March 4, 2019.

In Studies 3001, 3002, 3003, and 3005, there were 24 serious adverse events (SAEs) reported across esketamine and placebo treatment groups in 16 patients during both the double-blind and follow-up phases. SAEs were reported more in the esketamine group (12) than in the placebo (4) group. Most SAEs were reported by only a single patient. There were five SAEs of suicidal ideation, five of depression, and two of increased blood pressure in patients in esketamine treatment groups. There were two SAEs of suicidal ideation and one of depression in patients in the placebo groups. Based on evaluation of Columbia Suicide Severity Rating Scale data, the odds ratio for suicidal ideation (0.82) suggests of a lower risk with esketamine treatment; however, this finding is not statistically significant (p=0.26, 95% confidence interval 0.57 to 1.16).

The most common cause for discontinuation in esketamine groups was depression (three subjects). Blood pressure increase, headache, nausea and panic attack each led two subjects in esketamine groups to discontinue. The remainder of the AEs leading to discontinuation were reported in one subject each.

The adverse events of greatest concern in the clinical development program were sedation, dissociation, and increases in blood pressure. Most of these events occurred within the first 2 hours following drug administration. Cognitive function impairment, liver injury, and interstitial or ulcerative cystitis have been reported with long-term use of ketamine, primarily in the context of abuse. In the esketamine clinical program, there was no evidence of a higher rate of cognitive impairment or liver injury with esketamine relative to placebo. There were no reported cases of ulcerative or interstitial cystitis, but esketamine-treated patients had a higher incidence of lower urinary tract adverse events.

The AEs occurring in esketamine-treated patients at an incidence ≥ 5% and at least twice that of placebo include dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. Adverse events that appear to be dose-related include sedation, dissociation, increased blood pressure, and nausea/vomiting.

As noted in Clinical Pharmacology, above, the time course for sedation, dissociation, and increases in blood pressure closely follows the pharmacokinetic profile of esketamine, peaking at approximately 40 minutes post-dose and resolving within 2 to 4 hours. In most phase 1 and 2 studies, esketamine treatment was also associated with increases in heart rate. However, increases in heart rate were inconsistent in phase 3 studies. In two studies, the increase was less than 2 beats per minute; in the third, it was nearly 5 beats per minute. The time course of heart rate effects demonstrated a pharmacokinetic/pharmacodynamic relationship.

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. Liver injury has been reported with intravenous ketamine use (primarily abuse); in contrast, intranasal esketamine was associated with an average reduction in liver enzymes relative to baseline and placebo. The magnitude of this change was small and not likely to be clinically meaningful.

There were no events suggestive of hypersensitivity reactions with esketamine treatment. However, because ketamine labeling includes a contraindication for hypersensitivity, we will include similar language in the esketamine label.

The Applicant submitted subgroup analyses by age (18 to 44, 45 to 64, 65 to 74, and ≥75 years), 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.

The results of the Human Factors (HF) validation study based on the Applicant's initial package presentation proposal did not demonstrate that the user interface supports the safe and effective use of this product. The Applicant initially proposed 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). Of particular concern were errors and confusion observed regarding strength and dosing for this product.

The Applicant also evaluated the effect of intranasal esketamine on driving performance in an on-road driving test using the standard deviation of lateral position as the primary end point. The results from two individual studies (i.e., 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) if they met other requirements for discharge. Two subjects from Study 1006 discontinued the driving test due to persistent and worsening of treatment-emergent adverse events. No information on the driving performance between 0 to 6 hours post-dose is available.

The applicant conducted a human abuse potential (HAP) study as recommended by the Agency's Controlled Substance Staff (CSS, review by Martin Rusinowitz dated October 20, 2015). This recommendation was based on the potential for differences in abuse potential between esketamine and racemic ketamine. Nonclinical abuse potential studies were not recommended. HAP Study #54135419TRD1015.

8. Advisory Committee Meeting

This application was presented at a joint meeting of the Pharmacological Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management Committee (DSARM) on February 12, 2019. Three voting questions and two discussion questions were presented to the committees.

- **VOTE**: Has the Applicant provided substantial evidence of the effectiveness of esketamine for the treatment of treatment-resistant depression?

  Vote Result: ***Yes: 14*** ***No: 2*** ***Abstain: 1***

- **VOTE**: Has the Applicant adequately characterized the safety profile of esketamine for the treatment of treatment-resistant depression?

  Vote Result: ***Yes: 15*** ***No: 2*** ***Abstain: 0***

- **VOTE** Given the effectiveness and safety of esketamine and the FDA's proposed risk evaluation and mitigation strategy (REMS), do the benefits outweigh the risks of esketamine for the treatment of treatment-resistant depression?

  Vote Result*:* ***Yes: 14*** ***No: 2*** ***Abstain: 1***

- **DISCUSSION:** Discuss whether the FDA's proposed REMS would assure safe use of esketamine and what additional safeguards would be needed, if any.

  The panel members had concerns about defining the setting in which esketamine will be administered. Committee members commented that esketamine should be available in a practice setting capable of providing comprehensive medical and psychiatric care. Members also voiced concerns about patients 65 years and older, drug-interactions, and the need for registry to record concomitant sedatives, opioids and over-the counter drugs (such as cannabidiol). Members recommended specific advice on frequency of blood pressure monitoring and use of standardized scales to monitor sedation, suicidal ideation and behavior, etc. should be specified in the Risk Evaluation and Mitigation Strategy (REMS). However, they also expressed that making the REMS too restrictive which would limit access to the esketamine.

  Post-AC action to address these issues: The REMS will require certification of healthcare facilities (see Safety, above, and Postmarketing, below, for REMS details). Efficacy in patients older than 65 years was not established, but the data do not suggest a firm cutoff for the indication at 65; therefore, the indication will not refer to an upper age boundary, but we will include a summary of Study 3005 in section 8.5 (Geriatric Use) in labeling. Although drug-drug interactions were not discussed at length during the Applicant or FDA presentations, they were evaluated (see Clinical Pharmacology, above). We will include information about potential pharmacodynamic interactions in product labeling. The REMS patient monitoring form includes specific time points for blood pressure monitoring. Rather than scales for sedation and dissociation, the monitoring form asks whether (yes/no) and when (30-minute increments) these events occurred, whether they resolved within two hours and, if not, when they did resolve. Although the label includes antidepressant class language in the Boxed Warning and Warnings and Precautions, monitoring for suicidal ideation and behavior is not a goal of the REMS.

- **DISCUSSION**: Are additional data needed pre- or post-approval to address outstanding issues? Discuss whether such data should be required prior to approval.

  Some members wanted to see more data on the functional outcomes and quality of life. Some members wanted to see a study to further characterize the risk of suicide. Studies to examine esketamine's effectiveness in individuals over 65 years of age were suggested as well. Studies on informed decision making (who signs up for treatment), heterogeneity of response (sub-groups of responders that may benefit the most), long-term effectiveness and adverse effects, patients with psychosis, patients with alcohol and drug use disorders (including patients on naltrexone), patients intolerant to Electroconvulsive Therapy (ECT) and anti-

psychotics were all recommended by the panel. There were also members who suggested looking at the mechanism of action and continue to further investigate the rapid anti-depressant effect in acutely suicidal patients.

Post-AC action to address these issues: The committees did not request any additional pre-market studies. There will be a postmarketing commitment to complete the ongoing 3-year open-label safety study; this study should address some of the committees' concerns related to long-term safety. The other suggestions noted above will not be postmarketing requirements or commitments, but some may be facilitated by the patient registry in the REMS.

9. Pediatrics

The esketamine for treatment of TRD development program did not include pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) requesting a full waiver for pediatric studies in October 2013; the Agency reviewed the plan and issued an Agreed iPSP in January 2014.

A full waiver of pediatric studies will be granted based on:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section505B(a)(4)(A)(i) of the Act)

    - The Applicant cited the lower prevalence of MDD in pediatric populations than adults, the preference for non-pharmacological interventions before pharmaceutical treatment, and the low prevalence of TRD even in adolescents.

    - Designing a study for TRD in adolescents is not practically possible. Failure of two previous antidepressants at adequate doses and duration is required for enrollment in a TRD study. But, only two antidepressants are approved for pediatric MDD. Having failed both available options, there would be no remaining options for concomitant oral antidepressant treatment in the double-blind treatment phase.

10. Other Relevant Regulatory Issues

Sites with large effect sizes were selected for inspection. 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. No significant conduct issues were noted at that site on inspection. Overall, there were no major findings from site inspections affecting interpretation of the phase 3 esketamine study results.

There were three investigators with disclosable financial interests based on payments for consulting work with the Applicant but on products other than esketamine. The number of subjects involved at these investigators' sites was very small and unlikely to affect the overall results.

11. Labeling

There were two primary sources of disagreement between the Agency and the Applicant with regard to labeling:

- Packaging configuration
  The Applicant initially proposed 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 indicating potential for confusion between the proposed packages regarding strength and dosing, and potential to contribute to product selection medication errors and wrong dose errors, the Agency advised the Applicant to that this configuration was not acceptable. After discussing several options, we agreed to a configuration that included 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), with changes to the carton and container labeling to make the proper mode of administration more obvious. The cartons will be labeled as "dose kits," with the total dose provided by the devices within the carton displayed prominently to clarify that the entire contents of the carton is required to achieve the labeled dose. A portion of the carton side panel for the 84-mg dose kit is displayed below.

Figure 4: Partial Carton Side Panel for 84-mg Dose Kit

- Geriatric dosing
  The Applicant initially proposed including specific dosing recommendations for patients ≥ 65 years of age. Given that the dedicated study in patients older than 65 years was unable to detect a treatment effect, we disagreed and did not include specific advice for dosing in geriatric patients. A description of Study 3005 and its lack of a statistically significant finding was included in section 8.5 (Geriatric Use).

  Given the highly unusual pattern of response over time relative to studies in adults < 65 years of age, we were unsure how to interpret Study 3005. In addition, even though the study failed on its primary endpoint, there was no basis to believe that there is a specific age limit for efficacy. Also of note, although all patients who received esketamine in Study 3005 initiated treatment with the 28-mg dose, most patients ultimately received the

higher doses used in studies of patients < 65 years of age; despite the age-related PK differences, the safety profile for patients 65 years and older was similar to that of patients younger than 65 years. Therefore, we did not include an upper limit on the indicated population.

Other Labeling Review Issues

Esketamine will be approved for use in conjunction with an oral antidepressant. The 28-mg dose will not be approved and there will be no single-device package presentation. The label includes advice to evaluate the patient for evidence of benefit at the end of the induction phase (first 4 weeks) to determine need for continued treatment. In general, patients who do not respond within this timeframe should be spared the risks and inconveniences of continued treatment. Dosage and Administration instructions also include a directive to monitor patients for two hours after dosing and instructions to consider returning to an earlier dosing schedule in the event of missed treatment sessions and clinical worsening.

Given the risk for increased blood pressure, the label will include a contraindication for use in patients with aneurysmal vascular disease, arteriovenous malformation, or a history of intracerebral hemorrhage. Although no hypersensitivity events were observed in the esketamine development program, we cannot exclude the S-enantiomer's involvement in such events observed with racemic ketamine; therefore, we have included a Contraindication for patients with hypersensitivity to esketamine, ketamine, or any of the excipients.

In addition to REMS-related warnings, the Boxed Warning will also include class warning language for suicidal thoughts and behaviors. The warning for increased blood pressure will include advice to monitor pre-dose, 40 minutes post-dose, and 2 hours post-dose, with additional assessments and referral for treatment as needed if blood pressure is not decreasing. Patients will be advised not to drive or operate machinery until the day after dosing. Additional warnings based on known risks with racemic ketamine (cognitive impairment, ulcerative or interstitial cystitis) will also be included in labeling.

There were no clinically important pharmacokinetic drug-drug interactions, so none are listed in the label. However, given the possibility for additive effects on sedation and blood pressure, three potential pharmacodynamic interactions were listed in the label: central nervous system depressants (sedation), psychostimulants (blood pressure), and monoamine oxidase inhibitors (blood pressure). In the absence of data to support specific recommendations regarding when to discontinue one of these medications relative to timing of esketamine administration, or regarding the degree to which these drugs might impact the safety of esketamine, the label advises prescribers to use caution when administering esketamine if patients are also taking a drug in one of these classes.

As discussed in Nonclinical Pharmacology/Toxicology, neuronal apoptosis is predicted to occur with esketamine exposure during pregnancy and the product label will include a warning for embryofetal toxicity as well as language in sections 8.1 (Pregnancy) and 8.2 (Lactation). Section 8.3 (Females and Males of Reproductive Potential) will include language under the "Contraception" subheading advising pregnancy planning and prevention for females of reproductive potential.

Esketamine is a controlled substance in Schedule III of the Controlled Substance Act (CSA), as ketamine, its salts, isomers and salts of isomers are Schedule III substances under the CSA [21 CFR 1308.13 (c)(7)]. The Applicant did not request a scheduling change for esketamine. In addition to the REMS and Warnings & Precautions language, information describing the risks of abuse and dependence, including data from the HAP study, will be included in section 9 (Drug Abuse and Dependence).

In a randomized, double blind, placebo- and positive-controlled cross-over thorough QTc study in 60 healthy subjects using both intranasal (84 mg) and intravenous infusion (0.8 mg/kg as a 40 min), treatment with esketamine did not prolong the QTc interval. A large increase (>10 bpm) in heart rate was observed in both esketamine treatment groups in this study. A similarly large effect was not observed in the phase 3 trials, though increases in heart rate were observed. We will include the heart rate data from the thorough QT study along with the effect on QT in section 12.2 (Pharmacodynamics), and a line listing for "tachycardia" (2% of patients in esketamine treatment arms vs 0.5% in placebo arms) in the common adverse reactions table in section 6.2 (Adverse Reactions).

The clinical studies section will include a figure illustrating time to response in Study 3002. We were unable to reach agreement with the Applicant by the goal date on language to describe time course of the treatment effect. A nominally significant effect can be observed on Day 2 of treatment with esketamine, and the drug-placebo difference remains fairly consistent through Day 28 in the double-blind short-term studies in patients < 65 years of age. We do not want to imply that the "full treatment effect" (i.e., how prescribers might interpret change from baseline) is present at Day 2. In fact, given how impaired patients were at baseline, even a nearly 10-point change on the MADRS at Day 2 still leaves patients with moderate to severe symptoms. Both treatment groups continued to improve through Day 28.

We initially proposed that the label should only include a figure displaying the time course of effect from Study 3002. However, the Applicant noted the precedent set by language in the vortioxetine label ("In the 6 to 8 week placebo-controlled studies, an effect of TRINTELLIX based on the primary efficacy measure was generally observed starting at Week 2 and increased in subsequent weeks with the full antidepressant effect of TRINTELLIX generally not seen until Study Week 4 or later.") to support their proposal to include a text description of time course even though the effect at 24 hours was not significant based on the prespecified statistical plan. We worked to craft language that could describe the time course of treatment without being overly promotional or implying more benefit at Day 2 than what was observed. We ultimately reached agreement on, "Figure 4 shows the time course of response for the primary efficacy measure (MADRS) in Study 1. Most of SPRAVATO's treatment difference compared to placebo was observed at 24 hours. Between 24 hours and Day 28 both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 28."

12. Postmarketing

Risk Evaluation and Management Strategies (REMS)

Intranasal esketamine is being approved with a REMS. The goal of the REMS is to mitigate the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse. Under the REMS, esketamine will only be dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients; pharmacies and healthcare settings that dispense esketamine will need to be certified; each patient must be informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring; and all patients will be enrolled in a registry to further characterize the risks and support safe use.

The monitoring requirements stipulate that patients must remain at the treatment facility for at least two hours. The healthcare provider is instructed to monitor for sedation and dissociation and record whether these symptoms are present in 30-minute increments. The restricted distribution and requirement for administration under direct supervision by a healthcare provider are intended to mitigate the risk of abuse and misuse.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The application will be approved with two PMRs and one PMC.

PMR 3577-1 Conduct a 3-year open-label safety study to characterize the long-term effects of esketamine on cognitive function and urinary symptoms. Ongoing trial TRD 3008 will be adapted to meet this requirement.

The purpose of this PMR is to continue collecting long-term safety data. The study includes specific assessments for cognitive function and urinary tract symptoms, and will allow better characterization of the risks of long-term treatment.

PMR 3577-2 To further characterize the potential risk of increasing thyroid stimulating hormone levels, analyze biobank samples taken at screening and predose on Days 1, 8, 25 or early withdrawal visits from patients who participated in the TRD3001 and TRD3002 Phase 3 studies.

Increases in TSH were observed in some phase 1 studies, but thyroid parameters were not assessed over time in the phase 2 and 3 clinical studies. The Applicant retained samples from Studies 3001 and 3002 and will analyze them.

PMC 3577-3 Conduct a study to evaluate the efficacy of esketamine monotherapy for the treatment of treatment-resistant depression. The study design must be agreed to by the Division prior to initiating the study.

The clinical studies supporting this application all involved initiation of a new oral antidepressant in conjunction with IN esketamine. Oral antidepressants typically require several weeks of treatment before a treatment effect is observed, so the apparent early effects observed in the esketamine program suggest an independent effect; therefore, we have obtained a commitment from the Applicant to conduct a study evaluating esketamine in monotherapy. Several options for study design were discussed, but we were not able to reach agreement with the Applicant prior to the goal date. To fulfill the PMC, the Division must agree to the study design prior to initiation.

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/

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